



Survival, cardiorespiratory fitness and quality of life after renal transplantation in childhood: Data from the HENT study.

Trine Tangeraas

**Oslo University Hospital, Rikshospitalet
Department of Pediatric Medicine
Faculty of Medicine
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TABLE OF CONTENTS

1. PREFACE	4
<i>ACKNOWLEDGEMENTS</i>	4
<i>ABBREVIATIONS</i>	6
<i>SUMMARY OF THESIS</i>	8
<i>LIST OF PAPERS</i>	11
2. INTRODUCTION	12
2.1 Definition and classification of chronic kidney disease in children	12
2.2 Epidemiology of ESRD in children	12
2.3 Causes of ESRD in children	12
2.4 Renal replacement therapy	12
2.5 Historical overview of pediatric renal transplantation	13
2.5.1 Immunosuppressive drugs.....	13
2.5.2 Immunosuppressive eras - advances in medical treatment.....	14
2.5.3 Acute rejections and chronic allograft nephropathy	15
2.5.4 Graft survival and donorship in pediatric renal transplantation.....	16
2.6 Comorbidities of chronic kidney disease and after renal transplantation	16
2.6.1 Childhood growth with chronic kidney disease and after renal transplantation	17
2.6.2 Chronic kidney disease and cardiovascular risk	17
2.7 Cardiovascular risk factors after pediatric renal transplantation	18
2.7.1 Long-term outcome after pediatric renal tx and cardiovascular disease.....	18
2.7.2 Chronic kidney disease.....	18
2.7.3 Hypertension	19
2.7.4 Left ventricular hypertrophy.....	19
2.7.5 Overweight/obesity	20
2.7.6 Glucose intolerance/ diabetes, hyperlipidemia and metabolic syndrome	20
2.8 Physical activity and cardiorespiratory fitness in CKD and after tx	21
2.9 Psychosocial/quality of life issues	21
3. AIMS OF THE STUDY	23
4. SUBJECTS AND METHODS	24
4.1.1 Design – papers I-IV	24
4.1.2 Subjects – paper I	24
4.1.3 Subjects – papers II and IV	25
4.1.4 Subjects – Paper II.....	25
4.1.5 Subjects – paper III.....	27
4.2 Methods	29
4.2.1 Child physical Activity Questionnaire (paper II)	29
4.2.2 Adult physical activity questionnaire (paper III).....	30
4.2.3 The Strength and Difficulties Questionnaire (paper IV)	31
4.2.4 The Pediatric Quality of Life Inventory (paper IV).....	31

4.2.5 The General Health Questionnaire (paper IV).....	31
4.2.6 The Quality of Life Scale (paper IV).....	31
4.2.7 Exercise testing (papers II and III)	32
4.2.8 24-hour ambulatory blood pressure (ABPM).....	33
4.2.9 Renal function, biochemistry and metabolism	34
4.3 Anthropometrics and dual-energy X-ray absorptiometry	34
4.4 Outcomes and definitions	35
4.5 Statistical analyses	37
4.6 Ethical considerations.....	38
5. MAIN RESULTS.....	39
5.1 Graft and patient survival after renal transplantation in childhood (paper I)	39
5.2 CR fitness in renal tx children and adolescents compared to healthy children (paper II).....	43
5.3 CR fitness in adults with a history of renal tx in childhood (paper III).....	45
5.4 Renal tx children and their caregivers' perceptions of mental health and quality of life after renal tx (paper IV).....	46
6. DISCUSSION	48
6.1 Graft and patient survival after renal transplantation in childhood (paper I)	48
6.2 CR fitness in renal tx children and adolescents compared to healthy children (paper II).....	49
6.3 CR fitness in adults with a history of renal tx in childhood (paper III).....	51
6.4 Renal tx children and their caregivers' perceptions of mental health and quality of life after renal tx (paper IV).....	52
6.5 Strengths of the studies.....	53
6.6 Limitations	54
6.6.1 Study design	54
6.6.2 Selection bias, information bias and confounding.....	54
6.6.3 Interpretation of $\dot{V}O_{2peak}$ (papers II-III).....	56
6.6.4 Other methodological limitations	57
7. CONCLUSIONS AND CLINICAL IMPLICATIONS.....	59
8. FUTURE RESEARCH	61
9. REFERENCES	62
10. ERRATA.....	75

PAPERS I-IV

APPENDICES

1. PREFACE

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ABBREVIATIONS

ABPM	ambulatory blood pressure measurement
Adult-tx	young adults with a renal transplant in adulthood (≥ 19 years of age)
ALL	acute lymphoblastic leukemia
AR	acute rejection
ATG	anti-thymocyte globulin
AZA	azathioprine
BP	blood pressure
CKD	chronic kidney disease
CNI	calcineurin inhibitor
CR fitness	cardiorespiratory fitness
CS	cross-sectional
CV	cardiovascular
Cya	cyclosporine
DD	deceased donor
DXA	dual-energy X-ray absorptiometry
ESRD	end stage renal disease
FEV1	forced expiratory volume in one second
FEV1%	forced expiratory volume in one second in % of expected of age/height/sex
FFM	fat free mass
FM	fat mass
FM %	fat mass in percent of total body mass
FMI	fat mass index
FVC	forced vital capacity
FVC %	forced vital capacity in percent of expected of age/height/sex
GFR	glomerular filtration rate
GHQ	general health questionnaire

HC	healthy controls
Hgb	hemoglobin
HRQOL	health related quality of life
IGT	impaired glucose tolerance
IPAQ	international physical activity questionnaire
IS	immunosuppressive
LBM	lean body mass
LD	living donor
MET	metabolic equivalent task
MVPA	moderate to vigorous activity
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NRR	Norwegian Renal Registry
OGTT	oral glucose tolerance test
OUS	Oslo University Hospital
PA	physical activity
PedsQL	pediatric quality of life inventory
Ped-tx	young adults with a renal transplant in childhood (< 16 years of age)
RER	respiratory exchange ratio
SDQ	strength and difficulties questionnaire
Tac	tacrolimus
Tx	transplantation
USRDS	United States Renal Data System
V _{O₂peak}	peak oxygen uptake

SUMMARY OF THESIS

Renal transplantation (tx) restores kidney function temporarily and improves the prospects of a normal life as compared to dialysis. During the last forty years great progress has been made in renal transplantation and its follow up treatment. However, preserving long-term graft function is still a major challenge. Therefore, it is crucial to review our practices in pediatric transplantation and to evaluate patient outcome as the first step in enhancing future prospects. Following renal tx a chronic multifactorial physical and mental condition persists both for the child and its caregivers. Life-long dependence on immunosuppressive treatment (IS) and concomitant comorbidities after tx (e.g. progressive decline in renal function, hypertension, hyperlipidemia and excessive weight gain) render these children at increased risk for future cardiovascular (CV) morbidity and mortality. Based on structural and functional echocardiographic findings post-tx, these children have been forecast a rather gloomy CV prognosis including cardiomyopathy and heart failure in adult life. However, little attention has so far been paid to the levels of physical activity and cardiorespiratory fitness (CR fitness, VO_{2peak}) as global markers of CV health and physical functioning in tx children and adult survivors. Furthermore, more knowledge is required of the impact of tx on health related quality of life (HRQOL) for the child and its caregivers following, predominantly, parental kidney donation.

Aims

The overall aim of this study was to evaluate long-term outcome after renal tx in childhood. In paper I, the purpose was to investigate the long-term patient and graft survival during 1970-2006 in a pediatric cohort receiving renal grafts mainly from living donors (LD).

In the cross-sectional (CS) studies (papers II-IV) the objective was to increase the knowledge of health outcomes after tx in childhood, with emphasis on the level of CR fitness as a marker of CV function. Moreover, in recipients of predominantly parental donor organs, the aim was to investigate the children and their caregivers' perceptions of mental health and HRQOL.

Design

The HENT study (Helse Etter Nyre Transplantasjon i barnealder) was designed as a national follow-up study after renal tx in childhood consisting of 1) a historical cohort study (2007, paper I) and 2) a cross-sectional (CS) study of children and adolescents (papers II and IV) and young adults (paper III) renal tx after 1983. The CS studies were performed during 2008-2010.

Methods

Survival data and baseline characteristics were obtained from the Norwegian Renal Registry and medical records. Crude patient and graft survival were calculated using the Kaplan-Meier method. Cox proportional hazards model was used to determine predictors of graft survival. In the CS studies, CR fitness (VO_{2peak}) was assessed with treadmill exercise testing. 24-hour ambulatory blood-pressure monitoring (ABPM), oral glucose tolerance test (OGTT), estimation of glomerular filtration rate (eGFR), blood sampling and anthropometric measures were also performed. Physical activity (PA) and quality of life issues were self-reported by questionnaire. Body composition was measured by dual-energy X-ray absorptiometry (DXA, adults only).

Main Results

Living donor graft (84% of all transplantations) was the only significant positive predictor for graft survival, with estimated median graft survival being twice as long for LD (median 16.7 years) as compared to that of deceased donors (DD) (median 7.7 years). Graft survival did not improve significantly across treatment eras. Twenty years patient survival was 84.4% and one third of the deaths were caused by cardiovascular disease/sudden death (paper I).

Tx children obtained a median VO_{2peak} of 66% of healthy controls, with the majority reporting low levels of physical activity (paper II). Reduced CR fitness was associated with the clustering of CV risk factors (>1 of impaired glucose intolerance, hypertension and BMI z-score >2) (paper II). Tx children's mental health, psychosocial adjustments and quality of life were for most criteria significantly impaired on both self-reports and mothers' proxy reports compared with healthy controls, and in several areas also lower than children with acute lymphoblastic leukemia (ALL). CR fitness was positively associated with quality of life; while a higher BMI z-score was negatively associated with mental health score (papers II and IV).

In the young adults who received a renal tx in childhood (ped-tx), median $\dot{V}O_{2\text{peak}}$ was reduced by 15% as compared to healthy controls. $\dot{V}O_{2\text{peak}}$ was not significantly reduced compared to adult recipients of similar age tx in adulthood (adult-tx).

Conclusions and future perspectives

The use of LD organs offers the best premise for graft survival and pre-emptive tx is the first-line preventive strategy to reduce CV risk. The future challenge is to translate the use of more potent IS treatment and reduced acute rejection rates into prolonged graft survival while concomitantly addressing weight gain, hypertension and physical inactivity. A multifactorial approach is needed in the rehabilitation of these children, recognizing that physical functioning, body habitus and quality of life measures are interdependent measures. Optimizing psychosocial outcome requires in-depth interviews with the child and the parents and relevant interventions regarding their perceived barriers to quality of life. Larger prospective studies are proposed to investigate the role of $\dot{V}O_{2\text{peak}}$ as a prognostic marker for future CV events in tx populations. While awaiting such results, physical activity should be encouraged in chronic kidney disease (CKD) and be a mandatory part of the rehabilitation program for tx children and adolescents hand-in-hand with medical and psychosocial support. This strategy may ameliorate the potential hazards of inactivity and enhance social interaction.

LIST OF PAPERS

Paper I

Tangeraas T, Bjerre A, Lien B, Kyte A, Monn E, Cvancarova M, Leivestad T, Reisæter AV. Long-term outcome of pediatric renal transplantation: The Norwegian experience in three eras 1970-2006. *Pediatr Transplant* 2008 12:762-768

Paper II

Tangeraas T, Midtvedt K, Fredriksen PM, Cvancarova M, Bjerre A. Cardiorespiratory fitness is a marker of cardiovascular health in renal transplanted children. *Pediatr Nephrol* 2010 Nov;25(11):2343-50.

Paper III

Tangeraas T, Midtvedt K, Hirth A, Cvancarova M, Tonstad S, Fredriksen PM, Isaksen G, Bjerre A. Cardiorespiratory fitness in young adults with a history of renal transplantation in childhood. *Pediatr Nephrol* 2011 May 4 [Epub ahead of print] DOI 10.1007/s00467-011-1898-6.

Paper IV

Diseth T, Tangeraas T, Reinfjell T, Bjerre A. Kidney transplantation in childhood: Mental health and quality of life of children and caregivers. *Pediatr Nephrol* 2011 Apr 26. [Epub ahead of print] DOI 10.1007/s00467-011-1887-9.

2. INTRODUCTION

2.1 Definition and classification of chronic kidney disease in children

The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease (CKD) as either kidney damage (proteinuria) or a decreased kidney glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m² for three or more months (88). CKD is stratified into five stages: Stage I (GFR >90ml/min/1.73m²), stage II (GFR 60-90), stage III (30-59), stage IV (15-29) and stage V (GFR<15 ml/min/1.73m²= end stage renal disease, ESRD) (70). The classification stages have been applied to adults and children with CKD, including renal allograft recipients (70;177).

2.2 Epidemiology of ESRD in children

The annual incidence of renal replacement therapy (RRT) among European children (< 15 years old) was 6.5 per million age related population (pmarp) in 2007 (161). The point prevalence was 33.6 pmarp, of whom two-thirds had a functioning renal graft and the remaining third were on dialysis. In 2009 a total of 292 people received renal tx in Norway, of whom eight were less than 15 years old, thus children represented 2.7% of all renal transplants.

2.3 Causes of ESRD in children

Most renal diseases in childhood leading to ESRD are (in descending frequency); congenital structural abnormalities (aplasia/hypoplasia/dysplasia/obstructive uropathy); hereditary diseases and acquired diseases. The relative distribution varies by race and classification (63) and some diseases are more prevalent due to ethnicity (e.g. Finnish-type nephrotic syndrome). Structural malformations occur more frequently in young children whereas glomerulonephritis, nephronophthisis and focal segmental glomerulosclerosis account for the majority of renal diseases in older children and adolescents (63).

2.4 Renal replacement therapy

The point where chronic kidney disease reaches end stage marks the start of a lifelong dependence on renal replacement therapy (RRT). The options for RRT include dialysis (hemodialysis or peritoneal dialysis), preemptive renal tx or renal tx preceded by dialysis.

Although renal tx is the best choice for quality of life and survival, dialysis is the alternative option to sustain life, most often used as a bridge to renal tx. Despite advances in dialysis technology and expertise dialysis treatment still has a four and 30 times higher mortality risk compared to those receiving tx and healthy children, respectively (99). Cardiovascular diseases are the most common cause of death in children with ESRD, ranging from 23-57% of causes of death (99;128). Projected life expectancy of adolescents >18 years exposed to RRT from childhood onwards, is estimated at 63 years for those transplanted but only 38 years for those remaining on dialysis (82). The importance of pre-emptive tx and avoidance of long-term dialysis has been emphasized as a major preventive strategy for later CV disease (176).

2.5 Historical overview of pediatric renal transplantation

In 1959 Goodwin and Murray performed the first successful transplantation between identical twins in Boston. Murray was rewarded with the Nobel Prize in 1990 for this pioneering work (124). The first successful non-twin pediatric transplant was performed in 1962 by Starzl et al in The United States. A 12-year old boy received a kidney from his mother, the graft lasted 3 years under cover of Azathioprine (AZA)/ prednisolone and irradiation treatment (152). The first pediatric renal transplantation in Norway took place two years later in 1964, when a father donated a kidney to his 8 year old son. The graft survived three years (personal communication; Dagfinn Albrechtsen). In 1970 the Norwegian children`s official tx program was established, resulting in dramatically improved life expectancy for children with end stage renal disease (ESRD). Living donor (LD), in particular living related donor tx, has been the treatment of choice since the inception of the program. Except for three pediatric patients, tx at Oslo University Hospital (OUS) Ullevål prior to 1983, all renal tx in children has been performed at OUS, Rikshospitalet (National Transplant Center from 1983).

2.5.1 Immunosuppressive drugs

The calcineurin inhibitors (CNIs) comprise of cyclosporine (Cya), originally isolated from a fungus, and tacrolimus (Tac), a macrolide antibiotic. Cya and Tac exert their immunosuppressive action by inhibiting the calcineurin enzyme responsible for activation of DNA binding proteins that stimulate the production of IL-2, one of the cytokines involved in leukocyte proliferation (126).

Azathioprine (AZA), an imidazolyl derivate of 6-mercaptopurine, antagonizes purine metabolism and inhibits the synthesis of DNA, RNA and proteins. An alternative to azathioprine is Mycophenolate (MMF), which acts by inhibiting de novo purine synthesis.

Widely used prednisolone, is a synthetic corticosteroid which has predominantly glucocorticoid activity. Prednisolone exerts its immunosuppressive effect (albeit incompletely understood) by decreasing the expression of several cytokines, chemokines and growth factors. Among the effects are poor antigen presentation by antigen-presenting cells and reduced T-lymphocyte response and effect (cellular immunity).

Basiliximab and daclizumab (induction therapy agents) are interleukin-2 (IL-2) receptor antagonists and work by binding to the CD25 antigen at the surface of activated T-lymphocytes and thereby inhibit IL-2 mediated lymphocyte activation, an important step in cellular immune response in allograft rejection. Other treatments that act on lymphocytes include the lymphocyte depleting agents such as: antithymocyte globulin (ATG); antilymphocyte globulin (ALG) and monomurab-CD3. ATG is used in steroid resistant rejections at Oslo University Hospital, Rikshospitalet.

The mammalian target of rapamycin inhibitor(s) (mTORi) sirolimus and everolimus, have emerged as complementary immunosuppressive alternatives.

Calcineurin inhibitors still constitute the cornerstone of IS treatment in children. Cya has been superseded by Tac, currently accounting for 74% of the CNI's (63). Tac is commonly combined with MMF and daily low-dose steroids/alternate day steroids. However, steroid withdrawal or even avoidance has shown promising results under the cover of induction therapy (57;69).

2.5.2 Immunosuppressive eras - advances in medical treatment

AZA was the first effective immunosuppressive option in addition to corticosteroids, and these two agents became the first line anti-rejection treatment in Norway from 1970-1983 (era I). Previously, acute rejections were managed with steroids and irradiation of the graft (108).

In the early 1980s, Cya was introduced as a new immunosuppressive agent. Cya represented a major turning point for organ tx worldwide as the drug reduced acute rejections and increased short term survival of the renal graft (119). Cya was included in the Norwegian tx program from January 1983, either in combination with steroids or in triple treatment with AZA until 1999 (era II). It was about this time that it was noticed that steroid dosages could be lowered

post-tx leading to better conditions for growth (41). However, after the success of Cya it soon became evident that the short-term benefit of Cya on graft survival was at the expense of chronic nephrotoxicity reducing long-term graft survival (81). The dependence on CNI's in pediatric IS treatment has been a double edged sword ever since. Improvements in Cya formulations evolved from a hydrophobic agent to a microemulsion formulation (Neoral, available in Norway from 1995), which lead to a more consistent absorption rate (126).

From the year 2000 onwards (era III), basiliximab was added as an induction therapy at the day of surgery and at the fourth postoperative day. Simultaneously, Cya was replaced with Tac as the CNI treatment of choice. Until recently, the Norwegian pediatric maintenance IS protocol consisted of induction therapy (basiliximab), duotherapy with CNI (Tac) and prednisolone. As of October 2010, triple therapy with tacrolimus, prednisolone and MMF has been introduced as the preferred maintenance IS treatment, similar to the adult protocol.

2.5.3 Acute rejections and chronic allograft nephropathy

In the pioneering days of transplantation, hyperacute and acute allograft rejection was the main obstacle towards graft survival. An acute rejection episode involves injury to the graft driven by T cells and/or antibodies reacting to donor antigens (MHC molecules) expressed on the surface of donor cells (113). The development of new potent IS combinations, better immunological matching, pharmacokinetic monitoring (125) and use of protocol biopsies, have been some of the factors contributing to lowering the rate of acute rejections (113). According to the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry report, acute rejection rate has decreased steadily over the years from >60% in 1987-1990 to about 13% since 2007 (146).

Historically, the slow decline in graft function was named “chronic rejection” and the diagnosis was rarely accompanied by graft biopsies in the early years but instead relied on measuring increasing levels of serum creatinine. The term has later been replaced with “chronic allograft nephropathy”(CAN) or IF/TA (interstitial fibrosis/ tubular atrophy) (149). The causes of CAN/ IFTA are multifactorial and include: chronic antibody-mediated rejection; hypertension and CNI toxicity (113). CAN remains the most common cause of graft loss, accounting for 40% of cases (146).

2.5.4 Graft survival and donorship in pediatric renal transplantation

At the turn of the millennium, long-term follow-up studies of ESRD/ renal tx from childhood emerged from several tx centers in Europe. One, five, ten and twenty year estimated graft survival in European countries (tx during 1970-2001) ranged from 85-86%, 59-77%, 46-66%, and 30.9-38%, respectively. Patient survival ranged from 91-95%, 89-98%, 86-89% and 71-89% at 1, 5, 10 and 20 years, respectively (31;32;59;102;133;159). The introduction of Cya in the 1980s significantly improved short and medium-term graft survival (102;119;133).

LD organ graft survival has been superior to that of deceased donors (DD) in all centers. The 10 year graft survival ranges from 54- 74% for LD recipients and 43-51% for DD recipients (31;32;59;102;133;159). LD and in particular living related donors, confers several benefits to the recipient beyond that of increased graft survival and is increasingly advocated (67;72). It reduces time on the waiting list, and in most cases surgery can be planned and performed without prior dialysis thus avoiding dialysis-related morbidity. Moreover, LD recipients experience improved growth (127) and the prevalence of post-tx hypertension is lower (150). There has been a steady increase in LD recipients over time, comprising 50% -60% in the American pediatric tx registries (67;114). However, DD organs still constitute the majority of the kidneys grafted in most tx centers in Europe (82;133;159). Sweden is the exception; LD kidneys currently comprise approximately 78 % of donated grafts (personal communication Ulla Berg).

Irrespective of RRT, no changes in patient survival for either dialysis or transplant patients occurred between the study periods 1992-1999 versus 2000-2007 according to a recent Canadian registry report (135). The finding is consistent with the NAPRTCS and the United States Renal Data System (USRDS) reports; patient and graft survival has remained static for pediatric ESRD/ tx patients for the last two decades (11;114). Thus, strategies that may improve long-term outcomes by preventing late allograft loss will increase life expectancy and is therefore a current priority in pediatric renal tx.

2.6 Comorbidities of chronic kidney disease and after renal transplantation

Progressive CKD and the ensuing tx entails unique challenges that require constant evaluation besides monitoring graft survival issues. Potential comorbidities include adverse effects on linear growth, osteodystrophy, risk of infections, hypertension, reduced glucose tolerance/diabetes, dyslipidemia, weight gain and in the long run CV diseases and malignancies. Lastly, the burden of a persisting chronic disease and its consequences affects family functioning and the quality of life of children and their parents.

2.6.1 Childhood growth with chronic kidney disease and after renal transplantation

Historically, growth retardation has been the hallmark of CKD in childhood. Linear growth is hampered as a consequence of the metabolic and inflammatory changes of CKD (acidosis, malnutrition and derangements in the growth hormone axis) (40). Post-tx, linear growth generally improves but is counteracted by corticosteroids and residual renal failure (33). Moreover, age at tx plays a major role; the younger recipients (<6 years of age) have the greater height deficits at time of tx than older children, but experience better catch-up growth post tx compared to older children (66). Adequate nutrition prior to tx, minimizing steroid exposure (57) and the introduction of recombinant human growth hormone have contributed to decreased growth deficits in the last two decades. Data obtained from the NAPRTCS registry have shown a steady improvement in linear growth, as the z-score at tx has improved from -2.4 in 1987 to -1.3 in the 2007 cohort. However, 25% of those currently reaching adult height are growth retarded (height z-score<-2) (114). Favourable final height results were recently presented in a Swedish report on outcome after renal tx in childhood; mean adult height was 171cm for males (-1.35 SDS) and 161 cm for females (-0.67SDS) (116).

2.6.2 Chronic kidney disease and cardiovascular risk

Children with chronic kidney disease have a higher prevalence both of the “classical” CV risk factors as well as the “non-classical” (uremic) CV risk factors, as compared to healthy children. The classical risk factors include hyperlipidemia, hypertension and insulin resistance, the most significant being hypertension in terms of its role in vascular damage and re-modelling (92). Research on the complex mechanisms of “non-classical CV risk factors” has led to a better understanding of the precursors of vasculopathy that occur early in pediatric CKD. Dysregulations in the calcium-phosphate metabolism and vitamin D axis, including secondary hyperparathyroidism, are believed to be the driving force of vascular damage leading to media calcification in the arteries (141;143). Vascular calcification and the ensuing vascular stiffness starts to develop in the early stages of CKD, increasing with time on dialysis and is not reversed by renal tx in the short term (142;143). In pediatric patients with CKD, uremic derived factors are believed to be the main contributors to cardiovascular morbidity and mortality rather than atherosclerosis (91).

2.7 Cardiovascular risk factors after pediatric renal transplantation

The prevalence of young adults with a history of renal tx during childhood is currently increasing (82). However, despite increased life prospects survivors of childhood tx have more than a 10-fold increased risk of cardiovascular (CV) death compared to the general population (133). At present only a minority of the renal tx child population has yet reached middle age (>50 years), when the cumulative effect of age, heredity and CV burden since childhood will reach its full impact.

Successful kidney tx corrects many of the metabolic abnormalities associated with ESRD, but the post-tx state introduces its own comorbidities related to IS treatment such as persistence of renal insufficiency and consequences of a chronic disorder per se. Renal tx children/ children with CKD have been classified in the highest risk stratum for future CV disease along with children with diabetes type I and homozygous familial hypercholesterolemia (77).

2.7.1 Long-term outcome after pediatric renal tx and cardiovascular disease

The Late Effects of Renal Insufficiency in Children (LERIC) study is a comprehensive Dutch cohort study on physical and psychological effects after ESRD onset in childhood between 1972-1992 (58;59). Cardiovascular sequela in adult survivors (mean age 29.2, n=140) included left ventricular hypertrophy (LVH) in 47% of males and 39% of females; 19% had aortic valve calcifications, and arterial stiffness was increased compared to controls (60). In another study by Oh et al, coronary artery calcifications were found in 92% of young adults (19-39 years old) with childhood onset ESRD (120). However, the predictive value of coronary calcifications on future CV morbidity and mortality has not yet been established. Infections and cardiovascular disease comprise the most prevalent causes of death in tx children, accounting for 27-56% (133;156;159) and 21-41 % (61;99;119;133;156) respectively. As CV events and death are rare in childhood and young adulthood after tx (lack of significant numbers), intermediate CV risk factors have been used as alternative outcome measures since they occur more frequently (46), some of which are given below.

2.7.2 Chronic kidney disease

Tx is not a cure from chronic kidney disease; CKD stage III-IV exists in 48%-62% of children post-tx (36;173), and as such GFR has been claimed to be underappreciated as a key factor inherent of several complications post- renal tx (38), including its role as a risk factor for CV death (103). Approximately 50% of those undergoing tx in childhood will need a second renal tx before the age of 25 years (52).

2.7.3 Hypertension

Post-transplant hypertension (HT) is a common complication after renal tx and affects 60-87% depending on the method of BP measurement, definition and the normative data used (137). Moreover, in 30-62% of subjects high blood pressure (BP) is insufficiently treated (37;37;138). The etiology of HT is multifactorial and includes native kidneys, CNIs, steroids, obesity, and reduced GFR (137). Ambulatory blood pressure measurement (ABPM) is generally regarded superior to office blood pressure, both in children and adult tx recipients (37;105;106;154) and is increasingly incorporated in routine surveillance of pediatric renal tx recipients. As opposed to causal BP measurements, ABPM reveals night-time hypertension, uncovers masked and white coat hypertension and provides a better overall assessment of antihypertensive treatment efficacy (85;100;137). In fact, as showed by Krmar et al, repeated monitoring of ABPM at regular intervals improves BP control (85).

Hypertension is a risk factor for graft loss (150) and is a predictor of CV mortality in adults (95). However, in contrast to adult studies, most reports have failed to show a correlation between hypertension and left ventricular hypertrophy (LVH) in tx children (100;109). Furthermore BP control (measured by ABPM) over time has not been shown to improve carotid intima media thickness (cIMT) in children, suggesting that factors other than hypertension are more decisive contributors to both LVH and increased cIMT in childhood (84). On the other hand, in young adults with ESRD since childhood (Dutch Cohort study), hypertension was shown to be an independent risk factor for LVH (62).

2.7.4 Left ventricular hypertrophy

LVH is a common cardiac abnormality in pediatric CKD and after tx. LVH is a predictor of mortality among adults (42). In children with CKD, LVH is particularly frequent in ESRD due to volume overload and hypertension (104). LVH improves after tx, but does not resolve completely and has been associated with persistent diastolic dysfunction several years after renal tx (80;105). The frequency of LVH reported post-tx ranges from 6% to 82% (9;97;105;107) depending on the tx cohort investigated and definitions used for LVH. Nevertheless, concern has been raised as to whether concomitant diastolic dysfunction acquired in childhood will progress and limit physical functioning, or even develop into congestive heart failure in adulthood (105).

2.7.5 Overweight/obesity

In the western world healthy children and adults are facing an obesity epidemic as a result of the imbalance of energy intake and expenditure. This trend is also currently being adopted in children with CKD (39) and after tx, (65) leading to further aggravation of the CV risk in these patients. Post-tx the increase in appetite as a result of steroids and regain of renal function is welcomed by most parents, but is unfortunately not balanced by an adequate activity level. Longitudinal studies have shown the prevalence of obesity in tx children (BMI>95th percentile) to increase from 13% at tx to >30% 3-12 months post-tx (24), and persisting thereafter (45) to act as an independent predictor of hypertension (24). According to a report from the NAPRTCS, obese (BMI>95th percentile) children aged 6-12 years have a higher relative risk (RR 2.9-3.6) for death than non-obese tx children (65). In adult recipients, BMI at 1 year post-tx is a strong predictor of death and graft failure (71).

2.7.6 Glucose intolerance/ diabetes, hyperlipidemia and metabolic syndrome

Diabetes is less common in pediatric than in adult renal recipients. Registry data from the USRDS found a 3-year incidence of diabetes of 7% in pediatric renal tx; the risk factors being obesity and the use of tacrolimus versus cyclosporin (16). Hyperlipidemia is a common side-effect of IS treatment following pediatric renal tx and contributes to the risk for CV disease. Hypercholesterolemia (total cholesterol>200mg/dl, 6.1mmol/l) post-tx has been reported in 15-45% of tx children, elevated LDL (>130mg/dl) in 10-13%, while triglycerides >150mg/dl (>1.7mmol/l) has been reported in 30-45% in renal tx children (10;144;145).

Coexistence or clustering of CV risk factors is a common finding after renal tx in childhood. However, controversy exists around whether metabolic syndrome (MS) is applicable in the context of renal tx patients since tx in itself constitutes a distinct metabolic risk profile attributable to persistent renal failure and use of immunosuppressives. Furthermore, in children no uniform definition on MS has been established on whether obesity, with its close link to insulin resistance, is a mandatory criterion of MS or not. Depending on the definition used, MS in children post-tx ranges from 25-37% in single center studies (131;175). Whether a constellation of metabolic CV risk factors in childhood tx track to adulthood, and furthermore is predictive for CV diseases in adulthood has yet to be determined.

2.8 Physical activity and cardiorespiratory fitness in CKD and after tx

In children with progressive CKD participation in physical activity may be reduced due to the physical and psychological consequences of renal failure. Uremia, acidosis and anemia contribute to fatigue and muscle wasting (44). The chronic disease in itself and time spent away from peers renders the child at risk for a sedentary lifestyle creating a vicious circle of inactivity and isolation. Several studies point to the lack of physical activity and decreased CR fitness both prior to and after pediatric tx in this patient group (13;35;50;83;96;121;139;167). Only one longitudinal study with 9 pediatric participants explored the change in VO_{2peak} from dialysis until 3 months post-tx (121). No significant spontaneous improvements in CR fitness were found in this small study, whereas in adult recipients CR fitness appears to improve after tx, but does not normalize (122).

In the adult population VO_{2peak} is a strong predictor of morbidity and mortality, both in healthy individuals and in those with established CV disease (34) (12;112). In fact CR fitness / exercise capacity has been claimed to be a more powerful predictor of CV outcome than hypertension, hyperlipidemia and obesity (111). Repeated exercise testing has shown that changes in CR fitness is strongly associated with changes in mortality (34). Adult tx recipients in general have reduced CR fitness compared to healthy subjects (122) but muscle strength, CR fitness and quality of life improves significantly with exercise (79). At present, no studies have assessed the effect of improved CR fitness on long-term mortality or morbidity in tx recipients. Nevertheless, the importance of exercise in adults with CKD and post-tx, has been increasingly acknowledged; A whole issue of the *Advances in Chronic Kidney Disease* was recently devoted to the importance of physical exercise in CKD populations (Vol 16, No 6, November 2009).

2.9 Psychosocial/quality of life issues

Tx is a milestone for children and their families after years lived with declining renal function. The child regains energy, appetite and renal function. However, contrary to the expectations of both the parents and the child, living with a transplant is yet another chronic disease with its own hazards and comorbidities. Rejection of the graft and subsequent graft loss is a constant threat for both the child and the caregivers. Frequent hospital visits and daily medications with cosmetic side effects are reminders of an everlasting chronic disease.

Previous research in children with advanced CKD has generally confirmed an increased risk of impaired mental health, psychosocial functioning and quality of life (55;101). Tx children report better psychosocial functioning and HRQOL than children on dialysis, but worse than

their healthy counterparts (6;55;64;101). Only a few studies have focused on the parents' psychosocial functioning and HRQOL after LD kidney donation. Despite overall improvement in family functioning following tx, including better personal relationship with their child (117), several parents express psychological distress and uncertainty about their child's future (76). Most HRQOL studies on CKD children and adolescents have highlighted on the psychosocial effects, with less attention paid to its relation to physical effect, but higher levels of PA have been associated with better HRQOL (64).

3. AIMS OF THE STUDY

The purpose of our study was to establish a historical overview of pediatric graft and patient survival and to evaluate measures of health outcome after renal tx with emphasis on CR fitness and quality of life.

The main research questions to be addressed were (1-4):

1. What is the overall graft and patient survival after renal transplantation in childhood across eras, and what are the predictors of graft survival?
2. What is the level of CR fitness of tx children and adolescents as compared to healthy controls?
 - Are physical activity and CR fitness associated with other CV risk factors in renal tx children?
3. What is the level of CR fitness in childhood tx subjects reaching adult life compared to adult recipients and healthy controls?
4. Given the predominance of parental organ donation in Norway, what are the children's and their caregivers' perceptions of mental health and quality of life following renal transplantation?
 - Are somatic health variables associated with mental health and quality of life measures?

4. SUBJECTS AND METHODS:

4.1.1 Design – papers I-IV

The HENT study (“Helse Etter Nyre Transplantasjon i barnealder”) was designed as a national follow-up study after renal tx in childhood, consisting of: 1) a historical cohort study (paper I) and 2) a cross-sectional (CS) study of Norwegian tx children and adolescents (papers II and IV) and young adults (paper III). The historical prospective cohort study was carried out during 2007; the CS studies were performed during 2008-2010.

4.1.2 Subjects – paper I

Patient and graft survival were assessed in children undergoing their first renal tx from 1970 until December 31st 2006 (n=178). Tx data on children aged 1-16 years were obtained from the Norwegian Renal Registry (NRR) and the medical records at OUS Rikshospitalet and Ullevål and were reviewed for supplementary patient data. Information retrieved included baseline clinical characteristics, native kidney disease, donor characteristics, pretransplant dialysis time, patient and graft survival, acute rejection episodes, causes of graft failure and causes of death.

Ethnicity

Eighteen children (10 %) were of non-Norwegian descent, including patients from Pakistan (n=8), India (n=1), Vietnam (n=1), South-America (n=3), Macedonia (n=1), Turkey (n=2), Albania (n=1) and Nigeria (n=1) (unpublished data from medical records).

Immunosuppressive treatment eras

In order to reflect different treatment protocols throughout the years and their possible impact on graft survival we divided the study period 1970-2006 in three treatment eras:

1. 1970-1982, when AZA and prednisolone were maintenance treatment; 2. 1983-1999 when Cya was introduced either in conjunction with prednisolone alone, or as a combined triple regimen including AZA;
3. 2000-2006, when antibody induction therapy (basiliximab) was combined with Tac and prednisolone.

4.1.3 Subjects – papers II and IV

Tx children in Norway pay annual visits to OUS Rikshospitalet until transition to adult care at about 18 years of age. From this population, children and adolescents aged 2-19 years old, receiving tx between 1993 until 31.12.2006 were invited with their respective parents to participate in a CS study involving a two-day comprehensive medical investigation program (Table 1). The inclusion criterion for participation in the CS study was a functioning graft for at least one year (GFR>20). Of a pool of n = 56 children and adolescents, four patients were excluded due to graft loss (dialysis) and two patients died. Thus, 50 eligible children/parents were invited and thirty-eight (76%) agreed to participate in whole or in parts of the program, Figure 1. Participants were enrolled from May 2008 to June 2009. There were no significant differences in sex, renal function, or proportion of LD recipients between the 38 participants and those who declined participation (n=12) but non-participants were significantly older than the participants; median age 13 (3-19) versus 16.9 (6-20) years (paper IV).

4.1.4 Subjects – Paper II

Of the 38 participants in the CS study, 26 were eligible for treadmill testing. Exclusion criteria for the exercise test were children < 8 years old (too young for test requirements, n=7) and patients with orthopedic limitations (n= 5). Two adolescent girls who participated in the CS study refused exercise testing. Two adolescent boys ended the test before maximal effort was attained. Thus, twenty-two participants completed the exercise testing (Figure 1). Eligible non-participants (> 8 years of age, n=13^a, Figure1) were significantly older than the participants; 17.4 (13-20) years versus median 14.5 (8.6-18.9) years, respectively (p=0.01) otherwise no significant differences were found regarding sex, proportion of overweight, GFR or number of transplants.

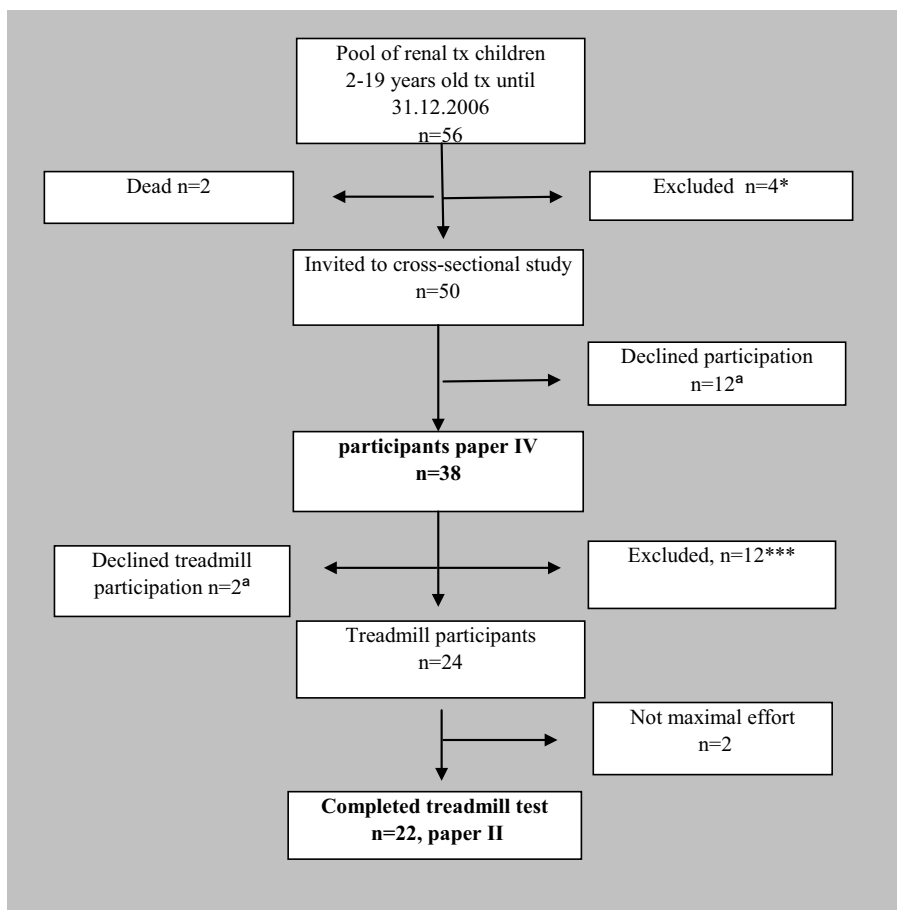


Figure 1: Recruitment of participants paper II and IV.

- *exclusion criteria: Dialysis, < 1 year since last tx.
- ^aeligible non-participants paper II: $n = 2 + 12 - 1$ (aged < 8 years of age) = 13.
- ***Children < 8 years old or physical restrictions (n=7 and n=5 respectively).

Table 1: The schedule for investigations in the CS studies.

The investigations presented in papers II-IV are shown in **bold**.

DAY 1	DAY 2
Anthropometrics	iohexol GFR
Interview/questionnaires*	
Fasting blood samples	
Start 24-h ABPM^a	Stop 24-h ABPM^a
Oral glucose tolerance test^a	Echocardiogram
Dual-X-ray absorptiometry	Treadmill exercise test
Bone density/Body composition***	
	Summary with investigator

*questionnaires on physical activity and quality of life/mental health (pages 29-31)

***performed in adults only (paper III).

^apublished in children and adolescents only (paper II)

4.1.5 Subjects – paper III

Subjects > 19 years old with a history of tx in childhood transitioned to the adult local nephrology centers, were identified from the NRR. Inclusion criteria were: functioning graft >1 year; no major locomotor or musculoskeletal restrictions on weight bearing activities; no symptomatic cardiac disease and undergoing first tx > 1983¹. Subjects on dialysis or <1 year since last tx (n=6), > 3 renal tx (n=1), orthopedic restrictions (n=3), conditions involving mental retardation and/or blindness (n=6), heart failure following myocardial infarction (n=1), severe epilepsy/ hydrocephalus (n=2) and lost-to follow up (n=1), were excluded. Twelve patients died. In total fifty-seven patients aged 19-41 years, transplanted between 1983-2002 met the inclusion criteria at the start of the study and were invited to participate (Figure 2). Participants had to be free of recent infections and acute rejections (2 weeks and 3 months

¹ Two patients, one tx in 1981 and the other in December 1982, were included in the study (both were started on Cya from 1983 onwards).

prior to study start, respectively). Forty one (70%) agreed to participate. During the inclusion period an additional 9 adults were excluded due to loss of graft function (n=3), infections (n=2) and another five adults cancelled/ did not show up. Information regarding s-creatinine, weight and height in eligible non-participants, was obtained from the NRR annual report (2009). There were no significant differences between the final treadmill participants (n=31) versus eligible non-participants (n=21) with regard to age, sex, eGFR (MDRD), time since first tx, BMI, pretransplant dialysis time or proportion of LD (tx1). Participants tended to be retransplanted more often; 14(45%) compared to 7/21 (33%) of non-participants, however the difference was not significant (p=0.1).

Controls paper III

A control group of adult-tx recipients tx after the age of 19 but < 35 years living within the suburban area of Rikshospitalet were identified from the NRR (n= 36). Seven had orthopedic restrictions and two were pregnant. Twenty-seven recipients were invited to participate. Six subjects did not respond to the invitation. Of the remaining 21 all agreed to participate but only 17 met at the scheduled treadmill/DXA test. Thirty-six Norwegian blood donors of comparable age and sex recruited from an ongoing prospective treadmill test study were included as a healthy control group for the treadmill test results. Results from the tx patients were also compared to Norwegian $\dot{V}O_{2peak}$ treadmill reference values recently published (3).

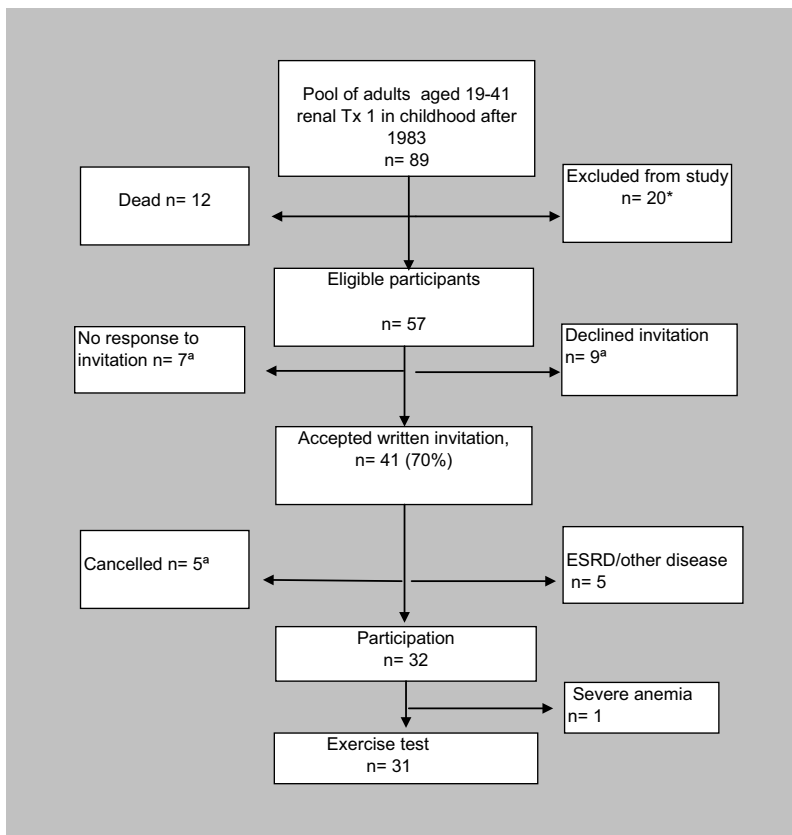


Figure 2: Recruitment of adult participants.

* Exclusion criteria, see paragraph 4.1.5, ^aeligible non-participants, $n= 9^a+5^a+7^a= 21$

4.2 Methods

4.2.1 Child physical Activity Questionnaire (paper II)

Children and adolescents completed a 7-day physical activity recall questionnaire consisting of 18 items including leisure physical activity and sedentary activities during one week (4;148) (appendix A). The questionnaire has previously been validated against an activity monitor (Actireg; Norway) in healthy 9-10 year old children and 13-14 year old children (4;148). The energy intensity for each activity was calculated as MET (metabolic equivalent task). MET expresses the intensity of each activity level as compared to resting energy

expenditure (1MET =3.5 ml oxygen consumed per kilogram of body weight). Each physical activity item was grouped in intensity-specific MET categories according to Ainsworth et al (1;2). Mean time spent on moderate activity (3-6 METs) and vigorous activity (> 6 METs) during one week was calculated and divided by a factor seven. Sedentary activities were defined as 1.3 METs and non-registered remaining time during 24 hours as 1.5 METs. The median MET level per 24 hours and self-assessed median time (in minutes) spent on moderate to vigorous activity (MVPA) per 24 hours was calculated.

4.2.2 Adult physical activity questionnaire (paper III)

Participants completed a self administered short version of The International Physical Activity Questionnaire (IPAQ short format, S7S, appendix A) which comprises a set of seven questions on the last seven days of physical activity (PA). The questions register the time spent (in bouts of at least 10 minutes and frequency per seven days) in three types of PA; walking, moderate and vigorous intensity activities, respectively. It also includes leisure time physical activity such as domestic chores and gardening (yard) activities, work-related physical activity and transport-related physical activity. Each intensity category of PA was weighted according to their respective energy requirements expressed in metabolic equivalents (METs) according to IPAQ definitions (www.ipaq.ki.se): Walking = 3.3 METs; Moderate PA = 4.0 METs and Vigorous PA = 8.0 METs. Total MET-minutes for each intensity category was computed by multiplying the MET level by minutes per day and days per week. Subjects accumulating > 600 METs-min per week of moderate and vigorous activity were categorized as sufficiently active according to international recommendations (68). IPAQ short format has been developed for international use and has been validated in 12 countries for the age group 18-65 (20). The IPAQ short format has recently demonstrated acceptable reliability for moderate and vigorous PA in Norwegian males against an activity monitor (intraclass correlations 0.3-0.8) and satisfactory validity for IPAQ vigorous PA against an objective measure of $\dot{V}O_{2peak}$ ($r = 0.41$) (87). In Swedish adults, moderate validity ($r=0.34$) was demonstrated for self-reported total PA (IPAQ) as compared to total PA assessed by accelerometry (30).

4.2.3 The Strength and Difficulties Questionnaire (paper IV)

The Strength and Difficulties Questionnaire (SDQ, appendix B) was used to assess the mental and psychosocial health in children and adolescents (56). A proxy version was given to parents. There are 5 subscales: Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems and Prosocial Behavior; the first four adding up to the Total Difficulties Score. Subscores are generated for different subscales. The SDQ shows satisfactory reliability and validity (56;118). For further details, see the subject and methods section of paper IV.

4.2.4 The Pediatric Quality of Life Inventory (paper IV)

The Pediatric Quality of Life Inventory (PedsQL™4.0) was used to measure HRQOL in children and adolescents (27), appendix B. The 23-item PedsQL is grouped into 4 domains of HRQOL: 1) Physical Functioning (8 items); 2) Emotional Functioning (5 items); 3) Social Functioning (5 items) and 4) School Functioning (5 items). Child self-reports included ages 5 to 7, 8 to 12 and 13 to 18 years. Parent proxy-reports included ages 2 to 4, 5 to 7, 8 to 12 and 13 to 18 years, and assessed parents' perceptions of their child's HRQOL. The PedsQL 4.0 has achieved excellent reliability for the Total Scale score ($r=0.89$) and has been shown to differentiate between healthy children and children with chronic health conditions (165). For further details, see the subject and methods section in paper IV.

4.2.5 The General Health Questionnaire (paper IV)

The General Health Questionnaire (GHQ, appendix B) is a widely used screening instrument for assessing the presence of distress, psychopathology and overall well-being in adults, and has showed acceptable reliability and validity (53). For further details, see the subject and methods section in paper IV.

4.2.6 The Quality of Life Scale (paper IV)

The Quality of Life Scale (QOLS, appendix B) is a questionnaire measuring adult's overall satisfaction with life based on different life domains (15). The QOLS questionnaire contains additional information on areas not usually included in health-related quality of life measures, such as independence, material comfort, work satisfaction and recreation. For further details, see the subject and methods section in paper IV.

4.2.7 Exercise testing (papers II and III)

To assess CR fitness ($\dot{V}O_{2\text{peak}}$) the tx participants (papers II and III) and healthy controls performed a graded treadmill exercise test until volitional fatigue on a motor-driven treadmill (Technogym, Italy,) using the Oslo protocol (48). Spirometry measurements (forced vital capacity (FVC) and forced expiratory volume in one second (FEV1)) were performed while standing prior to the exercise test. The best FEV1/ FVC values of three measurements were recorded and expressed as percent predicted of age, height and gender (110;130). The Oslo protocol starts at a comfortable walking speed of 5 km h⁻¹ with 2% inclination, thereafter the inclination (in 2% steps) and speed (in 1 km h⁻¹ increments) is increased every other minute until exhaustion. The healthy adult controls in paper III were tested with a modified Bruce protocol on a Woodway (Germany) treadmill (21). A Medical Graphics cardiopulmonary exercise system (Sensormedics V-max29, Yorba Linda, Calif.) was used, and expired gas was sampled using a Rudolph mask. The expiratory gas was collected and conveyed to a spirometer and to oxygen and carbon dioxide detectors. The measurement system was calibrated before each test. Oxygen consumption, carbon dioxide production and ventilation were measured continuously breath-by-breath. Mean 30second respiratory values were used in all calculations. Heart rate was recorded and a 12-lead electrocardiogram was assessed throughout the test (Cardiosoft ECG). Oxygen uptake at peak effort was determined and referred to as $\dot{V}O_{2\text{peak}}$. Respiratory exchange ratio (RER) was calculated as the ratio of CO₂ production to $\dot{V}O_2$ consumed.

In children and adolescents (paper II) a correction for differences in body mass was used by multiplying by the factor kg^{-0.67} (129). The weight-adjusted maximal oxygen uptake (ml kg^{-0.67} min⁻¹) was defined as CR fitness, also expressed in terms relative to body weight (ml kg⁻¹ min⁻¹). $\dot{V}O_{2\text{peak}}$ in participants was compared to a national pediatric reference (n=196) tested by the same protocol and assessed by the same scaling factor (kg^{-0.67}) (49). A previous study from our Department showed good reproducibility in $\dot{V}O_{2\text{peak}}$; the majority of healthy children varied less than 5% in $\dot{V}O_{2\text{peak}}$ when retested using the Oslo protocol (48). In the adults (paper III) $\dot{V}O_{2\text{peak}}$ was expressed in terms of l min⁻¹, ml kg⁻¹min⁻¹ and relative to fat free mass (ml FFM⁻¹ min⁻¹).

Requirements for a maximal test in children (paper II)

The test was considered maximal if the participant was unwilling to continue exercising despite extensive encouragement from the test supervisor, maximal heart rate (peak HR) $\geq 90\%$ of the age predicted value ($220 \text{ bpm} - \text{age}$) and respiratory exchange ratio (RER) reached 1.0 or more. Subjective annotations from the test leader (rapid breathing/unsteady running) were also included in the evaluation of a maximal test.

Requirements for a maximal test in adults (paper III)

The test was terminated when the participant was unwilling to continue exercising despite extensive encouragement from the test supervisor. The criteria for a maximal test was a RER value ≥ 1.05 at peak exercise and self-perceived exertion rated ≥ 17 according to the Borg scale (14). Borg's self-perceived exertion scale ranges from 6 to 20, where 6 means "no exertion at all", 15 is "hard effort", 17 corresponds to "very hard" (90% effort) and 20 is "complete exhaustion".

4.2.8 24-hour ambulatory blood pressure (ABPM)

24-hour ambulatory blood pressure monitoring (ABPM) was performed using a validated portable oscillometric ambulatory blood pressure monitor (Oscar 2, SunTech Medical Instruments, USA). Blood pressure (BP) recordings in children were programmed every 20 minutes from 0600 am to 2200 pm and every 30 minutes from 22pm to 0600 am. Only tests with more than 40 recordings with a minimum of 8 readings during the night, were included (178). Sex and height adjusted mean daytime and nighttime systolic and diastolic BP were converted to centiles using the LMS method (178). Thresholds for hypertension ($\text{BP} \geq 95^{\text{th}}$ percentile) were given by Wuhl et al (178). Hypertension was defined in subjects with mean daytime and/or nighttime systolic and/or diastolic blood pressure ($\text{SBP/DBP} \geq 95^{\text{th}}$ percentile or using antihypertensive treatment (AT). Uncontrolled hypertension was defined as $\text{SBP/DBP} \geq 95^{\text{th}}$ percentile whether on AT or not. Participants were regarded normotensive if both SBP/DBP were $< 95^{\text{th}}$ percentile without AT. Loss of nocturnal decline in blood pressure (BP), also designated as the nondipping phenomenon, was defined using adult criteria as a night-time BP decline less than 10% for SBP and/or DBP of the corresponding daytime BP. ABPM measurements in children have shown higher reproducibility than office BP (85;94). However, a single 24hr recording has been shown to be less reliable in characterizing the circadian BP profile (94).

4.2.9 Renal function, biochemistry and metabolism

Measured glomerular filtration rate (mGFR) was measured in tx children and adults (ped-tx) using a single intravenous injection of iohexol (0.5 ml/kg) with blood sampling after three hours (73;151). In adults only (paper III) GFR (in ml/min/1.73m²) was also estimated using the MDRD formula, corrected for s-creatinine, race, gender and sex (89). Values > 60 ml/min/1.73m² were coded as 60 when GFR was used as a continuous variable. Venous blood samples were obtained after an overnight fast and analyzed for Biochemistry at the Medical Laboratory, Rikshospitalet. Plasma-cholesterol, triglycerides, high -density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were determined by the enzymatic colorimetric method (Roche, Norway). An oral glucose tolerance test (OGTT) was performed after an oral glucose load of 1.75g of glucose per kilogram of bodyweight, maximum 75g. Serum-insulin was analyzed by enzyme-labeled chemiluminescent immunometric assay (Siemens Medical Solutions Diagnostic, AS). Plasma- glucose was measured by enzymatic photometry (Roche, Norway).

4.3 Anthropometrics and dual-energy X-ray absorptiometry

Height was measured to the nearest 0.1cm using a stadiometer. Weight was measured to the nearest 0.1kg on a digital scale wearing light clothing. Waist circumference was measured at the midpoint between the bony markers of the ribs and superior iliac crest (paper II) (47). Body Mass Index (BMI) was calculated as kg/m². In children and adolescents (papers II and IV), anthropometric data were converted to standard deviation scores (BMI-z-score and height z-score) based on Cole's LMS method (19). In children the calculations of z-scores were performed using the Pfizer International Growth Database (KIGS) Auxology Calculator for PC software (Pfizer Endocrine Care™). Overweight and obesity in children and adolescents were defined according to age and sex adjusted BMI centile cut-off limits corresponding to BMI > 25 kg/m² and >30 kg/m² at age 18 (18). Adults >19 years of age (paper III) were defined as underweight if BMI < 18.5 kg/ m², normal weight if BMI was 18.5-24.9, overweight if their BMI was 25-29.9 and obese if BMI >30 kg/m².

In adult renal tx recipients (paper III), body composition was measured by means of dual-energy X-ray absorptiometry (DXA). Whole-body and segmental body composition (upper limbs, lower limbs and trunk) were measured using a GE Lunar Prodigy densitometer (GE Medical Systems Lunar Corp., Madison, WI, USA). The obtained data were evaluated using

enCORE 2006 software (v10.10; GE Healthcare, Madison, WI, USA), which calculates the fat mass (FM; kg), percentage of fat mass of the total body mass (FM %) and lean body mass (LBM; kg). Fat-free mass (FFM; kg) was calculated as the sum of LBM and bone mineral content. Fat mass index (FMI) was calculated as FM/m^2 .

4.4 Outcomes and definitions

Acute rejection

The term acute rejection (AR) included both early and late acute rejection episodes. Early acute rejection episodes were defined by a rise in s-creatinine of at least 20% or as decided by the physician, accompanied by antirejection therapy within 6 months after tx.

Chronic rejection

Progressive decline in renal function expressed as a slow increase in serum creatinine, excluding other causes if possible.

CKD- stratification

Measured GFR (iohexol) and estimated GFR (MDRD) were stratified into 5 stages of CKD as presented on page 12.

Standard deviation score (SDS/ Z-score) for height/BMI

Patient's height/BMI - mean height/BMI for age/ standard deviation of height/BMI for age.

Metabolic syndrome

Metabolic syndrome was defined when three or more of the following criteria were fulfilled, modified after Weiss et al (169): BMI z-score ≥ 2 ; hypertension defined as age and sex matched mSBP/mDBP $\geq 95^{\text{th}}$ percentile and/or use of antihypertensive medication; P-HDL $< 40\text{mg/dl}$ ($< 1.03\text{mmol/l}$); P-Triglycerides $> 150\text{mg/dl}$ ($\geq 1.7\text{mmol/L}$); impaired glucose tolerance (IGT) defined as two hours sampling glucose level $> 140\text{mg/dl}$ but less than 200mg/dl ($> 7.8\text{mmol/l}$ and $< 11.1\text{mmol/l}$, respectively).

Definition of $V_{O_2\text{ peak}}$ / CR fitness

Maximal oxygen uptake ($V_{O_2\text{ max}}$) is defined as the maximal capacity of the cardiopulmonary system to supply oxygen to the working muscles and the ability of muscles to use oxygen through the process of aerobic metabolism(166). $V_{O_2\text{ max}}$ describes the highest attainable oxygen uptake that does not rise further despite an increase in work rate (166). As the real $V_{O_2\text{ max}}$ is rarely achievable during treadmill testing, the highest oxygen uptake achieved during testing is termed $V_{O_2\text{ peak}}$. The concepts CR fitness and $V_{O_2\text{ peak}}$ are used

interchangeably throughout the thesis. Other terms used in the literature that refer to $\dot{V}O_{2\text{peak}}$ are aerobic capacity and aerobic fitness.

Ergometry methods

$\dot{V}O_{2\text{peak}}$ is generally assessed either by cycle or treadmill ergometry, both in children and adults. The treadmill test is regarded the best objective assessment of $\dot{V}O_{2\text{peak}}$ since it engages a larger muscle mass than the cycle ergometer, and the $\dot{V}O_{2\text{peak}}$ is therefore more likely to be limited by central (cardiac output) rather than peripheral factors (muscle) (115). Cycle ergometry is to a greater extent dependent on muscle power in the quadriceps muscle and increases the likelihood of premature termination of the test due to anaerobic metabolism and muscle pain (115).

Allometric scaling (AS)

Allometric scaling describes the method whereby $\dot{V}O_{2\text{peak}}$ is adjusted to body weight raised to a given power other than unity (e.g. $\text{ml kg}^{-0.67} \text{min}^{-1}$) to better account for differences in body weight as $\dot{V}O_{2\text{peak}}$ (l min^{-1}) does not increase linear to body weight.

Physical activity

Physical activity (PA) encompasses all kinds of body movement during leisure time or work that increases skeletal muscle work and energy consumption. The dimensions of physical activity can be described by the intensity, frequency, duration and type of activity performed. PA and CR fitness are strongly linked, but represent two complementary ways of measuring physical health (157). PA is difficult to measure due to its complex nature, while CR fitness is easier to assess objectively by direct gas exchange measurements during maximal exercise.

Exercise capacity

In this thesis is defined as the duration of exercise on the treadmill.

RER

Respiratory exchange ratio: The ratio of CO_2 production to $\dot{V}O_2$ consumption. A ratio >1.0 and ≥ 1.05 was one of the requirements for a maximal exercise test in children and adults, respectively.

MET

Metabolic equivalent: One MET is the amount of energy used by an average adult at rest = 3.5 ml oxygen consumed per kilogram of bodyweight.

Ped-tx

Young adults with a history of first renal tx in childhood (< 16 years old).

Adult-tx

Young adults with a history of first renal tx in adulthood (≥ 19 years old).

4.5 Statistical analyses

General, Papers I-IV

Data were described with median and range (continuous variables), or as proportions and percentages (categorical variables). 95% confidence intervals (CI) for proportions were constructed using the f-distribution approximation. For continuous variables, the differences between groups were analyzed using an unpaired (two-sided) t-test (normally distributed data) or Mann-Whitney Wilcoxon test (variables with skewed distribution). The non-parametric Wilcoxon signed rank test was used to analyze the difference between two continuous variables when the same individual was measured several times. Associations between categorical variables were assessed using a Chi-squared test or Fisher's exact test for small samples. The strength of crude associations between normally distributed continuous variables was measured using Pearson's correlation coefficient or Spearman's correlation coefficient when the variables had a skewed distribution. All statistical tests were two-sided, a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS ver 13-16.

Paper I

Crude patient and graft survival were calculated using the Kaplan-Meier method and computed with follow up times of 5, 10, 15 and 20 years. Crude survival curves between groups were compared with the log-rank-test. Graft survival was defined as the time from transplantation to the graft loss or to the end of study (31.12.2006). Graft loss (event) was defined as 1) the date of death with functioning graft (uncensored death), 2) the date for return to dialysis or 3) the date of a new pre-emptive transplant. Patient survival was defined as the time from tx to death or to the end of the study. Censoring: survival time was censored for those who had not yet experienced an event by the end of study (31.12.2006). No patients in our study were lost to follow-up. To evaluate possible predictors of graft survival measured at the time of tx, Cox proportional hazards model was fitted and adjusted for LD/DD, diagnosis, dialysis prior to tx, donor age, sex, and immunosuppressive era. The model was stratified by age-groups (0-6 years, 7-11 years and 12-15 years) due to non-proportionality.

Paper III

Possible predictors of $\text{VO}_{2\text{peak}}$ (l min^{-1}) as the dependent variable were evaluated using univariate linear regression analysis. Variables with a p-value < 0.1 from the univariate analyses were entered into a multiple linear regression model. Highly correlated independent variables ($r > 0.7$) could not be entered in the same model (due to multi-collinearity); thus the variables sex and height were not included because of their high correlation with the variable FFM ($r=0.78$ and 0.79), which we regarded as more clinically relevant. A careful check of the model assumptions including an investigation of residual plots was performed.

Sample size

No previous study has compared the level of $\text{VO}_{2\text{peak}}$ between adult survivors of childhood tx to that of adult tx subjects. Therefore, in paper III we had little or no guidance to quantify the clinically relevant (mean $\text{VO}_{2\text{peak}}$) difference between the tx groups. We based our assumption on other $\text{VO}_{2\text{peak}}$ studies in adult tx patients, in which mean $\text{VO}_{2\text{peak}}$ was reduced with 20-25% as compared with healthy controls (79). To detect a mean $\text{VO}_{2\text{peak}}$ ($\text{ml kg}^{-1}\text{min}^{-1}$) difference of ~20% between ped-tx and adult-tx, we calculated (two sample t-test, SD 10) that the study would require 25 patients in each group (power of 80% and a significance level of 5%, <http://statpages.org>).

Paper IV

A multiple linear regression analysis was used to assess possible explanatory variables as predictors for mental health (SDQ) and quality of life (HRQOL). Variables with $p < 0.05$ from the univariate analyses were included in the multiple linear regression model. Possible explanatory variables included age, sex and the physical correlates (height, BMI, $\text{VO}_{2\text{peak}}$) and maternal correlates (GHQ, QOLS). A careful check of the model assumptions, including an investigation of residual plots was performed.

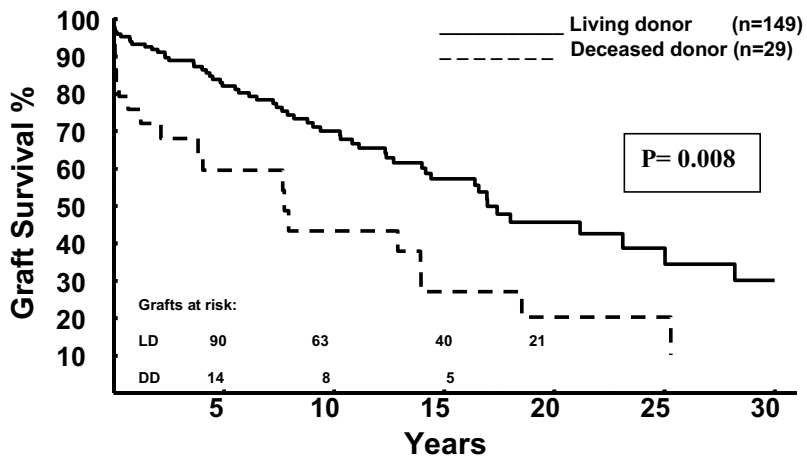
4.6 Ethical considerations

Written informed consent was obtained prior to study start from children and adults > 16 years of age or their parents if less than 16 years old. Participants were informed that they could withdraw from the study at any time. The Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics in South Eastern Norway approved the HENT study.

5. MAIN RESULTS

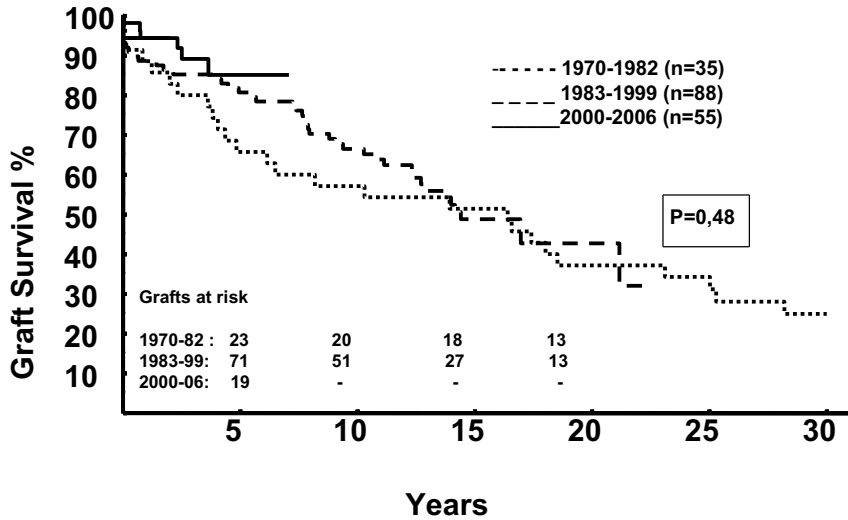
5.1 Graft and patient survival after renal transplantation in childhood (paper I)

During 1970-2006, 178 children underwent their first renal tx at a median age of 11.1 (0.8-15.9) years. Eighty-four percent of pediatric recipients received a kidney from a LD, predominantly parents (86 %). Fifty-one percent were transplanted pre-emptively, dialysis time prior to tx was median 3 months. The unadjusted estimated median graft survival was 16.9 years for LD grafts versus median 7.7 years for DD organs (log rank, $p=0.008$, Figure 3). LD graft was the only significant predictor of better graft survival (HR=2.1, 95% CI [1.1-4] as compared to DD grafts when adjusted for pretransplant dialysis, diagnosis, sex, donor age and immunosuppressive era. There was a trend towards improved 1 and 5-year graft survival from era II (1983-1999) to era III (2000-2006) (Figure 4), however the difference was not statistical significant. Acute rejection rates decreased from 61.5 % in era I to 14.5% in era III ($p=0.002$). Estimated cumulative 20 year patient survival rate was median 84.4% (Figure 5). The main causes of death were infections (38%) and cardiovascular events (33%). Chronic rejection (60%) was the far most common cause of graft loss.



Donor	Graft survival 1970-2006 (tx1, %)				
	1 year	5 years	10 years	15 years	20 years
LD (n=149)	93.2	82.0	68.8	57	45.1
DD (n=29)	75.9	59.6	43.3	27.1	

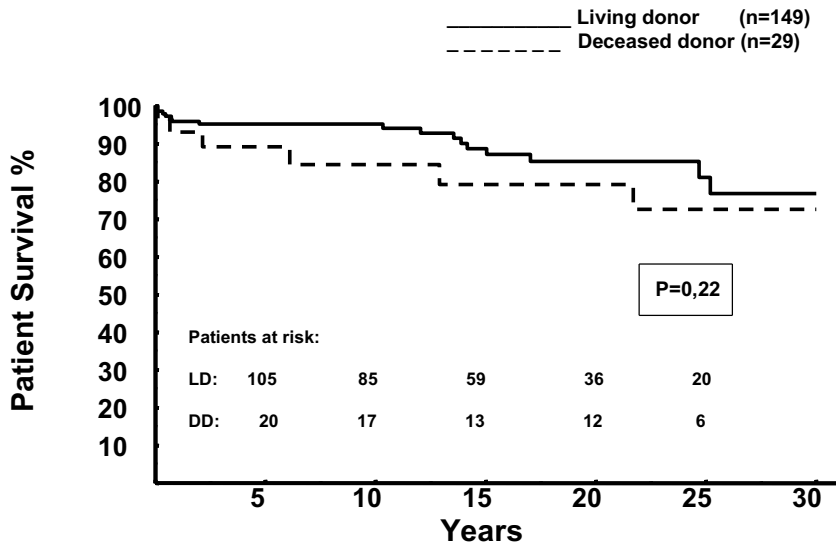
Figure 3: Graft survival of living donor transplantation versus deceased donor:



Era of tx	Graft survival (%)					
	1 year	5 years	10 years	15 years	20years	25years
1970-1982 (n=35)	88.6	65.7	57.1	51.4	37.1	31.2
1983-1999 (n=88)	88.6	80.7	65.1	48.6	42.1	
2000-2006 (n=55)	94.4	84.6	-			
2000-2010 (n=71)*	96	85	72			

* Extending the last era until June 2010: There was a trend towards increased 1 year graft survival from 1983-1999 to 2000-2010, $p=0.097$, unpublished data.

Figure 4: Graft survival in three eras



Donor	Patient survival 1970-2006 (tx1, %)				
	1 year	5 years	10 years	15 years	20 years
LD (n=149)	95.9	95.2	95.2	89.8	86.3
DD (n=29)	93.1	89.2	84.5	79.2	79.2

Figure 5: Patient survival 1970-2006

5.2 CR fitness in renal tx children and adolescents compared to healthy children (paper II)

- Associations of CR fitness with CV risk factors in renal tx children (paper II)

In this cross-sectional follow-up study, 24 (63% of eligible) children and adolescents participated in a two day comprehensive study (Table 1) which included the assessment of $\dot{V}O_{2peak}$, a maximal treadmill test and a self-reported physical activity questionnaire. Twenty-two participants completed the treadmill test until exhaustion and were included in further analysis (Figure 1). Median age was 14.5 (8.6-18.5) years and time since tx 1 was median 5.2 (1.1-14.2) years. All patients had $GFR > 20 \text{ ml/min/1.73m}^2$ and $Hgb > 10\text{g/dl}$. All were non-smokers, none had overt cardiac disorders. Nineteen children (86%) reported less than 60 minutes of recommended daily MVPA. $\dot{V}O_{2peak}$ was significantly correlated with MVPA ($r = -0.49, p = 0.03$). $\dot{V}O_{2peak}$ was median 33.5 (18-59) $\text{ml kg}^{-1}\text{min}^{-1}$ in tx children and 53 (35-72) $\text{ml kg}^{-1}\text{min}^{-1}$ in the reference population ($n = 196, p < 0.001$, Figure 6). When $\dot{V}O_{2peak}$ was expressed relative to body weight $^{-0.67} \text{ min}^{-1}$ the study subjects obtained median 66% (36 to 97) of expected $\dot{V}O_{2peak}$ of healthy Norwegian children of comparable age and sex. Only three participants obtained $\dot{V}O_{2peak}$ within the expected range of healthy references (i.e. $\dot{V}O_{2peak}$ z-score > -2).

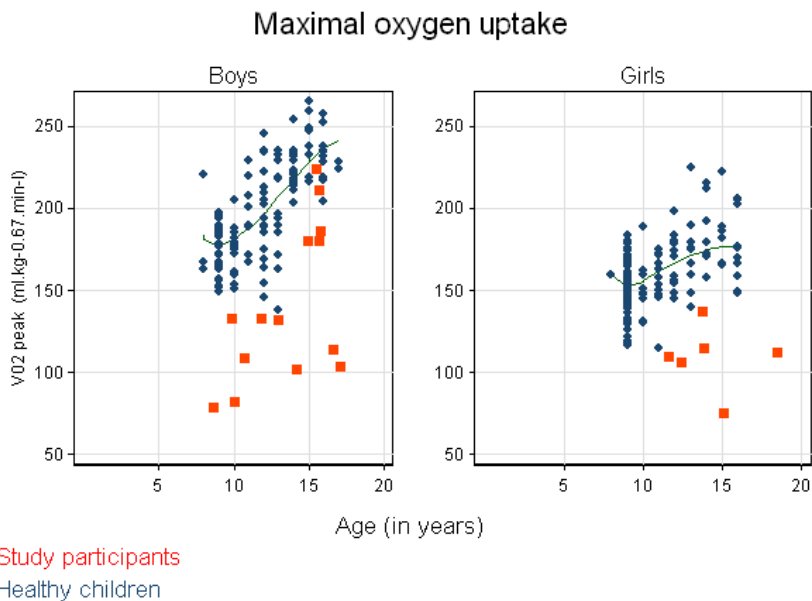


Figure 6. Comparison of pediatric renal tx male and female peak treadmill exercise values (VO_{2peak}) to a reference child population (49).

Sixteen (73%) of the treadmill participants were either hypertensive on ABPM or treated with antihypertensive medication. Eight children (36%) were overweight (n=4) or obese (n=4), median BMI z-score was 0.6 (-1.8-6.9). P-cholesterol was elevated (>200mg/dl) in five children. P-TG >150mg/dl was found in 2/22 and decreased HDL (< 40mg/dl) in n= 4 children. None of the children were receiving lipid- lowering agents at the time of the study. Three children had impaired glucose tolerance, none had overt diabetes. Four children (18%) fulfilled the criteria for the metabolic syndrome.

Children with at least 2 of 3 metabolic risk factors (hypertension, overweight and glucose intolerance, n=7) achieved significantly lower VO_{2peak} compared to those with one or none of these risk factors (median VO_{2peak} = 45% and 73% of expected, respectively, p=0.003). Children with one or less metabolic risk factors reported significantly more daily physical activity than children with two or three risk factors (median MVPA 36 minutes versus 23 minutes, respectively, p =0.02).

5.3 CR fitness in adults with a history of renal tx in childhood (paper III)

- Compared to adult transplanted subjects (adult-tx) and healthy controls

Study participants were enrolled in this cross-sectional study from September 2009 to November 2010. Of the eligible adults with a history of renal tx in childhood (ped-tx), 41 (70%) agreed to participate, 31 (~60%) completed a treadmill exercise test (Figure 6). Seventeen adults of comparable age transplanted in adulthood (adult-tx) were recruited as controls (page 28). Forty-eight young adults, 31 ped-tx and 17 adult-tx were tested on a maximal treadmill test until exhaustion. Thirty-six Norwegian blood donors of comparable age and sex, previously treadmill tested in an ongoing prospective study, were included as a healthy control group (HC). Median age was 26.9 (19-41) years, 28.6 (23.5-34) years and 33.5 (20-42) years in the three groups, respectively. Time since first tx was median 18.1 (7-29) years for ped-tx participants and 3.7 years (1.2-12.6) for adult-tx. There were no significant differences regarding age, sex or BMI between ped-tx, adult-tx and HC. Moreover, there were no significant differences between ped-tx and adult-tx in terms of total time spent on dialysis prior to tx, FM%, self-reported total PA, s- Hgb or GFR (MDRD).

$V_{O_{2peak}}$ was median 37.9 (12.5-56.3), 40.8 (26.5-57.5) and 44.4 (29.5-65.6) ml kg⁻¹min⁻¹ in the ped-tx, adult-tx and HC, respectively (Figure 7). Ped-tx had significantly lower $V_{O_{2peak}}$ compared to HC (p=0.01). Ped-tx achieved on average 85% of the $V_{O_{2peak}}$ of HC. $V_{O_{2peak}}$ was not significantly lower in ped-tx compared to adult-tx when expressed relative to body weight (ml kg⁻¹min⁻¹) but tended to be reduced in ped-tx when expressed as FFM ($V_{O_{2peak}}$ 55.2 (30-68) and 58.1 (39.7-64.5) ml FFM⁻¹min⁻¹, respectively, p=0.09). Adult-tx had higher exercise capacity (test duration) compared to ped-tx (median 10.5 (7.5-16) and 9 (6-14) minutes, respectively (p=0.016). In multiple linear regression analysis, test duration in minutes, fat-free mass (FFM, kg) and Hgb (g/dl) were significant predictors of $V_{O_{2peak}}$ explaining 86% of its variance. Total PA, tx participant group and FVC were not independent predictors of $V_{O_{2peak}}$ when adjusting for other covariates.

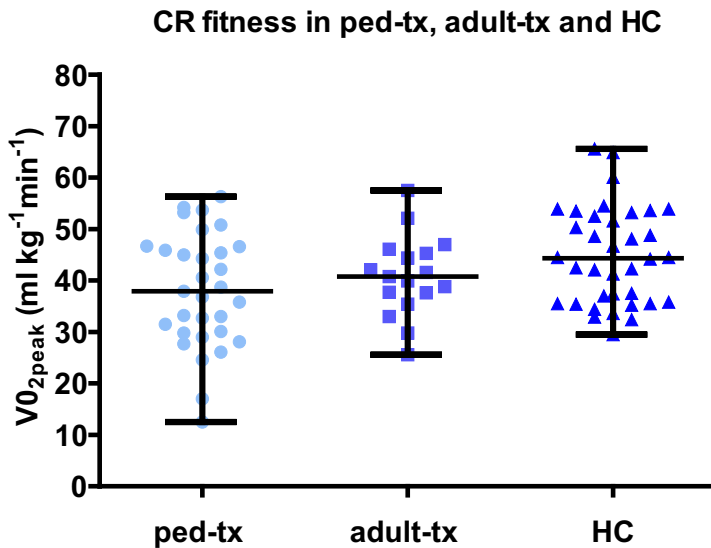


Figure 7. Treadmill exercise values

The horizontal lines indicate min-max and median values.

Ped-tx: young adults renal tx in childhood (< 16 years of age); adult-tx: young adults renal tx in adulthood (≥ 19 years of age) and HC: healthy controls

5.4 Renal tx children and their caregivers' perceptions of mental health and quality of life after renal tx (paper IV)

- Associations between somatic health variables and mental health and quality of life issues

In this paper, the purpose was to assess mental health and health-related quality of life (HRQOL) in children and their parents after renal tx compared to healthy controls and to children previously treated for Acute Lymphoblastic Leukemia (ALL), and to identify possible health-status variables associated with mental health and HRQOL.

Thirty-eight tx children and adolescents participated (76%), median age 13 years (range 3-19). The majority (n=34, 89%) had received a kidney from a LD of which 27 (79%) were donated from parents. Parental information was obtained from 32 mothers, median age 40.5

years. Healthy children (n=42) and children previously diagnosed with ALL (n=40) (and their respective mothers) were included as controls and comparison groups, respectively. Both tx children and their mothers (proxy version) reported significantly higher total SDQ difficulty scores on the mental/psychosocial health questionnaire than healthy control children and the children with ALL. Moreover, tx children and their mothers (proxy version) reported significantly lower HRQOL scores on all PedsQL items except for emotional functioning, than healthy controls and the ALL group.

The mothers of tx children reported significantly more mental health problems (GHQ-case) than the mothers of healthy controls, but the QOLS scores in mothers of tx children did not differ significantly from that obtained from the general Norwegian population.

BMI z-score was the only significant predictor of tx children's mental health outcome (SDQ total score as the dependent variable) in multiple linear regression, explaining 32% of the variance ($p=0.018$). Using PedsQL total score as the dependent variable, $V\dot{O}_{2peak}$ was the only significant predictor of quality of life outcome (n=22), explaining 42% of the variance ($p=0.005$). Age, gender, height, and the parental correlates (GHQ, HRQOL scores) were not independent predictors for the quality of life (PedsQL) or mental health (SDQ total score).

6. DISCUSSION

6.1 Graft and patient survival after renal transplantation in childhood (paper I)

The main finding of this study was that LD organs (84%) provided the best graft survival. Cumulative patient survival (84% after 20 years) and graft survival were comparable with other long-term reports on children receiving predominantly LD organs (31;140;147).

The benefits of LD organ donation on graft survival and reduced mortality is increasingly being recognized (22;67;132). However, in most tx centers in Europe DD kidneys still comprise the majority of the organs grafted (82;133;159). In the Nordic countries, only Sweden has from the inception had the same tx policy as Norway with a high proportion of LD organs and with the intention to minimize dialysis prior to tx (31). Shroff et al has shown that the vascular calcification, a marker of arteriosclerosis, increases with time in dialysis, and may only be partially reversed after renal tx (143). The extra mortality risk associated with dialysis is manifested as reduced projected life expectancy, being approximately 25 years shorter for adolescents remaining in dialysis versus those with a functioning graft (82). Thus, preemptive tx and avoidance of long-term dialysis remains the key strategy in reducing exposure to CV risk factors in children with ESRD (99;176).

There was a tendency towards, but not a significantly improved overall graft survival across eras of emerging new treatment strategies, nor was the "era effect" a predictor for LD graft survival, despite a decreased number of acute rejections across the last eras. Due to a limited number of events our study may have been underpowered to detect a small improvement in graft survival over time. In addition, with concomitant progress in expertise and more potent IS treatment there has been counteracting effects such as the acceptance of children < 2 years in the tx programs after 1988, contributing to an increased non-renal comorbidity and risk of early graft loss. From 2000 onwards, the shift to Tac as the preferred CNI drug was done gradually, thus the era effect on graft survival could be shrouded by lack of protocol consistency. Moreover, until recently the Norwegian pediatric tx program diverged from other centers as the maintenance protocol consisted of duotherapy of CNIs and prednisolone only. Hence, the possibility of relatively more nephrotoxic effects of CNIs could be partly responsible for the lack of improvements in graft survival between the last two eras. Thus, as of October 2010, MMF has been added (triple regimen) as a CNI minimizing strategy.

The success of pediatric transplantation as measured by patient and graft survival yielded good results in agreement with other comparable tx programs. Our next step was to evaluate health outcome aspects after renal tx in childhood; given in the following papers.

6.2 CR fitness in renal tx children and adolescents compared to healthy children (paper II)

- Associations of CR fitness with other CV risk factors in renal tx children

Our main finding was that in a group of stable renal tx children (n=22), median $\dot{V}O_{2\text{peak}}$ was only 66% of that of healthy controls, and most of the participants rated themselves as physical inactive (86% < 60 min PA per day). Our findings are in agreement with other reports on PA in renal tx children; although PA levels are measured differently in each study, and therefore limits comparison, they all point to low PA (13;35;50;64;83;96). Our favorable pre-tx conditions with no or minimal dialysis did not yield more favorable CR fitness results but were in line numerically (expressed in $\text{ml kg}^{-1} \text{min}^{-1}$) with the few published treadmill exercise studies reporting $\dot{V}O_{2\text{peak}}$ values in tx children (83;121).

To put it in perspective, our finding is comparable to $\dot{V}O_{2\text{peak}}$ results of children with Fontan circulation previously treadmill tested with the same protocol, test leader and healthy control population as in our study (98). These children obtained a mean $\dot{V}O_{2\text{peak}}$ of 70% of the expected age and gender reference values comparable to our results. CR fitness of children with Fontan circulation was limited by hemodynamic changes and reduced lung function (98). The explanation for the poor test result in the group of tx children is probably complex, possibly related to central (cardiac) or peripheral (muscle) restrictions as a consequence of CKD/IS treatment. However, we believe sedentary lifestyle to be one of the main contributors to the poor $\dot{V}O_{2\text{peak}}$ results. Firstly, most participants reported low levels of PA and a median of 7.5 hours of screen time per day. Secondly, the young adults (ped-tx) performed at 85% of the $\dot{V}O_{2\text{peak}}$ of healthy controls (paper III), relatively better than the tx children, and despite longer exposure to CKD and IS treatment. This serves as an argument against CV sequela being the main limiting factor of decreased CR fitness. However, this assumption relies on the two tx groups (in paper II and paper III) both being representative for the eligible tx sample.

Pediatric tx recipients are, by virtue of persistent chronic kidney disease and exposure to medication side effects, at risk for developing CV disease in adulthood. The importance of addressing hypertension, hyperlipidemia and excessive weight gain after tx is well recognized and established. In the group of 22 children the proportion of children with $\text{BMI} > 25 \text{kg/m}^2$

was twice that of the healthy Norwegian children (75), and the majority were hypertensive, demonstrating the burden of CV risk challenges in this group of tx children. Children with two or three metabolic risk factors (IGT, hypertension and BMI z-score >2) had decreased CR fitness and PA compared to children with one or no risk factors. This finding must be interpreted with caution, as the sample size was small. Population studies in healthy children and adolescents have reported low levels of physical activity and/or CR fitness to be associated with single CV risk factors and clustering of CV risk factors (5;17;28;93) but this finding remains to be confirmed in larger studies in the pediatric renal tx population.

Reduced CR fitness in CKD/renal tx children and adolescents has been described in single reports for two decades (13;50;86;121;139;167), yet in the general guidelines on CKD management, no PA recommendations exist pre or post-tx, presumably due to the lack of prospective studies showing an exercise effect on CV risk factors and mortality. The ideal goal must be to preserve muscle strength/PA once progressive CKD is established, to prevent a sedentary lifestyle from developing and to counteract muscle wasting in advanced stages of CKD (44) further compromised by surgery and steroids post-tx (43). Implementing exercise programs for the first time while children are established on dialysis is a difficult task since the children with ESRD have been accustomed to inactivity and are fatigued (162). The Norwegian LD tx program involves no or minimal time on dialysis for the majority of children, offers an opportunity to reach children and caregivers and encourage PA before severe physical deconditioning has taken place. Weight bearing exercise should be encouraged and implemented in the general care of children with CKD before and after tx for a number of other potential benefits including attainment of peak bone mass, counteracting weight gain after tx and not at least to enhance these children`s ability to participate in sports and play – a key to social interaction with peers.

6.3 CR fitness in adults with a history of renal tx in childhood (paper III)

- As compared to adult transplanted subjects and healthy controls

This is the first study presenting CR fitness data in adults with a history of predominantly LD organ tx in childhood. Providing long-term outcome data in young adults undergoing tx in childhood is of great importance to both the pediatrician and adult nephrologist in order to counsel patients and their caregivers, to initiate preventive measures and guide treatment strategies. Our purpose was to evaluate the impact of CKD from childhood on CR fitness, as a proposed indirect marker of CV function and physical functioning.

Our main finding was that the median $\dot{V}O_{2\text{peak}}$ level in adulthood was on average reduced by 15 % in ped-tx survivors compared to HC despite exposure to CKD and IS treatment for many years. Thus, long-term exposure to IS treatment and CKD do not necessarily attenuate cardiorespiratory performance, but the interindividual variations ranged from excellent to very poor CR fitness. Echocardiographic studies using sensitive techniques have previously showed incomplete resolution of LVH and persistent diastolic dysfunction up to 5 years after pediatric renal tx (80;105). A current concern is that subclinical cardiac dysfunctions acquired in childhood will progress and limit physical functioning or even develop into congestive heart failure in adulthood (105). However, only two of the participants, as a consequence of their extreme obesity (BMI of 47 and 53 kg m^{-2}), were classified within the $\dot{V}O_{2\text{peak}}$ classification range for mild to moderate heart failure (i.e. $\dot{V}O_{2\text{peak}} < 20\text{ml kg}^{-1}\text{min}^{-1}$) (168).

Another purpose was to put $\dot{V}O_{2\text{peak}}$ levels in former tx children into perspective, comparing two groups both subjected to renal tx and IS treatment but at different stages of life. We compared ped-tx to a group of adults undergoing renal tx first time as adults (adult-tx). The large differences in final height between ped-tx and adult-tx/HC (Table 1, paper III) demonstrate the impact of long-standing CKD and steroid medication on the growing child. The height discrepancy probably contributed to significantly better exercise capacity (i.e. test duration) in the adult-tx since longer legs and fewer steps are less energy demanding. Due to inadequate power, no significant difference were found in $\dot{V}O_{2\text{peak}}$ ($\text{ml kg}^{-1}\text{min}^{-1}$) or ($\dot{V}O_{2\text{peak}}$ $\text{FFM}^{-1}\text{min}^{-1}$) between ped-tx and adult-tx participants. It was nevertheless reassuring that the difference in CR fitness was not larger, given the considerable longer exposure time of CKD/IS in the ped-tx participants.

In multivariate analysis, Hgb, FFM and duration time on the treadmill were the main predictors of $\dot{V}O_{2\text{peak}}$. That is, FFM as a proxy to skeletal muscle function was a determinant for $\dot{V}O_{2\text{peak}}$ when adjusted for duration and Hgb. Neither FM nor tx participant group were

independent determinants for absolute $\dot{V}O_{2peak}$, suggesting that interindividual physiological properties were more decisive for $\dot{V}O_{2peak}$ than the group affiliation. Whether long-term use of IS treatment/CKD restricts peripheral muscle function or cardiac function beyond that of physical inactivity remains to be determined.

6.4 Renal tx children and their caregivers' perceptions of mental health and quality of life after renal tx (paper IV)

- Associations between somatic health variables and mental health and quality of life measures.

The primary aim of this study was to explore aspects of mental health, psychosocial adjustment and health-related quality of life (HRQOL) in children, adolescents and their caregivers compared to healthy controls and children with another severe pediatric chronic disease (ALL). The study showed that the tx children's mental health, psychosocial adjustment and quality of life for most areas were significantly impaired on both self-reports and proxy reports compared with healthy controls, and in several areas also lower compared to the ALL group. The impaired HRQOL in renal tx children and adolescents compared to healthy controls is consistent with findings from other studies using PedsQL (6;55;64;101).

Our study puts the impact of tx on HRQOL into perspective as compared to ALL – another severe pediatric chronic disease (134). The treatment protocol for ALL is 2.5 years and the follow-up is for most children and their parents confined to 5 years thereafter. The majority experience permanent remission. Tx children on the other hand must attend frequent hospital visits and take daily medications as lifelong reminders of a chronic disease.

In this study the “parents' perceptions” were represented by the mothers as they were the ones who accompanied their children to the investigation. While the mothers' self-rated mental health was impaired compared to controls, it was reassuring that the mothers' own overall satisfaction with life (HRQOL) did not diverge from that of the general Norwegian population. Although the numbers were small it is however worth noting that the mothers of children with a parental donor reported significantly more mental health problems and a tendency towards lower HRQOL than mothers of children receiving a kidney from non-parental donors. Mothers are more often involved in the daily care of a chronically ill child compared to the father at the expense of work and personal life (23;174). The fathers are often underrepresented as research participants and tend to be more involved in other aspects of everyday life and they keep their worries to themselves (26;78). Recognition of psychological trauma among the parental donors is especially important to address as parental functioning in

general is a strong contributor to mental and psychological adjustments in children with chronic diseases (25). Moreover the results may act as an incitement to clarify the ethical controversies concerning the parental donorship. Further knowledge seems best provided by in-depth interviews involving the perceptions of both parents. Development of standardized psychosocial evaluations of parental donors is a suggested approach to protect donor interests (155).

The children's own perceived mental health and HRQOL were related to BMI and CR fitness/ VO_{2peak} , respectively, consistent with findings in adult renal tx (122;123). Several studies have reported separately on either low exercise capacity or reduced HRQOL in CKD and tx children (54;121;167) but no studies have to date explored the relation between an objective measure on CR Fitness (VO_{2peak}) and HRQOL in renal tx children. Regular physical activity, on the other hand, has been shown to have significant physical and mental health benefits, including reduced anxiety, improved body image, self-esteem, mood and quality of life(64;172). Our study points out the importance of an overall approach in the rehabilitation of these children; early interventions to promote weight control and to increase physical fitness must go hand-in-hand with psychosocial support.

6.5 Strengths of the studies

The major strength within our study was that all but three patients were transplanted at the same center (OUS Rikshospitalet). All patients benefited from the same surgical expertise and were followed by the era specific IS protocol. We were provided with accurate survival data, meticulously collected by the guardian of the Norwegian Renal Registry (Torbjørn Leivestad). That is, no patients were lost to follow-up in terms of graft and patient survival data, so that a possible bias caused by informative censoring was therefore avoided. Moreover, as data were obtained from a single center we avoided the introduction of bias when comparing data from different centers. The registry data enabled identification of all available patients eligible for invitation to our CS study. The fact that all patients shared a childhood tx history from the same center as the study location may have reduced the drop-out from the CS study.

Both children and adults in the CS studies participated in a comprehensive program including several investigations (papers II-IV, Table 1). Ped-tx participants were invited to volunteer for several reasons for this study besides exercise testing. If the study had involved only a treadmill test we would have presumably only sampled a group that was physically fitter and more motivated than this patient population as a whole.

We used the maximal treadmill exercise test to assess CR fitness – generally regarded as the “gold standard” in assessing VO_{2peak} . Treadmill testing has been a well-established procedure at our Pediatric Department for more than a decade and includes a test lab with experienced test leaders, a test protocol developed and validated for children with a chronic disease (74) and not least, it has undergone substantial research activity.

6.6 Limitations

6.6.1 Study design

Assessing possible causal relationship in clinical studies is always an important purpose. The randomized controlled study (RCT) ranks highest in the hierarchy of evidence as it, through the randomization process, minimizes the risk of confounding (158). It is the gold standard when investigating the effect of a health intervention or treatment. However, as our overall purpose with the study was mainly a descriptive one, measuring the occurrence of graft loss and patient outcomes, the observational (cohort) study was a more suitable approach (paper I). It would have been considered unethical, unpractical and inappropriate to randomize children with ESRD to either LD organ or DD organ recipients. Observational studies have less potential to determine causal relations than RCT's, but confounding can be reduced through stratification and regression analyses.

The cross-sectional study design (papers II-IV) is well suited for descriptive purposes and for the generation of hypotheses but restricts interpretation of causal relations. Accordingly, whether lower CR fitness was a consequence of clustering of metabolic CV risk factors or vice versa (paper II) could not be determined with this design. Furthermore, we could not state with certainty whether low CR fitness entailed low HRQOL, or whether low HRQOL contributed to impaired physical activity and therefore lower VO_{2peak} (paper IV). We acknowledge that a prospective exercise study, incorporating the temporal aspect of exposure and outcome, would have been a more appropriate design to answer whether better CR fitness reduces clustering of CV risk factors and improves HRQOL.

6.6.2 Selection bias, information bias and confounding

The internal validity of an epidemiological study can be affected by random error and systematic errors. Random errors (variation in the data due to measurement imprecision) can

be reduced by increasing the sample size. Systematic errors are unaffected by sample size, but affects the validity of the study and includes selection bias, information bias and confounding (30).

The CS study provides a snap-shot of the prevalence of risk factors in a population. However, estimates of prevalence are vulnerable to selection bias. A selection bias arises when factors affect study participation in such a way that the outcomes measured are not representative for the non-responders or the population as such. For example, one might select a sample from a sub-population of individuals of a particular age or condition which are not the same as in the population of interest. As the main study aim (papers II and III) was to assess CR fitness, an unavoidable selection bias was introduced by the exclusion criteria (excluding comorbidities such as movement disorders or blindness) affecting the generalizability to the frame population of renal tx children and adults (reduced internal validity).

In paper II we claimed to have a representative sample of eligible tx children and adolescents. However, non-participants were older than participants although no other differences in basic demographics were found. We assume that age per se was not the most important factor governing CR fitness level, so given there were no other differences between participants and non-participants we regard our sample as representative for the eligible population of renal tx children. In paper IV a respondent (selection) bias was introduced by the mothers being the only “spokesperson” for the parents. Before we can conclude on parental opinions we must also include the fathers’ perceptions.

Use of questionnaires to collect information on physical activity has obvious limitations. The PA questionnaires used were developed for healthy children and adults and were not specifically validated for the group of renal tx recipients. To recall the intensity, duration and frequency of PA the previous week is difficult. The judgment of intensity level is highly subjective, and therefore prone to misclassification of subjects into the wrong PA intensity categories (misclassification bias). A Swedish validation study of IPAQ short format (used in paper III), pointed out that self-reported time spent in PA was overestimated as compared to accelerometry (7). The PA questionnaire used for children and adolescents (paper II) had only been validated for healthy 9-10 year old and 13-14 year old children and not for the whole age-span of participants of our study (>14 years of age), limiting its validity in older adolescents. The activity questions did not include information on type of PA, and participation in physical education during school-time was not included. Moreover, in children, the sporadic and intermittent nature of the physical activities make it difficult to capture reliable data via self-report (160). Lastly, in the validation study of the children’s

questionnaire, the correlation coefficient between MVPA and the activity monitor was low to moderate ($r=0.27-0.48$).

Confounding implies that the effect of an exposure on the outcome is mixed with the effect of another variable leading to spurious conclusions (153;171). Allometric scaling may alleviate the confounding effect of differences in body mass on $V_{O_{2peak}}$ but does not fully compensate for differences in body weight and size between individuals. It is possible that excessive weight (BMI z-score > 2) mediated or confounded the association between reduced CR fitness and the clustering of CV risk factors.

6.6.3 Interpretation of $V_{O_{2peak}}$ (papers II-III)

The conventional presentation of $V_{O_{2peak}}$ is relative to body weight (i.e. $\text{ml kg}^{-1} \text{min}^{-1}$), and has an advantage when reporting results compared to other exercise research. However, dividing absolute $V_{O_{2peak}}$ (l min^{-1}) by body weight has been questioned as it leads to overestimation of $V_{O_{2peak}}$ in lean subjects and underestimation of $V_{O_{2peak}}$ in obese subjects since changes in body weight and $V_{O_{2peak}}$ (l min^{-1}) are not linearly related (171). Allometric scaling (AS) is a method when $V_{O_{2peak}}$ is adjusted to body weight raised to a given power different from unity (e.g. $\text{ml kg}^{-0.67} \text{min}^{-1}$). AS may alleviate the confounding effect of differences in body mass (129) on $V_{O_{2peak}}$. However, the exponent of 0.67 used in paper II was theoretically based on the surface law (surface area = volume^{2/3}) applied for the reference group of healthy children (163), and not derived for the tx children in particular. In order to derive specific exponential factors for tx children a larger sample size would have been needed. Moreover, the tx children could differ in more than one scaling variable (e.g. gender and age) not captured by a universal exponent (8;29;164). Expressing $V_{O_{2peak}}$ divided by fat free mass ($V_{O_{2peak}} \text{FFM}^{-1} \text{min}^{-1}$), i.e. relative to the metabolically active tissue during exercise, has been suggested as an appropriate approach (51) and was the method of choice in paper III. Indeed, the difference in $V_{O_{2peak}}$ between overweight/ obese in our study was no longer significant when analysed in terms of FFM. However, it has been argued that $V_{O_{2peak}}$ ratioed to FFM could result in inappropriately high values for obese subjects (as the numerator is increased and denominator decreased), and thus “overcorrects” the effect of excess fat weight on the ability to do exhaustive work (46).

If the purpose is to evaluate the unadjusted or total $V_{O_{2peak}}$ on CV morbidity in a prospective study, $V_{O_{2peak}}$ in $\text{ml kg}^{-1} \text{min}^{-1}$ is suggested as a proper choice. However, if one is interested in the direct/adjusted effect of CR fitness on CV outcome, one has to adjust for differences in

body composition/ body dimensions as excessive weight could be a confounder on metabolic health outcome.

6.6.4 Other methodological limitations

The available number of participants eligible for recruitment was limited as pediatric renal tx is a rare event. Accordingly, the number of participants in the CS studies (papers II-IV, total n=69) were small and the findings have to be interpreted cautiously. In addition, reporting a single center experience may have limited external validity; as patient selection, treatment protocols and culture vary between centers/countries. Moreover, the heterogeneity of primary renal disease, the duration of CKD prior to tx not accounted for, differences in graft function and variable IS regimens could have contributed to the variability in outcomes that limited the ability to disclose significant differences between groups (136). Indeed, the standard deviation score in VO_{2peak} (paper III) was larger than expected and contributed to a reduction in the statistical power.

Death by cardiovascular cause was based on the diagnosis given in the registry reports and on information obtained from the medical records (paper I). For several of the “CV deaths”, autopsy reports were either lacking or inconclusive. Consequently we cannot exclude the possibility that some of the sudden deaths were caused by arrhythmias secondary to electrolyte disturbances and therefore misclassified as a cardiovascular cause.

Today, a biopsy will be performed early on the suspicion of an AR or chronic rejection. However, biopsies were not a tradition during the first two decades of renal tx in Norway. AR and chronic rejections were clinical diagnoses based on increasing levels of s-creatinine (and regarding AR, other clinical signs of rejections). Moreover, when a biopsy was performed the result was not always unambiguous. Thus the proportion of AR and chronic rejections could therefore have been overestimated/ misclassified based on the data obtained.

ABPM measurements were for most participants (paper II) performed during the two-day scheduled program and not in a typical daily life situation. It is possible that this procedure reduced the validity of the recordings performed in a “hospital environment” influenced by unconscious stress factors (conditional learning from previous history).

We concluded from our sample of renal tx children that they in general performed poorly on the treadmill tests and reported low levels of PA. Several aspects could contribute to overestimating the difference in VO_{2peak} between the tx children and the healthy reference group (paper II). Firstly, it is possible that the reference population was fitter than the child

population in general as they were recruited on a voluntary basis. Secondly, it is challenging to motivate sedentary children with a chronic disorder to perform at maximal effort, since they are unused to strenuous exercise – as demonstrated by significantly lower RER in tx children than the reference population; thus a true maximal effort was probably not achieved in all tx children. Thirdly, none of the children in the reference group were overweight (compared to 1/3 of the pediatric renal tx). Finally, renal tx children were significantly shorter than controls. It is possible that using their height age would have been a more appropriate approach than chronological age when comparing $\dot{V}O_{2\text{peak}}$ results to the healthy group of children, as has been proposed by Schaefer et al (170).

The mean difference in $\dot{V}O_{2\text{peak}}$ between ped-tx and adult-tx was $3 \text{ ml kg}^{-1} \text{ min}^{-1}$ and this difference was not statistically significant (paper III). Unfortunately, as we were limited by a small sample size our study was underpowered to exclude there being a statistically significant difference in CR fitness between ped-tx and adult-tx, but the size of this difference is smaller than $3 \text{ ml kg}^{-1} \text{ min}^{-1}$. Thus we cannot rule out making a type II error (fail to reject the null hypothesis when it in fact was false).

The use of transplant-specific HRQOL instruments in addition to generic HRQOL measures could have provided more useful information in a group of children with disease specific challenges (paper IV) (176). Moreover, the questionnaires were unable to identify the specific problems encountered by parents and the child leading to reduced quality of life.

7. CONCLUSIONS AND CLINICAL IMPLICATIONS

Children with ESRD are one of several groups of children with a severe chronic health condition whose survival prospects have increased dramatically due to advances in medical care and treatment. As outlined in this thesis, tx is no cure from chronic kidney disease or ensuing comorbidities. Providing knowledge on outcome after renal tx in childhood is important so as to allow guidance on treatment decisions and to counsel children, parents and adult survivors.

We have shown that long-term patient survival can be achieved for most children after renal tx and the best graft survival is obtained with LD organs. Pre-emptive tx and avoidance of long-term dialysis remains a key strategy in reducing exposure to CV risk factors in children with ESRD (90). The major challenge remains to further improve long-term graft survival, as preserving graft function is the cornerstone also for minimizing the associated CV risk factors. In this study the majority of tx participants had advanced kidney failure (CKD stage 3-4 ranging from 58-77%, paper III and II, respectively). Close monitoring of the graft function including (protocol) biopsies and pharmacokinetic monitoring are possible tools to slow the decline in GFR. The perfect combination of IS agents for maintenance of graft function while minimizing nephrotoxicity demands individually tailored immunosuppressive protocols, including corticosteroid avoidance in selected patients. The effects from steroid avoidance includes improved linear growth and reduction in CV risk factors (12).

Our study has contributed to increased awareness of the importance of enhancing physical functioning in renal tx children, recognizing that physical functioning, body habitus and quality of life are related measures. Early interventions to promote weight control post-tx, and proper monitoring, treatment and reassessment of hypertension are crucial to alleviate the decline in graft function and reduce CV risk. We have also shown that not just physical but mental health problems and psychosocial dysfunction can persist several years after tx, affecting the child's quality of life and parental functioning. Optimal treatment and follow-up of tx children and their parents require close collaboration between pediatricians and psychosocial experts including interventions to promote physical activity, healthy nutrition and coping strategies.

Long-term exposure to IS treatment and CKD did not necessarily attenuate cardiorespiratory performance in adults below that of healthy controls, but the interindividual variations ranged from excellent to very poor CR fitness. Exercise testing is underappreciated as a global outcome measure in renal tx patients. Not only can exercise tests identify those that can

benefit the most from exercise in a physical functioning/ quality of life point of view, but the level of CR fitness is a plausible prognostic factor for morbidity and mortality, as has been shown for the healthy population and patients with established CV disease. Exercise should be encouraged and included in the medical care of tx recipients irrespective of age.

Proposed PA strategies in children with CKD/tx:

1. Recommendations for sustaining physical activity are suggested and included in the existing guidelines on the treatment of CKD as a first step to acknowledging the importance of maintaining physical activity as chronic renal function deteriorates.
2. Physicians and health care personnel must encourage and inform children and their parents of the significance of maintaining PA, as physical functioning and quality of life are interconnected.
3. For those transplanted, an individually developed exercise education program should be started during the first three months when the child and caregiver are followed up at the tx center, and continued with local physiotherapists according to individual needs.
4. A dietician should be involved post-tx to help establish good nutritional habits to avoid excessive weight gain, particular for those predisposed.
5. At the regular outpatient visits PA participation in school and leisure time should be inquired about and encouraged.
6. Professional mental health guidance, which includes developmental and family perspective advice should be offered routinely to the tx patient and their parents.

8. FUTURE RESEARCH

First of all it could be worthwhile to review the outcome of pediatric renal tx again in ten years time to evaluate whether the impact of the current knowledge and progress in treatment leads to improved graft survival and physical functioning.

In this thesis we were more than once faced with inadequate power to answer the research questions, and the CS design restricted interpretation of causal relations. In the field of pediatric nephrology research is generally hampered by small sample size and the subsequent lack of power. To overcome these limitations one approach is to increase sample size through multicenter studies (for example through a Nordic research network).

No exercise intervention study has to date been performed in children with CKD prior to or post-tx. Thus, a proposed future study design may be a randomized controlled trial with 1-2 years exercise intervention compared to usual care, either in children with CKD or post-tx. Possible endpoints could be a) improvement in CR fitness/ muscle strength, b) body composition changes and c) HRQOL development. Another under – researched field is the impact of weight bearing exercise intervention programs on bone mineral accrual. Peak bone mass acquisition during adolescence is in general a key determinant of the lifetime risk for osteoporosis and fractures. Renal tx patients, and in particular tx children who are exposed to CKD and steroids from childhood have an increased risk for osteoporosis. Exercise intervention studies are also needed in adult survivors of childhood tx to study whether the functional response to exercise programs is the same as in healthy subjects, and to evaluate to what extent cardiac or peripheral muscle function is altered after many years on IS treatment. The prognostic value of CR fitness in this category of ‘at risk’ individuals on CV morbidity, remains to be evaluated in a longitudinal study. Outcome variables may include hospitalizations, CV events and even death. However, such a design is time consuming and multicenter studies may once again prove necessary to capture enough events.

Graft survival time remains the most traditional outcome variable to rate the success of a tx program. From the children’s and parents’ point of view the degree of rehabilitation towards over-all functional normality may be at least as important. To obtain further insight into the specific problems and range of opportunities encountered by children and their caregivers prior to and after tx further qualitative research is warranted.

9. REFERENCES

- (1) Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 1993 Jan;25(1):71-80.
- (2) Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000 Sep;32(9 Suppl):S498-S504.
- (3) Anderssen SA, Hansen B, Kolle E, Ohne-Seiler H, Edvardsen E, Olme I et al. Fysisk form blant voksne og eldre i Norge. [Physical fitness in adults and the elderly in Norway]. Norwegian Directorate of Health; 2010.
- (4) Anderssen SA, Solberg M. Methods to measure physical activity. Development and Validation of a Questionnaire used in children. Norway, Oslo: Directorate of Health and Social Affairs; 2005.
- (5) Anderssen SA, Cooper AR, Riddoch C, Sardinha LB, Harro M, Brage S, et al. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. *Eur J Cardiovasc Prev Rehabil* 2007 Aug;14(4):526-31.
- (6) Anthony SJ, Hebert D, Todd L, Korus M, Langlois V, Pool R, et al. Child and parental perspectives of multidimensional quality of life outcomes after kidney transplantation. *Pediatr Transplant* 2010 Mar;14(2):249-56.
- (7) Bailey RC, Olson J, Pepper SL, Porszasz J, Barstow TJ, Cooper DM. The level and tempo of children's physical activities: an observational study. *Med Sci Sports Exerc* 1995 Jul;27(7):1033-41.
- (8) Batterham AM, Vanderburgh PM, Mahar MT, Jackson AS. Modeling the influence of body size on V(O₂) peak: effects of model choice and body composition. *J Appl Physiol* 1999 Oct;87(4):1317-25.
- (9) Becker-Cohen R, Nir A, Ben-Shalom E, Rinat C, Feinstein S, Farber B, et al. Improved left ventricular mass index in children after renal transplantation. *Pediatr Nephrol* 2008 Sep;23(9):1545-50.
- (10) Becker-Cohen R, Nir A, Rinat C, Feinstein S, Algur N, Farber B, et al. Risk factors for cardiovascular disease in children and young adults after renal transplantation. *Clin J Am Soc Nephrol* 2006 Nov;1(6):1284-92.
- (11) Betesheda. United States Renal Data System: USRDS 2009 Annual Data Report. 2009.
- (12) Blair SN, Kampert JB, Kohl HW, III, Barlow CE, Macera CA, Paffenbarger RS, Jr., et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA* 1996 Jul 17;276(3):205-10.

- (13) Bonzel KE, Wildi B, Weiss M, Scharer K. Spiroergometric performance of children and adolescents with chronic renal failure. *Pediatr Nephrol* 1991 Jan;5(1):22-8.
- (14) Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970;2(2):92-8.
- (15) Burekhardt CS, Woods SL, Schultz AA, Ziebarth DM. Quality of life of adults with chronic illness: a psychometric study. *Res Nurs Health* 1989 Dec;12(6):347-54.
- (16) Burroughs TE, Swindle JP, Salvalaggio PR, Lentine KL, Takemoto SK, Bunnapradist S, et al. Increasing incidence of new-onset diabetes after transplant among pediatric renal transplant patients. *Transplantation* 2009 Aug 15;88(3):367-73.
- (17) Carnethon MR, Gidding SS, Nehgme R, Sidney S, Jacobs DR, Jr., Liu K. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA* 2003 Dec 17;290(23):3092-100.
- (18) Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000 May 6;320(7244):1240-3.
- (19) Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995 Jul;73(1):25-9.
- (20) Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003 Aug;35(8):1381-95.
- (21) Cumming GR, Everatt D, Hastman L. Bruce treadmill test in children: normal values in a clinic population. *Am J Cardiol* 1978 Jan;41(1):69-75.
- (22) Davis CL. Preemptive transplantation and the transplant first initiative. *Curr Opin Nephrol Hypertens* 2010 Nov;19(6):592-7.
- (23) de Paula ES, Nascimento LC, Rocha SM. Roles assessment in families of children with chronic renal failure on peritoneal dialysis. *Int J Nurs Pract* 2008 Jun;14(3):215-20.
- (24) Denburg MR, Pradhan M, Shults J, Jones A, Palmer JA, Baluarte HJ, et al. Longitudinal relations between obesity and hypertension following pediatric renal transplantation. *Pediatr Nephrol* 2010 Oct;25(10):2129-39.
- (25) Drotar D. Relating parent and family functioning to the psychological adjustment of children with chronic health conditions: what have we learned? What do we need to know? *J Pediatr Psychol* 1997 Apr;22(2):149-65.
- (26) Eiser C, Eiser JR, Stride CB. Quality of life in children newly diagnosed with cancer and their mothers. *Health Qual Life Outcomes* 2005;3:29.
- (27) Eiser C, Morse R. The measurement of quality of life in children: past and future perspectives. *J Dev Behav Pediatr* 2001 Aug;22(4):248-56.
- (28) Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with

- metabolic risk factors in children: the European youth heart study. *Diabetologia* 2007 Sep;50(9):1832-40.
- (29) Ekelund U, Franks PW, Wareham NJ, Aman J. Oxygen uptakes adjusted for body composition in normal-weight and obese adolescents. *Obes Res* 2004 Mar;12(3):513-20.
- (30) Ekelund U, Sepp H, Brage S, Becker W, Jakes R, Hennings M, et al. Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public Health Nutr* 2006 Apr;9(2):258-65.
- (31) Englund M, Berg U, Tyden G. A longitudinal study of children who received renal transplants 10-20 years ago. *Transplantation* 2003 Jul 27;76(2):311-8.
- (32) Englund MS, Berg UB, Bohlin AB, Tibell A, Tyden G. Ten years' experience of renal transplantation in children in the cyclosporine era. *Transplantation* 1993 Nov;56(5):1124-30.
- (33) Englund MS, Tyden G, Wikstad I, Berg UB. Growth impairment at renal transplantation--a determinant of growth and final height. *Pediatr Transplant* 2003 Jun;7(3):192-9.
- (34) Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. *Lancet* 1998 Sep 5;352(9130):759-62.
- (35) Feber J, Dupuis JM, Chapuis F, Braillon P, Jocteur-Monrozier D, Daudet G, et al. Body composition and physical performance in children after renal transplantation. *Nephron* 1997;75(1):13-9.
- (36) Feber J, Wong H, Geier P, Chaudry B, Filler G. Complications of chronic kidney disease in children post-renal transplantation - a single center experience. *Pediatr Transplant* 2008 Feb;12(1):80-4.
- (37) Ferraris JR, Ghezzi L, Waisman G, Krmar RT. ABPM vs office blood pressure to define blood pressure control in treated hypertensive paediatric renal transplant recipients. *Pediatr Transplant* 2007 Feb;11(1):24-30.
- (38) Filler G, Huang SH. Progress in pediatric kidney transplantation. *Ther Drug Monit* 2010 Jun;32(3):250-2.
- (39) Filler G, Reimao SM, Kathiravelu A, Grimmer J, Feber J, Drukker A. Pediatric nephrology patients are overweight: 20 years' experience in a single Canadian tertiary pediatric nephrology clinic. *Int Urol Nephrol* 2007;39(4):1235-40.
- (40) Fine RN. Management of growth retardation in pediatric recipients of renal allografts. *Nat Clin Pract Nephrol* 2007 Jun;3(6):318-24.
- (41) Flechner SM, Kolbeinson ME, Tam J, Lum B. The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. *Transplantation* 1989 May;47(5):806-10.
- (42) Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995 Jun;5(12):2024-31.

- (43) Forli L. [Nutritional status and post-transplantation risks]. *Tidsskr Nor Laegeforen* 2003 Jan 23;123(2):169-71.
- (44) Foster BJ, Kalkwarf HJ, Shults J, Zemel BS, Wetzsteon RJ, Thayu M, et al. Association of chronic kidney disease with muscle deficits in children. *J Am Soc Nephrol* 2011 Feb;22(2):377-86.
- (45) Foster BJ, Martz K, Gowrishankar M, Stablein D, Al-Uzri A. Weight and height changes and factors associated with greater weight and height gains after pediatric renal transplantation: a NAPRTCS study. *Transplantation* 2010 May 15;89(9):1103-12.
- (46) Foster BJ, Warady BA. Clinical research in pediatric nephrology: challenges, and strategies to address them. *J Nephrol* 2009 Nov;22(6):685-93.
- (47) Fredriks AM, van BS, Fekkes M, Verloove-Vanhorick SP, Wit JM. Are age references for waist circumference, hip circumference and waist-hip ratio in Dutch children useful in clinical practice? *Eur J Pediatr* 2005 Apr;164(4):216-22.
- (48) Fredriksen PM, Ingjer F, Nystad W, Thaulow E. Aerobic endurance testing of children and adolescents--a comparison of two treadmill-protocols. *Scand J Med Sci Sports* 1998 Aug;8(4):203-7.
- (49) Fredriksen PM, Ingjer F, Nystad W, Thaulow E. A comparison of VO₂(peak) between patients with congenital heart disease and healthy subjects, all aged 8-17 years. *Eur J Appl Physiol Occup Physiol* 1999 Oct;80(5):409-16.
- (50) Giordano U, Calzolari A, Matteucci MC, Pastore E, Turchetta A, Rizzoni G. Exercise tolerance and blood pressure response to exercise testing in children and adolescents after renal transplantation. *Pediatr Cardiol* 1998 Nov;19(6):471-3.
- (51) Gitin EL, Olerud JE, Carroll HW. Maximal oxygen uptake based on lean body mass: a meaningful measure of physical fitness? *J Appl Physiol* 1974 Jun;36(6):757-60.
- (52) Gjertson DW, Cecka JM. Determinants of long-term survival of pediatric kidney grafts reported to the United Network for Organ Sharing kidney transplant registry. *Pediatr Transplant* 2001 Feb;5(1):5-15.
- (53) Goldberg D, Williams P. A user's guide to the General Health Questionnaire GHQ. Windsor: NFER-Nelson; 2011.
- (54) Goldstein SL. Physical fitness in children with end-stage renal disease. *Adv Chronic Kidney Dis* 2009 Nov;16(6):430-6.
- (55) Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW. Health-related quality of life in pediatric patients with ESRD. *Pediatr Nephrol* 2006 Jun;21(6):846-50.
- (56) Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry* 1999 Jul;40(5):791-9.
- (57) Grenda R, Watson A, Trompeter R, Tonshoff B, Jaray J, Fitzpatrick M, et al. A randomized trial to assess the impact of early steroid withdrawal on growth in

pediatric renal transplantation: the TWIST study. *Am J Transplant* 2010 Apr;10(4):828-36.

- (58) Groothoff JW. Long-term outcomes of children with end-stage renal disease. *Pediatr Nephrol* 2005 Jul;20(7):849-53.
- (59) Groothoff JW, Cransberg K, Offringa M, van de Kar NJ, Lilien MR, Davin JC, et al. Long-term follow-up of renal transplantation in children: A Dutch cohort study. *Transplantation* 2004 Aug 15;78(3):453-60.
- (60) Groothoff JW, Gruppen MP, Offringa M, de GE, Stok W, Bos WJ, et al. Increased arterial stiffness in young adults with end-stage renal disease since childhood. *J Am Soc Nephrol* 2002 Dec;13(12):2953-61.
- (61) Groothoff JW, Gruppen MP, Offringa M, Hutten J, Lilien MR, van de Kar NJ, et al. Mortality and causes of death of end-stage renal disease in children: A Dutch cohort study. *Kidney Int* 2002 Feb;61(2):621-9.
- (62) Gruppen MP, Groothoff JW, Prins M, van der WP, Offringa M, Bos WJ, et al. Cardiac disease in young adult patients with end-stage renal disease since childhood: a Dutch cohort study. *Kidney Int* 2003 Mar;63(3):1058-65.
- (63) Gulati A, Sarwal MM. Pediatric renal transplantation: an overview and update. *Curr Opin Pediatr* 2010 Jan 30;22:189-96.
- (64) Hamiwka LA, Cantell M, Crawford S, Clark CG. Physical activity and health related quality of life in children following kidney transplantation. *Pediatr Transplant* 2009 Nov;13(7):861-7.
- (65) Hanevold CD, Ho PL, Talley L, Mitsnefes MM. Obesity and renal transplant outcome: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatrics* 2005 Feb;115(2):352-6.
- (66) Harambat J, Cochat P. Growth after renal transplantation. *Pediatr Nephrol* 2009 Jul;24(7):1297-306.
- (67) Hardy BE, Shah T, Cicciarelli J, Lemley KV, Hutchinson IV, Cho YW. Kidney transplantation in children and adolescents: an analysis of United Network for Organ Sharing Database. *Transplant Proc* 2009 Jun;41(5):1533-5.
- (68) Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007 Aug 28;116(9):1081-93.
- (69) Hocker B, Weber LT, Feneberg R, Drube J, John U, Fehrenbach H, et al. Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation. *Nephrol Dial Transplant* 2010 Feb;25(2):617-24.
- (70) Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice

- guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. *Pediatrics* 2003 Jun;111(6 Pt 1):1416-21.
- (71) Hoogeveen EK, Aalten J, Rothman KJ, Roodnat JI, Mallat MJ, Borm G, et al. Effect of Obesity on the Outcome of Kidney Transplantation: A 20-Year Follow-Up. *Transplantation* 2011 Feb 14.
- (72) Ishitani M, Isaacs R, Norwood V, Nock S, Lobo P. Predictors of graft survival in pediatric living-related kidney transplant recipients. *Transplantation* 2000 Jul 27;70(2):288-92.
- (73) Jacobsson L. A method for the calculation of renal clearance based on a single plasma sample. *Clin Physiol* 1983 Aug;3(4):297-305.
- (74) Jager KJ, Stel VS, Wanner C, Zoccali C, Dekker FW. The valuable contribution of observational studies to nephrology. *Kidney Int* 2007 Sep;72(6):671-5.
- (75) Juliusson PB, Eide GE, Roelants M, Waaler PE, Hauspie R, Bjerknes R. Overweight and obesity in Norwegian children: prevalence and socio-demographic risk factors. *Acta Paediatr* 2010 Feb 18.
- (76) Karrfelt HM, Berg UB, Lindblad FI. Renal transplantation in children: psychological and donation-related aspects from the parental perspective. *Pediatr Transplant* 2000 Nov;4(4):305-12.
- (77) Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. *J Cardiovasc Nurs* 2007 May;22(3):218-53.
- (78) Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. *J Pediatr Psychol* 2004 Apr;29(3):211-9.
- (79) Kempeneers G, Noakes TD, van Zyl-Smit R, Myburgh KH, Lambert M, Adams B, et al. Skeletal muscle limits the exercise tolerance of renal transplant recipients: effects of a graded exercise training program. *Am J Kidney Dis* 1990 Jul;16(1):57-65.
- (80) Kim GB, Kwon BS, Kang HG, Ha JW, Ha IS, Noh CI, et al. Cardiac dysfunction after renal transplantation; incomplete resolution in pediatric population. *Transplantation* 2009 Jun 15;87(11):1737-43.
- (81) Klintmalm G, Bohman SO, Sundelin B, Wilczek H. Interstitial fibrosis in renal allografts after 12 to 46 months of cyclosporin treatment: beneficial effect of low doses in early post-transplantation period. *Lancet* 1984 Oct 27;2(8409):950-4.

- (82) Kramer A, Stel VS, Tizard J, Verrina E, Ronnholm K, Palsson R, et al. Characteristics and survival of young adults who started renal replacement therapy during childhood. *Nephrol Dial Transplant* 2009 Mar;24(3):926-33.
- (83) Krasnoff JB, Mathias R, Rosenthal P, Painter PL. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. *Transplantation* 2006 Jul 27;82(2):211-7.
- (84) Krmar RT, Balzano R, Jogestrand T, Cedazo-Minguez A, Englund MS, Berg UB. Prospective analysis of carotid arterial wall structure in pediatric renal transplants with ambulatory normotension and in treated hypertensive recipients. *Pediatr Transplant* 2008 Jun;12(4):412-9.
- (85) Krmar RT, Berg UB. Blood pressure control in hypertensive pediatric renal transplants: role of repeated ABPM following transplantation. *Am J Hypertens* 2008 Oct;21(10):1093-9.
- (86) Krull F, Schulze-Neick I, Hatopp A, Offner G, Brodehl J. Exercise capacity and blood pressure response in children and adolescents after renal transplantation. *Acta Paediatr* 1994 Dec;83(12):1296-302.
- (87) Kurtze N, Rangun V, Hustvedt BE. Reliability and validity of the international physical activity questionnaire in the Nord-Trondelag health study (HUNT) population of men. *BMC Med Res Methodol* 2008;8:63.
- (88) Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003 Jul 15;139(2):137-47.
- (89) Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007 Apr;53(4):766-72.
- (90) Li L, Chang A, Naesens M, Kambham N, Waskerwitz J, Martin J, et al. Steroid-free immunosuppression since 1999: 129 pediatric renal transplants with sustained graft and patient benefits. *Am J Transplant* 2009 Jun;9(6):1362-72.
- (91) Lilien MR, Groothoff JW. Cardiovascular disease in children with CKD or ESRD. *Nat Rev Nephrol* 2009 Apr;5(4):229-35.
- (92) Litwin M, Wuhl E, Jourdan C, Trelewicz J, Niemirska A, Fahr K, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 2005 May;16(5):1494-500.
- (93) Lobelo F, Pate RR, Dowda M, Liese AD, Daniels SR. Cardiorespiratory fitness and clustered cardiovascular disease risk in U.S. adolescents. *J Adolesc Health* 2010 Oct;47(4):352-9.
- (94) Lurbe E, Redon J. Reproducibility and validity of ambulatory blood pressure monitoring in children. *Am J Hypertens* 2002 Feb;15(2 Pt 2):69S-73S.

- (95) Mangray M, Vella JP. Hypertension after kidney transplant. *Am J Kidney Dis* 2011 Feb;57(2):331-41.
- (96) Matteucci MC, Calzolari A, Pompei E, Principato F, Turchetta A, Rizzoni G. Abnormal hypertensive response during exercise test in normotensive transplanted children and adolescents. *Nephron* 1996;73(2):201-6.
- (97) Matteucci MC, Giordano U, Calzolari A, Turchetta A, Santilli A, Rizzoni G. Left ventricular hypertrophy, treadmill tests, and 24-hour blood pressure in pediatric transplant patients. *Kidney Int* 1999 Oct;56(4):1566-70.
- (98) Matthews IL, Fredriksen PM, Bjornstad PG, Thaulow E, Gronn M. Reduced pulmonary function in children with the Fontan circulation affects their exercise capacity. *Cardiol Young* 2006 Jun;16(3):261-7.
- (99) McDonald SP, Craig JC. Long-term survival of children with end-stage renal disease. *N Engl J Med* 2004 Jun 24;350(26):2654-62.
- (100) McGlothlan KR, Wyatt RJ, Ault BH, Hastings MC, Rogers T, DiSessa T, et al. Predominance of nocturnal hypertension in pediatric renal allograft recipients. *Pediatr Transplant* 2006 Aug;10(5):558-64.
- (101) McKenna AM, Keating LE, Vigneux A, Stevens S, Williams A, Geary DF. Quality of life in children with chronic kidney disease-patient and caregiver assessments. *Nephrol Dial Transplant* 2006 Jul;21(7):1899-905.
- (102) Mehrabi A, Kashfi A, Tonshoff B, Feneberg R, Mehls O, Schemmer P, et al. Long-term results of paediatric kidney transplantation at the University of Heidelberg: a 35 year single-centre experience. *Nephrol Dial Transplant* 2004 Jul;19 Suppl 4:iv69-iv74.
- (103) Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation* 2003 Apr 27;75(8):1291-5.
- (104) Mitsnefes MM, Daniels SR, Schwartz SM, Meyer RA, Khoury P, Strife CF. Severe left ventricular hypertrophy in pediatric dialysis: prevalence and predictors. *Pediatr Nephrol* 2000 Sep;14(10-11):898-902.
- (105) Mitsnefes MM, Kimball TR, Border WL, Witt SA, Glascock BJ, Khoury PR, et al. Abnormal cardiac function in children after renal transplantation. *Am J Kidney Dis* 2004 Apr;43(4):721-6.
- (106) Mitsnefes MM, Kimball TR, Daniels SR. Office and ambulatory blood pressure elevation in children with chronic renal failure. *Pediatr Nephrol* 2003 Feb;18(2):145-9.
- (107) Mitsnefes MM, Schwartz SM, Daniels SR, Kimball TR, Khoury P, Strife CF. Changes in left ventricular mass index in children and adolescents after renal transplantation. *Pediatr Transplant* 2001 Aug;5(4):279-84.
- (108) Monn E, Brodwall EK, Flatmark A. [Kidney transplantation in children]. *Tidsskr Nor Laegeforen* 1976 Mar 20;96(8):489-92, 496.

- (109) Morgan H, Khan I, Hashmi A, Hebert D, McCrindle BW, Balfe JW. Ambulatory blood pressure monitoring after renal transplantation in children. *Pediatr Nephrol* 2001 Nov;16(11):843-7.
- (110) Morris JF. Spirometry in the evaluation of pulmonary function. *West J Med* 1976 Aug;125(2):110-8.
- (111) Myers J. Exercise capacity and prognosis in chronic heart failure. *Circulation* 2009 Jun 30;119(25):3165-7.
- (112) Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002 Mar 14;346(11):793-801.
- (113) Nankivell BJ, Alexander SI. Rejection of the kidney allograft. *N Engl J Med* 2010 Oct 7;363(15):1451-62.
- (114) NAPRTCS. North American Pediatric Renal Trials and Collaborative Studies 2007 annual report. 2009 [cited 2011 Jan 3]; Available from: URL: <https://web.emmes.com/study/ped/annlrept/annlrept.html>.
- (115) Neil Armstrong, Joanne R. Welsman. Assessment and Interpretation of Aerobic Fitness in Children and Adolescents. *Exerc Sport Sci Rev* 1994;22(435):476.
- (116) Nemeth A, Berg U, Winiarski J. [Transplantation gives severely ill children a chance to life]. *Lakartidningen* 2010 Oct 20;107(42):2576-80.
- (117) Neuhaus TJ, Wartmann M, Weber M, Landolt MA, Laube GF, Kemper MJ. Psychosocial impact of living-related kidney transplantation on donors and partners. *Pediatr Nephrol* 2005 Feb;20(2):205-9.
- (118) Obel C, Heiervang E, Rodriguez A, Heyerdahl S, Smedje H, Sourander A, et al. The Strengths and Difficulties Questionnaire in the Nordic countries. *Eur Child Adolesc Psychiatry* 2004;13 Suppl 2:II32-II39.
- (119) Offner G, Latta K, Hoyer PF, Baum HJ, Ehrich JH, Pichlmayr R, et al. Kidney transplanted children come of age. *Kidney Int* 1999 Apr;55(4):1509-17.
- (120) Oh J, Wunsch R, Turzer M, Bahner M, Raggi P, Querfeld U, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 2002 Jul 2;106(1):100-5.
- (121) Painter P, Krasnoff J, Mathias R. Exercise capacity and physical fitness in pediatric dialysis and kidney transplant patients. *Pediatr Nephrol* 2007 Jul;22(7):1030-9.
- (122) Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, et al. A randomized trial of exercise training after renal transplantation. *Transplantation* 2002 Jul 15;74(1):42-8.
- (123) Painter PL, Luetkemeier MJ, Moore GE, Dibble SL, Green GA, Myll JO, et al. Health-related fitness and quality of life in organ transplant recipients. *Transplantation* 1997 Dec 27;64(12):1795-800.
- (124) Papalois VE, Najarian JS. Pediatric kidney transplantation: historic hallmarks and a personal perspective. *Pediatr Transplant* 2001 Aug;5(4):239-45.

- (125) Pape L, Ehrich JH, Offner G. Advantages of cyclosporin A using 2-h levels in pediatric kidney transplantation. *Pediatr Nephrol* 2004 Sep;19(9):1035-8.
- (126) Pape L, Ehrich JH, Offner G. Cyclosporine in pediatric kidney transplantation. *Transplant Proc* 2004 Mar;36(2 Suppl):203S-7S.
- (127) Pape L, Ehrich JH, Zivicnjak M, Offner G. Growth in children after kidney transplantation with living related donor graft or cadaveric graft. *Lancet* 2005 Jul 9;366(9480):151-3.
- (128) Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr* 2002 Aug;141(2):191-7.
- (129) Pettersen SA, Fredriksen PM, Ingjer E. The correlation between peak oxygen uptake (VO₂peak) and running performance in children and adolescents. Aspects of different units. *Scand J Med Sci Sports* 2001 Aug;11(4):223-8.
- (130) Polgar G. *Pulmonary Function Testing in Children: Techniques and standards.* Philadelphia: W.B.Saunders Co; 1971.
- (131) Ramirez-Cortes G, Fuentes-Velasco Y, Garcia-Roca P, Guadarrama O, Lopez M, Valverde-Rosas S, et al. Prevalence of metabolic syndrome and obesity in renal transplanted Mexican children. *Pediatr Transplant* 2009 Aug;13(5):579-84.
- (132) Rees L. Long-term outcome after renal transplantation in childhood. *Pediatr Nephrol* 2009 Mar;24(3):475-84.
- (133) Rees L, Shroff R, Hutchinson C, Fernando ON, Trompeter RS. Long-term outcome of paediatric renal transplantation: follow-up of 300 children from 1973 to 2000. *Nephron Clin Pract* 2007;105(2):c68-c76.
- (134) Reinjfjell T, Lofstad GE, Nordahl HM, Vikan A, Diseth TH. Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. *Eur J Cancer Care (Engl)* 2009 Jul;18(4):364-70.
- (135) Samuel SM, Tonelli MA, Foster BJ, Alexander RT, Nettel-Aguirre A, Soo A, et al. Survival in Pediatric Dialysis and Transplant Patients. *Clin J Am Soc Nephrol* 2011 Mar 10.
- (136) Schaefer F, Wuhl E, Feneberg R, Mehls O, Scharer K. Assessment of body composition in children with chronic renal failure. *Pediatr Nephrol* 2000 Jul;14(7):673-8.
- (137) Seeman T. Hypertension after renal transplantation. *Pediatr Nephrol* 2009 May;24(5):959-72.
- (138) Seeman T, Dusek J, Vondrak K, Simkova E, Kreisinger J, Feber J, et al. Ambulatory blood pressure monitoring in children after renal transplantation. *Transplant Proc* 2004 Jun;36(5):1355-6.
- (139) Sethna CB, Salerno AE, McBride MG, Shults J, Paridon SM, Sharma N, et al. Cardiorespiratory fitness in pediatric renal transplant recipients. *Transplantation* 2009 Aug 15;88(3):395-401.

- (140) Shapiro R. Living donor kidney transplantation in pediatric recipients. *Pediatr Transplant* 2006 Nov;10(7):844-50.
- (141) Shroff R. Dysregulated mineral metabolism in children with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2011 Mar 18.
- (142) Shroff R, Ledermann S. Long-term outcome of chronic dialysis in children. *Pediatr Nephrol* 2009 Mar;24(3):463-74.
- (143) Shroff R, Quinlan C, Mitsnefes M. Uraemic vasculopathy in children with chronic kidney disease: prevention or damage limitation? *Pediatr Nephrol* 2010 Nov 16.
- (144) Siirtola A, Antikainen M, Ia-Houhala M, Koivisto AM, Solakivi T, Jokela H, et al. Serum lipids in children 3 to 5 years after kidney, liver, and heart transplantation. *Transpl Int* 2004 Mar;17(3):109-19.
- (145) Silverstein DM, Mitchell M, Leblanc P, Boudreaux JP. Assessment of risk factors for cardiovascular disease in pediatric renal transplant patients. *Pediatr Transplant* 2007 Nov;11(7):721-9.
- (146) Smith JM, Fine RN, McDonald RA. Current state of pediatric renal transplantation. *Front Biosci* 2008;13:197-203.
- (147) Smith JM, Stablein DM, Munoz R, Hebert D, McDonald RA. Contributions of the Transplant Registry: The 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS). *Pediatr Transplant* 2007 Jun;11(4):366-73.
- (148) Solberg M, Anderssen SA. Methods to measure physical activity. Development and Validation of a Questionnaire used in adolescents and adults. Norway, Oslo: Directorate of Health and Social Affairs; 5 A.D. Dec 1.
- (149) Solez K, Colvin RB, Racusen LC, Sis B, Halloran PF, Birk PE, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). *Am J Transplant* 2007 Mar;7(3):518-26.
- (150) Sorof JM, Sullivan EK, Tejani A, Portman RJ. Antihypertensive medication and renal allograft failure: a North American Pediatric Renal Transplant Cooperative Study report. *J Am Soc Nephrol* 1999 Jun;10(6):1324-30.
- (151) Stake G, Monclair T. A single plasma sample method for estimation of the glomerular filtration rate in infants and children using iohexol, I: Establishment of a body weight-related formula for the distribution volume of iohexol. *Scand J Clin Lab Invest* 1991 Jun;51(4):335-42.
- (152) Starzl TE, Marchioro TL, Porter KA, Tanous DF. The role of organ transplantation in pediatrics. *Pediatr Clin North Am* 1966;13:381-422.
- (153) Steele RM, Brage S, Corder K, Wareham NJ, Ekelund U. Physical activity, cardiorespiratory fitness, and the metabolic syndrome in youth. *J Appl Physiol* 2008 Jul;105(1):342-51.

- (154) Stenehjem AE, Gudmundsdottir H, Os I. Office blood pressure measurements overestimate blood pressure control in renal transplant patients. *Blood Press Monit* 2006 Jun;11(3):125-33.
- (155) Sterner K, Zelikovsky N, Green C, Kaplan BS. Psychosocial evaluation of candidates for living related kidney donation. *Pediatr Nephrol* 2006 Oct;21(10):1357-63.
- (156) Tejani A, Sullivan EK, Alexander S, Fine R, Harmon W, Lilienfeld D. Posttransplant deaths and factors that influence the mortality rate in North American children. *Transplantation* 1994 Feb 27;57(4):547-53.
- (157) Torben Jørgensen, Lars B.Andersen, Karsten Froberg, Urs Maeder, Lisa Von Huth Smith, Mette Aadahl. Position statement: Testing physical condition in a population-how good are the methods? *European Journal of Sport Science* 2009;9(5):257-67.
- (158) Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. *Nephron Clin Pract* 2010;115(2):c94-c99.
- (159) Van Damme-Lombaerts R, Herman J, Coosemans W, Pirenne J. Pediatric renal transplantation: a single Belgian center experience over 20 years. *Pediatr Transplant* 2001 Dec;5(6):447-51.
- (160) van Stralen KJ, Dekker FW, Zoccali C, Jager KJ. Confounding. *Nephron Clin Pract* 2010;116(2):c143-c147.
- (161) van Stralen KJ, Tizard EJ, Verrina E, Schaefer F, Jager KJ. Demographics of paediatric renal replacement therapy in Europe: 2007 annual report of the ESPN/ERA-EDTA registry. *Pediatr Nephrol* 2010 Jul;25(7):1379-82.
- (162) van BM, Takken T, Engelbert R, Groothoff J, Nauta J, van HK, et al. Exercise training in pediatric patients with end-stage renal disease. *Pediatr Nephrol* 2009 Mar;24(3):619-22.
- (163) Vanderburgh PM. Two Important Cautions in the Use of Allometric Scaling: The Common Exponent and Group Difference Principles. 1998 ed. Lawrence Erlbaum Associates, Inc; 1998. p. 153-63.
- (164) Vanderburgh PM, Katch FI. Ratio scaling of VO₂max penalizes women with larger percent body fat, not lean body mass. *Med Sci Sports Exerc* 1996 Sep;28(9):1204-8.
- (165) Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population health measure: feasibility, reliability, and validity. *Qual Life Res* 2006 Mar;15(2):203-15.
- (166) Wasserman K. Principles of exercise testing and interpretation. Fourth edition ed. Philadelphia: Lippincott; 2005.
- (167) Weaver DJ, Jr., Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, et al. Decreased maximal aerobic capacity in pediatric chronic kidney disease. *J Am Soc Nephrol* 2008 Mar;19(3):624-30.
- (168) Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982 Jun;65(6):1213-23.

- (169) Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 2004 Jun 3;350(23):2362-74.
- (170) Weissberg-Benchell J, Zielinski TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, et al. Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL transplant module. *Am J Transplant* 2010 Jul;10(7):1677-85.
- (171) Welsman JR, Armstrong N, Nevill AM, Winter EM, Kirby BJ. Scaling peak VO₂ for differences in body size. *Med Sci Sports Exerc* 1996 Feb;28(2):259-65.
- (172) White K, Kendrick T YL. Change in self-esteem, self-efficacy and the mood dimensions of depression as potential mediators of the physical activity and depression relationship: Exploring the temporal relation of change. *Mental Health and Physical Activity* 2009;2:44-52.
- (173) White CT, Schisler T, Er L, Djurdjev O, Matsuda-Abedini M. CKD following kidney transplantation in children and adolescents. *Am J Kidney Dis* 2008 Jun;51(6):996-1004.
- (174) Wiedebusch S, Konrad M, Foppe H, Reichwald-Klugger E, Schaefer F, Schreiber V, et al. Health-related quality of life, psychosocial strains, and coping in parents of children with chronic renal failure. *Pediatr Nephrol* 2010 Aug;25(8):1477-85.
- (175) Wilson AC, Greenbaum LA, Barletta GM, Chand D, Lin JJ, Patel HP, et al. High prevalence of the metabolic syndrome and associated left ventricular hypertrophy in pediatric renal transplant recipients. *Pediatr Transplant* 2010 Feb;14(1):52-60.
- (176) Wilson AC, Mitsnefes MM. Cardiovascular disease in CKD in children: update on risk factors, risk assessment, and management. *Am J Kidney Dis* 2009 Aug;54(2):345-60.
- (177) Wong H, Mylrea K, Feber J, Drukker A, Filler G. Prevalence of complications in children with chronic kidney disease according to KDOQI. *Kidney Int* 2006 Aug;70(3):585-90.
- (178) Wuhl E, Witte K, Soergel M, Mehls O, Schaefer F. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. *J Hypertens* 2002 Oct;20(10):1995-2007.

10. ERRATA

Paper I

The p-value ($p=0.02$) in Figure 2 (page 765) is incorrect, **the correct p-value is $p=0.008$** (unadjusted log rank test between LD and DD graft survival).

Paper II

Methods/biochemistry, page 2: The phrase “Metabolic syndrome was defined when three or more of the following criteria were fulfilled.....” should have been rephrased to: “Metabolic syndrome was defined when three or more of the following criteria were fulfilled, *modified after Weiss et al...*”

Weiss et al used 95th percentile to define dyslipidemia, while we chose to use P-HDL < 40mg/dl (<1.03mmol/l), P-Triglycerides >150mg/dl (≥ 1.7 mmol/L) as the thresholds for dyslipidemia.

Results, page 4:

“Only 3 participants obtained V02peak within the expected range (i.e. V02peak z-score ≥ 2)”, should have been *V02peak z-score ≥ -2* . The same type of error occurs at the same page: “None of the children were underweight in terms of BMI z-score < 2” at TX, should have been changed to: “**None of the children were underweight in terms of BMI z-score < -2.**”

Paper III

Reference 23 is incorrect, the correct citation is:

Morris JF. Spirometry in the evaluation of pulmonary function. West J Med 1976 Aug;125(2):110-8.

Kidney transplantation in childhood: mental health and quality of life of children and caregivers

Trond H. Diseth · Trine Tangeraas · Trude Reinfjell · Anna Bjerre

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Abstract Our objective was to assess the mental health and health-related quality of life (HRQOL) in children and their parents after renal transplantation (TX) compared to healthy controls and children with acute lymphoblastic leukemia (ALL) and to identify possible health status variables associated with impaired mental health and HRQOL. Thirty-eight TX children with a median age of 13 (range 3–19) years were investigated. Mental health was assessed by the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and the Strength and Difficulties Questionnaire (SDQ-20). Each mother's own mental health and QOL were assessed by the General Health Questionnaire (GHQ-30) and the Quality of Life Scale (QOLS). Forty children with ALL [median age 11 (8.5–15.4) years] and 42 healthy children [median age 11 (8.9–15) years] served as controls. Treadmill exercise results from 22 of the

38 patients were included in the analysis. TX children showed significantly higher levels of mental health problems and lower HRQOL at 2 to 16 years after transplantation compared to both control groups. Body mass index and maximal oxygen uptake ($n=22/38$) were significant predictors of child mental health (SDQ) and child QOL (PedsQL), respectively. Based on these results, we suggest that rehabilitation after TX should include a focus on physical activity and QOL to reduce interconnected physical and psychological morbidity in kidney TX children.

Keywords Childhood kidney transplantation · Mental health · Quality of life · Body mass index · Cardiorespiratory fitness

T. H. Diseth
Department of Clinical Neurosciences for Children,
Women and Children's Division,
Oslo University Hospital and University of Oslo,
Oslo, Norway

T. Tangeraas · A. Bjerre
Department of Paediatric Medicine, Women and Children's
Division, Oslo University Hospital,
Oslo, Norway

T. Reinfjell
Department of Child and Adolescent Psychiatry,
St. Olavs University Hospital,
Trondheim, Norway

T. H. Diseth (✉)
Barne- og ungdomspsykiatrisk seksjon, Bameklinikken,
Oslo universitetssykehus HF, Rikshospitalet,
PO Box 4950 Nydalen, NO-0424 Oslo, Norway
e-mail: trond.diseth@oslo-universitetssykehus.no

Introduction

The Norwegian era of renal transplantation (TX) in children started in 1970 [1]. The TX option has resulted in a dramatic increase in the survival of children with end stage renal disease (ESRD) and has been the treatment of choice ever since its introduction. In Norway, 84% of pediatric renal transplants are provided from living related donors (LD), mostly parents (74%). The pre-transplant dialysis time is short (median 3 months), and 50% of transplantations are performed preemptively [1]; this provides good premises for graft survival and ensures a better quality of life (QOL) pre-transplant.

Over the decades, the introduction of more potent immunosuppressive medication and better pre- and post-transplant care have led to improvements in graft survival worldwide [2, 3]. In addition, increased surgical experience has made it possible to include infants (<2 years of age)

with ESRD in the TX program. The initial aim of TX has evolved from prolonging life to achieving long-term survival and enhancing the QOL to close to that of the age-matched general population.

However, both progressive chronic kidney disease (CKD) and the post-transplant period with mandatory immunosuppressive medication (IM) are associated with adverse physical and psychological consequences. This includes adverse effects on linear growth, weight gain, osteoporosis, reduced physical functioning, hypertension, reduced glucose tolerance and hyperlipidemia [4, 5]. Rejection of the graft followed by graft loss is a constant threat for both the child and caregiver. In the long run, children are at higher risk for cardiovascular disease, infections and malignancies, all of which contribute to increased long-term morbidity and mortality. Finally, the pre-, peri- and post-operative stress associated with renal transplantation per se and the fact that children during a transplantation are often isolated from their peer groups for long periods of time may increase the risk for mental and psychosocial disturbances, predisposing for a reduced QOL both for the child and the parents.

Previous research in children with advanced CKD until the need for renal replacement therapy has generally confirmed an increased risk of impaired mental health, psychosocial functioning and QOL [6–9]. However, most studies of psychosocial and QOL effects of CKD have included children with a wide variety of somatic status, and research has often failed to separate out the results by type of somatic status. Another challenge is that studies are performed at different stages of diagnosis or treatment and at various ages, with the patients having different developmental levels and psychological needs.

Earlier reports have stated good long-term QOL and psychosocial outcome after kidney TX during childhood [10–12]; however, these studies were conducted with adult patients and based on non-standardized questionnaires. There are only a few studies on health-related QOL (HRQOL) in CKD children and adolescents after kidney TX [8, 9, 13–22]. Most of these studies differ in their methodology and generally present conflicting results.

Studies on mental health and psychosocial functioning after kidney TX are even scarcer and diverge in their findings. Some indicate no differences between the transplant recipient and the healthy control [14, 23, 24], whereas others report an increased risk for maladaptive psychosocial sequelae with emotional disturbances, such as anxiety, fear, depression, anger, withdrawal and symptoms of posttraumatic stress [15].

There is no controversy on the superiority of LD organ in terms of graft survival. However, little is known on the extent to which the LD graft benefit translates into a better QOL for the parent and child. We hypothesized that LD

organ TX would have a more favorable QOL outcome for the child and parent relative to other severe pediatric chronic diseases. We also assumed that QOL issues are related to objective measures of physical functioning, as has been shown in studies of adult renal TX [25]. Therefore, the primary aim of this study was to explore aspects of mental health and HRQOL in children, adolescents and their caregivers after renal TX and compare these to those of healthy controls and children with another severe pediatric chronic disease, namely, acute lymphoblastic leukemia (ALL). The second aim was to investigate the potential associations between health status variables and mental health, psychosocial functioning and HRQOL.

Patients and methods

Subjects

All renal transplanted children in Norway undergo TX at the same University hospital and pay yearly visits, until transition to adult care at about 18 years of age. From this cohort, children and adolescents aged 2–19 years, transplanted between 1993 to 2006, were invited to participate in a cross-sectional study involving a 2-day comprehensive medical investigation program. Participants were enrolled from May 2008 to June 2009. Inclusion criteria were functioning graft for at least 1 year. Of the 50 patients asked to participate, 38 agreed [76%; 13 (34%) girls, 25 (66%) boys; median age 13 (range 3–19) years]. Parental information was obtained from 32 mothers [median age 40.5 (25–51) years]. Average time since first transplantation was median 4.9 (2–16) years. All patients except for one received prednisolone daily ($n=23$) or every other day ($n=14$) [median 0.08 (0.03–0.18) mg/kg/day]. There were no significant differences in sex, renal function, or proportion of LD recipients between the participants and non-participants, but non-participants ($n=12$) were significantly older than the participants [median age 16.9 (6–20) years]. Data regarding the total patient cohort demographics, primary renal disease, pretransplant dialysis treatment, donor issues and number of transplants have been published previously [1].

A subgroup of the participants ($n=22/38$) had previously been tested on the treadmill [26]. Of the 38 participants, children <8 years of age (too young for test requirements; $n=7$) and patients with orthopedic limitations ($n=5$) were excluded. Two adolescent girls eventually refused to be tested due to motivational problems and two adolescent boys ended the test before maximal effort was attained; these data were not included in the exercise test study.

The 38 transplanted children and adolescents were compared to 42 healthy controls [median age 11 (range 8.9–15.0)]

recruited from two elementary schools and two junior high schools from both urban and rural areas in the middle part of Norway and to a group of 40 children with ALL [median age 11 (8.5–15.4)]. The control and comparison groups which serve as reference material for the patients in the present study were studied in a previous study and are extensively elaborated on in the papers of Reinjfell et al. [27, 28]. There were no significant differences between the three groups in terms of gender, age or socio-demographic characteristics, such as family composition, parental age and educational level, community, home and economy.

The baseline socio-demographic characteristics for the patients and the control and comparison groups are shown in Table 1.

Measures

Anthropometrics and renal function

Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 0.1 kg on a digital scale. Body mass index (BMI) was calculated as kilograms per square meter. Anthropometric data were converted to standard deviation scores (BMI *z* score and height *z* score) based on Cole's LMS method [29]. Overweight and obesity were defined according to BMI cut-off limits proposed by The International Task Force (isoBMI >25 and isoBMI >30, respectively) [30]. Glomerular filtration rate (mGFR) was measured using a single intravenous injection of iohexol with blood sampling after 3 h as previously reported [26].

Exercise testing

Cardiorespiratory fitness (CR Fitness) was defined as maximal oxygen uptake ($\dot{V}O_{2peak}$, in $\text{ml kg}^{-0.67}\text{min}^{-1}$) and was assessed with an incremental treadmill test until exhaustion. The treadmill test procedure and the evaluation criteria for a maximal test have been described in more detail in a previous report [26].

Children's mental health, psychosocial functioning and QOL

The *Strength and Difficulties Questionnaire (SDQ)* was used to assess the mental and psychosocial health in children and adolescents [31]. The SDQ is a brief behavioral screening questionnaire consisting of 25 items in addition to a supplement on the impact of the difficulties for the child and family. Each item uses a three-point ordinal Likert format and can be answered with: "not true", "somewhat true" or "certainly true", rated 0–2 for negatively worded items and rated inversely 2–0 for positively

worded items. In this way, for all items, higher scores indicate more problematic attributes. There are five subscales: Emotional symptoms, Conduct problems, Hyperactivity, Peer problems and Prosocial behavior, with the first four adding up to the Total Difficulties Score. Subscores are generated for each subscale (range 0–10). A total difficulties score of ≥ 19 defines symptom "caseness" according to Goodman (www.sdqinfo.com) and adjusted to Norwegian cut-offs [32]. As such, a symptom score >90 percentile predicts a substantially raised probability of being diagnosed with a psychiatric disorder, and a score of 16–18 is defined as "borderline", i.e., symptom score within percentile 80–90. The prosocial subscale measures the child's ability to act prosocially independent of the difficulties measured by the other subscale. The SDQ also includes a brief impact supplement where the respondent is asked whether he thinks he has a problem and, if so, inquires further about chronicity, overall distress, social impairment related to the family, friends, learning situation and leisure activities and, lastly, about the burden on the environment. The impact questions have four response categories which correspond with a point scale 0–0–1–2. A total impact score of ≥ 2 defines impact "caseness", i.e. having variable functioning with sporadic difficulties or symptoms in several but not all social areas, and a score of 1 is defined as borderline, i.e. having difficulty in a single area but generally functioning pretty well. There are similar versions for parents. The SDQ shows satisfactory reliability and validity [31, 33]. Normative data based on a large representative Norwegian sample exist [32].

The *Pediatric Quality of Life Inventory (PedsQL) 4.0* [34–36] was used to measure HRQOL in children and adolescents [37]. The 23-item PedsQL, version 4.0 Generic Core Scales, can be grouped into four domains of HRQOL: (1) Physical functioning (8 items), (2) Emotional functioning (5 items), (3) Social functioning (5 items) and (4) School functioning (5 items). The Generic Core Scales are comprised of a child self-report, with included ages of 5–7, 8–12 and 13–18 years. Parent proxy-report includes ages 2–4, 5–7, 8–12 and 13–18 and assesses parents' perceptions of their child's HRQOL. The items for the self-report and proxy-report are essentially identical, differing in developmentally appropriate language and first-or third-person tense.

The instructions ask how much of a problem each item has been during the past 1 month. (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). Subjects are requested to rate how many problems they experienced during the past month with health (e.g. I hurt or ache), activities (e.g. It's hard for me to run) or feelings (e.g. I feel afraid or scared).

Items are reverse-scored and linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, 4=0) so that higher

Table 1 Socio-demographic characteristics of 38 children with kidney transplantation (TX) and their parents compared to children with acute lymphoblastic leukemia (ALL) and healthy controls. Treatment variables are reported for the children with TX and children with ALL

Socio-demographic characteristics	TX (n=38)	ALL (n=40)	Healthy (n=42)
Gender, n (%)			
Girl	13 (34)	21 (53)	21 (50)
Boy	25 (66)	19 (47)	21 (50)
Age at study (years)			
Mean ± SD	12.2 ± 4.0	11.8 ± 1.9	11.8 ± 1.9
Median (range)	13 (3–19)	11 (8–15)	12 (8–15)
Treatment			
GFR (ml/min/1.73 m ²), median (range)	51 (22–95)	-	-
Age at TX/diagnosis (ALL) in years, median (range)	1.1 (0–15)	3.1 (0–7)	-
Years since TX/treatment (ALL), median (range)	4.9 (2–16)	7.1 (4–12)	-
Parental characteristics	n=32		
Family composition, n (%)			
Both parents	25 (78)	31 (77)	29 (70)
Single parent	7 (22)	9 (23)	13 (30)
Age in years, median (range)			
Mother	40.5 (25–51)	40.0 (30–55)	40.0 (31–52)
Father	43.0 (28–58)	43.0 (32–58)	43.5 (34–72)
Education in years, median (range)			
Mother	13.0 (8–18)	14.0 (10–19)	13.0 (9–19)
Father	12.0 (9–17)	14.0 (10–20)	13.0 (10–19)
Community, n (%)			
Urban	16 (50)	15 (37)	18 (43)
Rural	16 (50)	25 (63)	24 (57)
Home, n (%)			
Own house	25 (78)	36 (90)	39 (93)
Own apartment	3 (9)	3 (8)	3 (7)
Renting apartment	4 (13)	1 (2)	0 (0)
Economy, n (%)			
Very satisfying	14 (44)	27 (67)	21 (50)
Good	16 (50)	8 (20)	21 (50)
Poor	2 (6)	5 (13)	0 (0)
Mothers mental health/QOL		n=34	n=37
GHQ case score (mean ± SD)	2.1 ± 4.8	3.3 ± 6.7	1.2 ± 3.3
n (%) cases; cut-off: 5–30	6 (18.8)	6 (17.6)	2 (5.4)*
QOLS score (mean ± SD)	90.4 ± 10.0	-	-

*Difference between TX and ALL/healthy respectively is significant at the 0.05 level (two-tailed)

TX, Transplantation (children with kidney transplantation); ALL, acute lymphoblastic leukemia; SD, standard deviation; GFR, glomerular filtration rate; GHQ, General Health Questionnaire; QOLS, Quality of Life Scale

scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). In addition to the four subscales, a Total Summary Health score (23 items) can be computed. A Psychosocial Health Summary score (15 items) can be computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning Subscales, and a Physical Health Summary score (8 items) is the same as the Physical Functioning subscale. The PedsQL 4.0 has achieved excellent reliability for the Total Scale score (0.89), and has been shown to differentiate between healthy children and children with chronic health conditions [38, 39]. PedsQL as a generic measure allows for the assessment of

common dimensions among both healthy and chronically ill children as well as for comparisons across populations [40]. PedsQL has been shown to be an appropriate assessment tool for both healthy children, children with ALL [27] and children with CKD [8, 9, 13]. A Norwegian version of the PedsQL 4.0, concerning psychometric properties, is presented in more detail in an earlier work [41]. The PedsQL has shown satisfactory psychometric properties [35, 41].

Maternal mental health and quality of life

The General Health Questionnaire (GHQ) [42] is a widely used screening instrument for assessing the presence of distress, psychopathology and overall well-being in adults,

showing acceptable and well-established reliability and validity. The GHQ includes both positive and negative questions, and the short version GHQ-30 contains 30 items covering symptoms considered to reflect psychological distress and well-being. Each question is answered on a four-point scale. The answers to each item may be treated both as a “Likert” score recommended for use in longitudinal studies when measuring change and have weights assigned to each position (0–1–2–3), with a possible scale of 0–90, and as “Case” score, with weights (0–0–1–1) and possible range of 0–30. When using the GHQ-30 as a screening instrument for overall psychological distress, as in this study, the Case-scoring has proved to provide acceptable values for sensitivity and specificity [43]. A conventional cut-off was used; scores of ≥ 5 were defined as “cases”.

The *Quality of Life Scale (QOLS)* [44] is a questionnaire measuring an adult’s overall satisfaction with life based on different life domains. It belongs to the category of global or overall QOL tools. The QOLS is a short questionnaire and contains additional information on areas not usually included in HRQOL measures, such as independence, material comfort, work satisfaction, recreation, etc. This scale has been widely used in health services research and has established psychometric properties and Norwegian norms [45]. The QOLS is a 16-item self-report and domain-specific instrument exploring factors such as physical and material well-being, personal development, relationships with others, participation in social, community and civic activities and recreation. The adults are asked to rate their present level of satisfaction with the above-mentioned factors on a seven-point scale. The scale is scored by adding up the items to obtain a total score with possible range 16–112. A higher score depicts a better quality of life.

Statistics and ethics

Continuous variables are presented as the mean \pm the standard deviation (SD) or if skewed as the median and range. Categorical variables are given as proportions and percentages. Differences between independent groups with regard to continuous variables were quantified with the two-sample *t* test, or with the Mann–Whitney–Wilcoxon test in the case of severe skewness in the data. Categorical variables were compared between groups using the chi-squared (χ^2) test or Fisher’s exact test for small samples. The strength of associations between normally distributed continuous variables was measured using Pearson’s correlation coefficient or Spearman’s correlation coefficient when the variables had a skewed distribution.

Forward linear regression analysis was used to analyze possible explanatory variables as predictors of mental health and QOL [46]. Variables with $p < 0.05$ from the

univariate analysis were included in the multiple linear regression model. A careful check of the model assumptions, including an investigation of residual plots, did not reveal any violation of the assumptions.

All analyses were performed in SPSS ver. 16.0 (SPSS, Chicago, IL). We chose a 5% statistical significance level.

Written informed consent was obtained from patients and/or their parents if less than 16 years of age prior to study start. The study protocol was approved by the National Committee for Research Ethics and carried out in accordance with the Declaration of Helsinki.

Results

Thirty-four children (89%) received a kidney from a LD, with 27 (79%) being donated from parents (13 mothers, 14 fathers), five from grandparents, one from a sibling and one from an aunt.

Anthropometrics and exercise testing

Thirteen patients (34%) were overweight ($n=8$) or obese ($n=5$); the proportion of overweight patients among the treadmill participants was 36% (8/22). Eleven patients (29%) were growth-retarded (height *z* score < -2). In the treadmill participants, median $\dot{V}O_{2\text{peak}}$ was 66% (range 36–97%) of the expected values compared with the healthy controls ($n=196$). Only three participants obtained $\dot{V}O_{2\text{peak}}$ within the expected range (i.e. $\dot{V}O_{2\text{peak}}$ *z* score ≥ -2) (previously published data [26]).

Child mental health, psychosocial functioning and QOL

The SDQ and PedsQL for TX children, the group of ALL and the healthy controls are presented in Table 2.

Both the TX children and their mothers reported significantly higher SDQ scores than the healthy controls in terms of total difficulties, emotional problems and peer problems with more total difficulties caseness and impact score caseness. Relative to the healthy controls, the mothers reported even significantly higher SDQ scores regarding conduct problems and hyperactivity problems but lower prosocial behavior. Compared to the ALL group, the TX children and their mothers reported significantly higher SDQ scores regarding total difficulties, emotional problems and impact score, with more total difficulties in terms of caseness. The SDQ scores for the healthy controls are not significant different than the SDQ norms or reference values from the general Norwegian population [32].

Both the TX children and their mothers reported significantly lower HRQOL scores on all PedsQL items, with the exception of emotional functioning, than the

Table 2 Health-related quality of life and Strength and Difficulties Questionnaire of 38 children with kidney transplantation (TX) compared to children with ALL and healthy controls

Mental health and quality of life scales	TX (n=38)	ALL (n=40)	Healthy (n=42)
PedsQL child self-report	n=30		
Total score	69.10 (17.98)	81.70 (12.56)***	88.98 (7.57)***
Psychosocial health	67.03 (18.05)	79.27 (13.99)**	87.22 (9.20)***
Physical functioning	74.89 (17.01)	86.25 (12.13)**	92.26 (6.45)***
Emotional functioning	69.48 (15.81)	75.13 (18.69)	83.21 (12.68)***
Social functioning	73.71 (21.54)	86.00 (14.11)**	92.50 (7.67)***
School functioning	63.10 (17.75)	76.63 (16.38)**	85.95 (12.98)***
PedsQL mother proxy-report	n=32	n=36	n=38
Total score	68.37 (19.17)	79.42 (12.50)**	89.62 (10.26)***
Psychosocial health	67.68 (18.93)	75.86 (14.22)*	88.07 (11.28)***
Physical functioning	69.36 (23.05)	86.14 (13.69)***	92.52 (10.47)***
Emotional functioning	70.00 (21.36)	70.28 (15.63)	85.00 (13.46)***
Social functioning	67.79 (27.07)	82.81 (15.54)**	93.16 (9.89)***
School functioning	62.90 (23.16)	74.44 (19.88)*	86.05 (14.57)***
SDQ child self-report	n=26	n=39	n=41
Total difficulties	11.58 (5.69)	7.44 (4.79)**	5.71 (4.28)***
No.(%) caseness, 19–40	2 (8)	1 (3) **	0 (0)**
No.(%) borderline, 16–18	6 (23)	0 (0)	1 (2)
Emotional problems	3.62 (2.10)	2.49 (2.11)*	1.80 (2.16)***
Conduct problems	1.85 (1.64)	2.10 (1.52)	1.80 (1.36)
Hyperactivity problems	3.58 (2.18)	3.05 (1.86)	3.27 (2.28)
Peer problems	2.54 (2.16)	2.33 (1.91)	1.56 (1.66)*
Prosocial behavior	7.89 (2.05)	7.64 (1.84)	7.85 (1.75)
Impact score	0.77 (1.42)	0.24 (0.68)*	0.24 (1.09)
No.(%) caseness, 2–10	6 (23)	3 (8)	2 (5)*
No.(%) borderline, 1	1 (4)	2 (5)	0 (0)
SDQ mother proxy-report	n=31	n=36	n=38
Total difficulties	10.74 (6.30)	7.61 (5.15)*	4.18 (3.57)***
No.(%) caseness, 19–40	4 (13)	2 (6)	0 (0)**
No.(%) borderline, 16–18	3 (10)	3 (8)	0 (0)
Emotional problems	2.68 (1.97)	1.64 (1.81)*	0.76 (0.94)***
Conduct problems	1.81 (1.54)	1.50 (1.34)	0.95 (1.16)**
Hyperactivity problems	3.68 (2.50)	2.83 (2.66)	1.71 (1.98)**
Peer problems	2.58 (2.49)	1.64 (1.85)	0.76 (0.97)***
Prosocial behavior	7.81 (2.15)	7.97 (1.86)	8.87 (1.39)*
Impact score	1.19 (2.01)	1.59 (2.39)	0.03 (0.16)***
No.(%) caseness, 2–10	9 (29)	7 (19)	0 (0)***
No.(%) borderline, 1	0 (0)	0 (0)	1 (3)

*Significant at the 0.05 level (two-tailed), **significant at the 0.001 level (two-tailed), ***significant at the .001 level (two-tailed) with respect to difference between TX and ALL/healthy patients/subjects
PedsQL, Pediatric Quality of Life Inventory; SDQ, Strength and Difficulties Questionnaire; HRQOL, health-related quality of life
Values are reported as the mean, with the SD in parenthesis unless stated otherwise

healthy controls and the ALL group. The SDQ and PedsQL scores were not associated with age, sex or years since the TX date. When the patients were classified into age groups according to the developmental perspective, i.e. 3–12 years and 13–18 years, we found no significant differences in the SDQ and PedsQL scores between the two groups. Furthermore, there were no significant differences between the scores of the children and the scores of their mothers on the SDQ or PedsQL.

Maternal mental health and QOL

The GHQ and QOLS for the mothers of TX children, the group of ALL and the healthy controls are presented in Table 1. The mothers of TX children reported significantly more mental health problems (GHQ-case) than the mothers of healthy controls, but their scores were comparable with those of the ALL group. The QOLS scores in the control group are not significant different than QOLS norms or

reference values from the general Norwegian population (mean 85.0, SD 12.3) [45]. When the patients were classified according to parental donorship ($n=27$) or not, the mothers in the parental donor group reported significantly more mental health problems (GHQ) ($t = 2.15, p = 0.043$) and a tendency towards significant lower QOL ($t = -2.01, p = 0.056$) than the mothers in the non-parental donor group. All six GHQ cases were found in the parental donor group.

Associations between physical variables, maternal variables and children’s mental, psychosocial and QOL outcome

There were significant correlations between the measures of physical status (height, BMI, CR Fitness), maternal variables (GHQ, QOLS) and the children’s mental health/ psychosocial functioning (SDQ) and QOL (PedsQL) outcomes (Table 3). Renal function (GFR) did not correlate with any of these outcome variables. Strong associations

($r > 0.60, p < 0.001$) were found between the PedsQL child self-report and PedsQL mother proxy-report in all PedsQL items, and between all SDQ child self-report and SDQ mother proxy-report.

Increased mental health problems (SDQ) were for some items significantly associated with physical outcomes—in most areas with increased BMI, but in some areas also with reduced CR Fitness and short stature—and with the mothers psychological distress (GHQ) and poorer QOL (QOLS).

Reduced PedsQL were for some items correlated with physical outcomes—in most areas with short stature and reduced CR Fitness, but in some areas also with increased BMI—and with the mothers psychological distress (GHQ) and poorer QOL (QOLS); see Table 3.

To investigate further the contribution of the independent physical and maternal variables in predicting mental (SDQ total score) and QOL (PedsQL total score) outcome, we used a multiple linear regression analysis. With SDQ total

Table 3 Significant associations between physical variables, parental variables and children’s mental, psychosocial and quality of life outcomes

Variables/outcomes	Height	Body mass index	CR Fitness	Mothers GHQ	Mothers QOL
Body mass index	-				
CR fitness	0.67***	-0.48*			
Mothers GHQ	-	0.37*	-		
Mothers QOLS	-	-	-	-0.57**	
PedsQL child					
Total	0.52**	-	0.66***	-	-
Psychosocial	0.56***	-	0.67***	-	-
Physical	-	-	0.51*	-	-
Emotional	0.44*	-	0.55*	-	-
Social	0.49**	-0.56***	0.50*	-	-
School	-	-	0.70***	-	-
PedsQL mother					
Total	0.45**	-0.44*	0.59**	-	0.52**
Psychosocial	0.45**	-0.50**	0.59**	-	0.52**
Physical	0.42*	-	0.51*	-	0.44*
Emotional	-	-	-	-	0.43*
Social	-	-0.56***	0.63**	-	-
School	0.38*	-	0.49*	-0.44*	0.59***
SDQ child					
Total	-	0.48*	-	-	-0.46*
Emotional	-0.42*	-	-0.53*	-	-0.49**
Peer	-	0.57**	-	-	-
Prosocial	-	-0.41*	-	-	-
Impact	-	0.46*	-	-	-0.44*
SDQ mother					
Total	-0.36*	0.39*	-	-	-0.48*
Emotional	-	-	-	-	-0.43*
Peer	-	0.35*	-	0.43*	-0.59***
Prosocial	-	-0.46**	0.47*	-	-
Impact	-	-	-	-	-0.47**

*Significant at the 0.05 level (two-tailed), **significant at the 0.001 level (two-tailed), ***significant at the .001 level (two-tailed)
CR Fitness, Cardiorespiratory fitness, was defined as maximal oxygen uptake (VO_{2peak})

score as the dependent variable, we entered age, gender, the physical correlates (height *z* score, BMI *z* score, VO_{2peak}) and maternal correlates (GHQ, QOLS) as explanatory variables (Table 4). The only significant predictor of mental health outcome was the BMI *z* score, explaining 32% of the variance ($p=0.018$).

Using the PedsQL total score as the dependent variable, we entered age, gender, the physical correlates (height, BMI, VO_{2peak}) and the maternal correlates (GHQ, QOLS) as explanatory variables. VO_{2peak} was the only significant predictor of QOL outcome ($n=22$), explaining 42% of the variance ($p=0.005$).

Discussion

The results of our study show that mental health, psychosocial adjustment and QOL of TX children are significantly impaired on both self-reports and proxy-reports compared with those of healthy controls and in several areas, they are lower compared than those of the ALL group. The children's own perceived mental health and HRQOL was related to physical functioning and body composition, i.e. VO_{2peak} and BMI, respectively. The mothers' own mental health was significantly reduced compared to that of the controls, but comparable to that of ALL mothers. Our results demonstrate that both children and their parents carry a significant burden that lasts up to several years after kidney TX and therefore reflect the documented psychological and social at-risk status for children with chronic health conditions reported in the literature [47, 48].

Our findings are consistent with those of studies using PedsQL [8, 9, 21, 22] in which HRQOL was found to be impaired in kidney TX children and adolescents in comparison to healthy controls. The currently improving medical strategies in renal TX have entailed an increased awareness that the optimal care of children and adolescents with ESRD requires attention not only to medical management but also to the mental and psychosocial factors; understanding this may provide insights into non-adherence and non-compliance. Relatively few studies to date describe these important aspects in pediatric kidney transplant recipients and their parents, and those that do differ in their methodology and generally present conflicting results.

Additionally, parents of children with serious or chronic diseases may themselves be at risk for psychological problems to the extent that they can no longer be an effective source of protection and support for the child [49]. Thus, QOL should also include the long-term effects for the whole family as well.

A lack of concordance between children and caregivers has been reported in healthy [50] and chronically ill [51] children, suggesting information provided by proxy respondents is not equivalent to that reported by the patient. The child perspective often diverges from parental perceptions, particularly in the emotional and social domains. Previous research in CKD children and their parents has emphasized that the caregivers' perceptions of their child may underestimate the patient's own perception [8, 13]. On the other hand, mothers with more psychological problems often rate their children as having more behavioral problems [7].

In opposite to others [8, 13, 22], it is noteworthy that our TX children and their mothers rate the child's mental health and quality of life in accordance to each other; also in emotional and social domains. Our findings may suggest that parental donors identify more with the child due to organ share, in particular expressed by the mothers since they were the ones that accompanied their child to the investigations and thus were the responders of the questionnaires.

Both TX children and their mothers reported significantly lower HRQOL scores than children with ALL in all areas except emotional functioning and higher SDQ total difficulties, emotional problems and impact scores. The two patient groups are equivalent in gender, age and socio-economic background, such as family composition, parental age and educational level, community, home and economy, thus eliminating these factors as possible confounders. Although ALL and renal TX are completely different disease entities, our findings demonstrate a greater total burden on the family and child after renal TX. Our study further highlights the impact CKD may have on HRQOL when compared to another severe pediatric chronic disease [9].

The study on survivors of childhood ALL [27, 28] was conducted at a mean of 7 years after treatment—which is a time when the fear of relapse is less pronounced. Moreover, ALL in children starts abruptly, the treatment period for

Table 4 Forward multiple regression analyses predicting mental health outcome (SDQ) and quality of life outcome (PedsQL) in children and adolescents after transplantation

Model	Independent variable	B	95% Confidence interval	Beta	<i>p</i> value	<i>R</i> ²
1. SDQ	Body mass index	1.79	(0.36, 3.23)	0.57	0.018	0.32
2. PedsQL	VO_{2peak}	0.22	(0.08, 0.36)	0.65	0.005	0.42

most ALL children lasts 2–2.5 years and the follow-up at the hospital ends 5–10 years after onset of disease. Renal TX is for the majority preceded with years with CKD, which affects both the child and its family. The frequent hospital visits and daily medications continue after TX and is a constant reminder of an everlasting chronic disease [7, 52].

At the same time, renal TX is a milestone for many families, even though the transition to normal life is difficult for both the parents and the child. The relief following regain of energy and appetite is hampered by strict surveillance of medication and blood samples several times a week in the early phase post TX. Parents may find it difficult to wean off habits of overprotection established before transplantation, reinforced by the wish to protect both their child and their own donated organ. In addition, the fear of rejection, non-compliance, risk of infections and poor graft function is a persistent threat. Moreover, approximately 50% of those transplanted in childhood will need a second kidney transplant before the age of 25 years [53].

Family functioning is one of the strongest contributors to psychosocial adjustment both in children with chronic health conditions and in healthy children [54]. It has been suggested that kidney donation and Tx have far-reaching implications for the whole family; each member will experience different changes that affect the family environment as a whole and the QOL of each person uniquely [55].

While some studies have evaluated the psychosocial functioning and QOL of CKD children and adolescents, there has been a lack of studies on parents' psychosocial functioning and HRQOL. In our study, mothers of TX children reported significantly more mental health problems than mothers of healthy controls, but their scores were comparable with those of the ALL mother comparison group. This is in accordance with one of few studies reporting that renal TX in children had a high impact on the parents, such as social isolation, emotional dysfunctioning, depression and posttraumatic stress symptoms [52]. Furthermore, in our study, the mothers of children with a parental donor had significantly more mental health problems than mothers of children receiving a kidney from non-parental donors; this is worrying, even though the numbers are low. This result is in contrast to previous research finding that the great majority of kidney donors and their partners experience no change or an improvement in their psychosocial health after donation [56, 57]. In a country like Norway, where LD in children has been a tradition since the start of the program, it is especially important to recognize the psychological trauma among the parental donors. Parents are subjected to a process of conflicting emotions. The donation of an organ is a life-saving procedure. At the same time, the parental donors must

cope with the unspoken concern of own health after donating a kidney. However, a more comprehensive understanding of the psychological consequences of the donation process on the parents requires further study in which the fathers are also involved.

Most HRQOL studies on CKD children and adolescents have highlighted the psychosocial effects with less attention paid to its relation to physical effects [58]. In our study we revealed that the health status variables BMI, height and CR Fitness correlated and even predicted mental health problems, psychosocial dysfunction and poor QOL. It is now well established that short stature [59] is associated with a negative impact on overall QOL.

Several studies have reported on the low exercise capacity in CKD and ESRD children [19, 58, 60], but no studies have as yet explored the relation between an objective measure on CR Fitness (VO_{2peak}) and HRQOL in renal TX children. Regular physical activity has been shown to have significant physical and mental health benefits [21, 61], including reduced anxiety, improved body image, self-esteem, mood and quality of life. CR Fitness (VO_{2peak}) is considered to be the best measure of aerobic fitness and improves with exercise [62]. In a previous study, we showed that renal TX children and adolescents achieved only 66% of the expected CR Fitness compared to healthy children and that the majority reported being physical inactive [26]. Physical activity is a necessary and natural constituent of a child's life. However, the fatigue of ESRD and the overprotection from parents and the health system after TX may deprive these children from participating in sports and activities. Physical inactivity is in itself a risk factor for reduced self-esteem and obesity and, perhaps most importantly, may impair social interaction with peers and increase the risk for psychosocial dysfunction.

Both short stature and physical inactivity may foreshadow poor long-term psychosocial outcomes that have previously been observed and highlight the importance of early interventions to improve both linear growth and normalize height and to increase physical fitness in CKD children.

Strength and limitations

The strength of our study is that the TX children were followed-up at the same hospital and compared to a relevant control group and comparison group. However, a number of limitations should be noted. This study has a cross-sectional design, and we were therefore unable to control for premorbid functioning and for the small size of our group of children and their mothers. Cross-sectional designs cannot determine causal relations, implying that the results should be treated with some caution.

As for most studies on children and adolescents with chronic diseases, including CKD, our study was based on self-reports and/or parental questionnaires. These general non-specific questionnaires underestimate the overall prevalence of psychosocial dysfunctioning and psychopathology. More specific psychosocial problems and mild psychopathology appear to be difficult to elicit by questionnaires, indicating the need for including semistructured psychiatric or qualitative interviews within disease-specific areas. For future studies in this field, one has to encourage both longitudinal and qualitative studies to further explore QOL issues in renal TX children, including patients with other types of solid organ TX and utilizing transplant-specific HRQOL instruments in addition to generic HRQOL measures [40].

Conclusion

Mental health problems and psychosocial dysfunction can persist several years after diagnosis and treatment with renal TX, affecting the TX child's QOL and parental functioning. Optimal treatment and follow-up of TX children require close collaboration between pediatricians and psychosocial experts from birth to adulthood. Professional mental health guidance which includes developmental and family perspectives should be offered routinely to the TX patient and their parents.

With respect to the health status variables' (height, BMI, CR Fitness) impact on mental health and QOL, our study highlights the importance of early interventions to improve linear growth, reduce weight gain after TX and increase physical fitness. Our results suggest that emphasis during the follow-up period of entire family has also to be placed on physical rehabilitation programs and even measurements of exercise capacity, as compulsory therapy hand in hand with medical and psychosocial support. Health care providers should be the first to inform parents and the child about the importance of participating with peers in play and sport. A holistic, multifactorial approach towards the TX child and family is undoubtedly the best strategy to achieve both long-term graft survival and ensure a good QOL for both the child and parents.

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References

1. Tangeraas T, Bjerre A, Lien B, Kyte A, Monn E, Cvancarova M, Leivestad T, Reisaeter AV (2008) Long-term outcome of pediatric renal transplantation: the Norwegian experience in three eras 1970–2006. *Pediatr Transplant* 12:762–768
2. Rees L (2009) Long-term outcome after renal transplantation in childhood. *Pediatr Nephrol* 24:475–484
3. Shapiro R, Sarwal MM (2010) Pediatric kidney transplantation. *Pediatr Clin N Am* 57:393–400
4. Dhamidhark VR, Araya CE, Benfed MR (2007) Organ Toxicities. In: Fine R, Webber S, Olthoff K, Kelly D, Harmon W (eds) *Pediatric solid organ transplantation*, 2nd edn. Blackwell, Oxford, pp 124–136
5. Filler G, Huang SH (2010) Progress in pediatric kidney transplantation. *Ther Drug Monit* 32:250–252
6. Garralda ME, Jameson RA, Reynolds JM, Postlethwaite RJ (1988) Psychiatric adjustment in children with chronic renal failure. *J Child Psychol Psychiatry* 29:79–90
7. Madden SJ, Hastings RP, V'ant Hoff W (2002) Psychological adjustment in children with end stage renal disease: the impact of maternal stress and coping. *Child Care Health Dev* 28:323–330
8. McKenna AM, Keating LE, Vigneux A, Stevens S, Williams A, Geary DF (2006) Quality of life in children with chronic kidney disease-patient and caregiver assessments. *Nephrol Dial Transplant* 21:1899–1905
9. Goldstein SL, Graham N, Burwinkle T, Warady B, Farrah R, Varni JW (2006) Health-related quality of life in pediatric patients with ESRD. *Pediatr Nephrol* 21:846–850
10. Morel P, Almond PS, Matas AJ, Gillingham KJ, Chau C, Brown A, Kashtan CE, Mauer SM, Chavers B, Nevins TE, Dunn DL, Sutherland DER, Payne WD, Najarian J (1991) Long-term quality of life after kidney transplantation in childhood. *Transplantation* 52:47–53
11. Krmar RT, Eymann A, Ramirez JA, Ferraris JR (1997) Quality of life after kidney transplantation in children. *Transplantation* 64:540–541
12. Kärrfelt HM, Berg UB (2008) Long-term psychosocial outcome after renal transplantation during childhood. *Pediatr Transplant* 12:557–562
13. Goldstein SL, Graham N, Warady BA, Seikaly M, McDonald R, Burwinkle TM, Limbers CA, Varni JW (2008) Measuring health-related quality of life in children with ESRD: performance of the generic and ESRD-specific instrument of the Pediatric Quality of Life Inventory (PedsQL). *Am J Kidney Dis* 51:285–297
14. Qvist E, Närhi V, Apajasalo M, Rönholm K, Jalanko H, Almqvist F, Holmberg C (2004) Psychosocial adjustment and quality of life after renal transplantation in early childhood. *Pediatr Transplant* 8:120–125
15. Falger J, Landolt MA, Latal B, Rütth EM, Neuhaus TJ, Laube GF (2008) Outcome after renal transplantation. Part II: quality of life and psychosocial adjustment. *Pediatr Nephrol* 23:1347–1354
16. Manificat S, Dazard A, Cochot P, Morin D, Plainguet F, Debray D (2003) Quality of life of children and adolescents after kidney or liver transplantation: child, parents and caregiver's point of view. *Pediatr Transplant* 7:228–235
17. Hasegawa A, Oshima S, Takahashi K, Uchida K, Ito K, Sonoda T (2005) Improvement of quality of life in tacrolimus-based pediatric renal transplant recipients and their caregivers, including donors. *Transplant Proc* 37:1771–1773
18. Gerson A, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush B, Furth S (2004) Anemia and health-related quality of life in adolescents with chronic kidney disease. *Am J Kidney Dis* 44:1017–1023
19. Eijssermans RM, Creemers DG, Helders PJ, Schröder CH (2004) Motor performance, exercise tolerance, and health-related quality of life in children on dialysis. *Pediatr Nephrol* 19:1262–1266
20. Sundaram SS, Landgraf JM, Neighbors K, Cohn RA, Alonso EM (2007) Adolescent health-related quality of life following liver and kidney transplantation. *Am J Transplant* 7:982–989
21. Hamiwka LA, Cantell M, Crawford S, Clark CG (2009) Physical activity and health related quality of life in children following kidney transplantation. *Pediatr Transplant* 13:861–867

22. Anthony SJ, Hebert D, Todd L, Korus M, Langlois V, Pool R, Robinson LA, Williams A, Pollock-BarZiv SM (2010) Child and parental perspectives of multidimensional quality of life outcomes after kidney transplantation. *Pediatr Transplant* 14:249–256
23. Soliday E, Kool E, Lande MB (2000) Psychosocial adjustment in children with kidney disease. *J Pediatr Psychol* 25:93–103
24. Kärrfelt HM, Lindblad FI, Crafoord J, Berg UB (2003) Renal transplantation: long-term adaptation and the children's own reflections. *Pediatr Transplant* 7:69–75
25. Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, Tomlanovich SL, Ascher NL (2002) A randomized trial of exercise training after renal transplantation. *Transplantation* 74:42–48
26. Tangeraas T, Midtvedt K, Fredriksen PM, Cvancarova M, Mørkrid L, Bjerre A (2010) Cardiorespiratory fitness is a marker of cardiovascular health in renal transplanted children. *Pediatr Nephrol* 25:2343–2350
27. Reinfjell T, Lofstad GE, Veenstra M, Vikan A, Diseth TH (2007) Health-related quality of life and intellectual functioning in children in remission from acute lymphoblastic leukaemia. *Acta Paediatr* 96:1280–1285
28. Reinfjell T, Lofstad GE, Nordahl HM, Vikan A, Diseth TH (2009) Children in remission from acute lymphoblastic leukaemia: mental health, psychosocial adjustment and parental functioning. *Eur J Cancer Care* 18:364–370
29. Cole TJ, Freeman JV, Preece MA (1995) Body mass index reference curves for the UK, 1990. *Arch Dis Child* 73:25–29
30. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. *Br Med J* 320:1240–1243
31. Goodman R (1999) The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatr* 40:791–799
32. Van Roy B, Grøholt B, Heyerdahl S, Clench-Aas J (2006) Self-reported strengths and difficulties in a large Norwegian population 10–19 years: age and gender specific results of the extended SDQ-questionnaire. *Eur Child Adolesc Psychiatr* 15:189–198
33. Obel C, Heiervang E, Rodriguez A, Heyerdahl S, Smedje H, Sourander A, Guethmundsson OO, Clench-Aas J, Christensen E, Heian F, Mathiesen KS, Magnusson P, Njårethvik U, Koskelainen M, Rønning JA, Stormark KM, Olsen J (2004) The Strengths and Difficulties Questionnaire in the Nordic countries. *Eur Child Adolesc Psychiatr* 13[Suppl 2]:II32–II39
34. Varni JW, Seid M, Rode CA (1999) The PedsQL: Measurement model for the Pediatric Quality of Life Inventory. *Med Care* 37:126–139
35. Varni JW, Seid M, Kurtin PS (2001) PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 39:800–812
36. Varni JW (1998) PedsQL TM Translation methodology. Available at: <http://www.pedsqol.org>
37. Eiser C, Morse R (2001) The measurement and quality of life in children: past and future perspectives. *Dev Behav Pediatr* 22(4):248–256
38. Varni JW, Burwinkle TM, Seid M (2006) The PedsQL 4.0 as a school population health measure: feasibility, reliability, and validity. *Qual Life Res* 15:203–215
39. Varni JW, Burwinkle TM, Seid M, Skarr D (2003) The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr* 3:329–341
40. Weissberg-Benchell J, Zieliński TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, Fredericks EM, McDiarmid S, Williams L, Limbers CA, Tuzinkiewicz K, Lerret S, Alonso EM, Varni JW (2010) Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL transplant module. *Am J Transplant* 10:1677–1685
41. Reinfjell T, Diseth TH, Veenstra M, Vikan A (2006) Measuring health-related quality of life in young adolescents: reliability and validity in the Norwegian version of the Pediatric Quality of Life Inventory 4.0 (PedsQL) generic core scales. *Health Qual Life Outcomes* 4:61
42. Goldberg D, Williams P (1988) A user's guide to the General Health Questionnaire GHQ. NFER-Nelson, Windsor
43. Malt UF (1989) The validity of the General Health Questionnaire in a sample of accidentally injured adults. *Acta Psychiatr Scand Suppl* 80(355):103–112
44. Burckhardt CS, Woods SL, Schultz AA, Ziebarth DM (1989) Quality of life of adults with chronic illness: a psychometric study. *Res Nurs Health* 12:347–354
45. Wahl AK, Rustøen T, Hanestad BR, Lerdal A, Moum T (2004) Quality of life in the general Norwegian population, measured by the Quality of Life Scale (QOLS-N). *Qual Life Res* 13: 1001–1009
46. Kleinbaum D, Kupper L, Muller K (1988) Applied regression analysis and other multivariable methods, 2nd edn. PWS-KENT, Boston
47. Wallander JL, Varni JW (1998) Effects of pediatric chronic physical disorders on child and family adjustment. *J Child Psychol Psychiatr* 39:29–46
48. Lavigne JV, Faier-Routman J (1992) Psychological adjustment to pediatric physical disorders: a meta-analytic review. *J Pediatr Psychol* 17:133–157
49. Varni JW, Setoguchi Y (1992) Screening for behavioral and emotional problems in children and adolescents with congenital or acquired limb deficiencies. *Am J Dis Child* 146:103–137
50. Achenbach TM, McConaughy SH, Howell CT (1987) Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull* 101:213–232
51. Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A, Castro CM, The Pediatric Cancer Quality of Life Inventory (PCQL) (1998) I. Instrument development, descriptive statistics, and cross-informant variance. *J Behav Med* 21:179–204
52. Wiedebusch S, Konrad M, Foppe H, Reichwald-Klugger E, Schaefer F, Schreiber V, Muthny FA (2010) Health-related quality of life, psychosocial strains, and coping in parents of children with chronic renal failure. *Pediatr Nephrol* 25:1477–1485
53. Gjertson DW, Cecka JM (2001) Determinants of long-term survival of pediatric kidney grafts reported to the United Network for Organ Sharing kidney transplant registry. *Pediatr Transplant* 5:5–15
54. Drotar D (1997) Relating parent and family functioning to the psychological adjustment of children with chronic health conditions: What have we learned? What do we need to know? *J Pediatr Psychol* 22:149–165
55. Hanson CL (2001) Quality of life in families of youths with chronic conditions. Brunner-Routledge, East Sussex
56. Neuhaus TJ, Wartmann M, Weber M, Landolt MA, Laube GF, Kemper MJ (2005) Psychosocial impact of living-related kidney transplantation on donors and partners. *Pediatr Nephrol* 20:205–209
57. Clemens KK, Thiessen-Philbrook H, Parikh CR, Yang RC, Karley ML, Boudville N, Ramesh Prasad GV, Garg AX, Donor Nephrectomy Outcomes Research (DONOR) Network (2006) Psychosocial health of living kidney donors: a systematic review. *Am J Transplant* 6:2965–2977
58. Goldstein SL (2009) Physical fitness in children with end-stage renal disease. *Adv Chron Kidney Dis* 16:430–436

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59. Gerson AC, Wentz A, Abraham AG, Mendley SR, Hooper SR, Butler RW, Gipson DS, Lande MB, Shinnar S, Moxey-Mims MM, Warady BA, Furth SL (2010) Health-related quality of life of children with mild to moderate chronic kidney disease. *Pediatrics* 125:e349–357
 60. Pattaragarn A, Warady BA, Sabath RJ (2004) Exercise capacity in pediatric patients with end-stage renal disease. *Perit Dial Int* 24:274–280
 61. White K, Kendrick T, Yardley L (2009) Change in self-esteem, self-efficacy and the mood dimensions of depression as potential mediators of the physical activity and depression relationship: Exploring the temporal relation of change. *Ment Health Phys Act* 2:44–52
 62. Bassett DR Jr, Howley ET (2000) Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc* 32:70–84

APPENDIX A

Child physical activity questionnaire

VEDLEGG NR 2

Skjemanummer:



Spørsmål om fysisk aktivitet 8. klasse



Les dette først!

På de neste sidene følger noen spørsmål om fysisk aktivitet. Du skal sette et kryss ved det svaret som passer best for deg. Det er viktig at du leser spørsmålet og svaralternativene nøye før du setter kryss. Dersom du ønsker å forandre et svar etter at du har satt kryss – sett da strek over krysset, og sett et nytt kryss på det svaret som passer best. Dersom det er noe du lurer på kan du spørre Magnhild om hjelp.

En liten oppfordring før du setter i gang – vær ærlig. Det er ingen svaralternativ som er mer riktige enn andre.

Før du begynner er det fint om du fyller ut alder og kjønn nedenfor.

Alder: _____ år

Kjønn: jente
 gutt

1) På skolen:

Hvor ofte blir du værende igjen på skolen etter skoletid for å trene, leke eller drive med sport?

- 1. Nesten aldri eller aldri → Gå rett til spørsmål 2
- 2. 1-2 ganger i uka
- 3. 3-4 ganger i uka
- 4. 5 ganger i uka

Spørsmål 1a og 1b fyller du bare ut dersom du på spørsmål 1 har krysset av for ett av alternativene fra 2 til 4:

1a) Hvor lenge varer aktiviteten om gangen? (i gjennomsnitt)

- 1. Mindre enn 5 minutter
- 2. 5-9 minutter
- 3. 10-14 minutter
- 4. 15-19 minutter
- 5. 20-24 minutter
- 6. 25-29 minutter
- 7. 30-34 minutter
- 8. 35-39 minutter
- 9. 40-44 minutter
- 10. 45-49 minutter
- 11. 50-54 minutter
- 12. 55-59 minutter
- 13. 60 minutter eller mer

1b) Hvor slitsom er aktiviteten?

- 1. Svært lett
- 2. Veldig lett
- 3. Lett
- 4. Litt anstrengende
- 5. Anstrengende
- 6. Veldig anstrengende
- 7. Svært anstrengende

2) På hverdager:

I tillegg til det du har svart på i spørsmål 1: Hvor ofte trener, leker eller driver du med sport utenom skoletid?

(Ta med aktiviteter i idrettslag, ungdomsklubb, speideren osv. Det er mulig å være i aktivitet flere ganger i løpet av en dag.)

1. Nesten aldri eller aldri → Gå rett til spørsmål 3
2. 1-2 ganger i uka
3. 3-4 ganger i uka
4. 5-6 ganger i uka
5. 7-8 ganger i uka
6. 9-10 ganger i uka
7. Mer enn 10 ganger i uka

Spørsmål 2a og 2b fyller du bare ut dersom du på spørsmål 2 har krysset av for ett av alternativene fra 2 til 7:

2a) Hvor lenge varer aktiviteten om gangen? (i gjennomsnitt)

1. Mindre enn 5 minutter
2. 5-9 minutter
3. 10-14 minutter
4. 15-19 minutter
5. 20-24 minutter
6. 25-29 minutter
7. 30-34 minutter
8. 35-39 minutter
9. 40-44 minutter
10. 45-49 minutter
11. 50-54 minutter
12. 55-59 minutter
13. 60 minutter eller mer

2b) Hvor slitsom er aktiviteten?

1. Svært lett
2. Veldig lett
3. Lett
4. Litt anstrengende
5. Anstrengende
6. Veldig anstrengende
7. Svært anstrengende

3) I helgene:

Hvor ofte trener, leker eller driver du med sport?

(Ta med aktiviteter i idrettslag, ungdomsklubb, speideren osv. Det er mulig å være i aktivitet flere ganger i løpet av en helgedag.)

1. Nesten aldri eller aldri → Gå rett til spørsmål 4
2. 1-2 ganger i måneden
3. 3-4 ganger i måneden
4. 5-6 ganger i måneden
5. 7-8 ganger i måneden
6. Mer enn 8 ganger i måneden

Spørsmål 3a og 3b fyller du bare ut dersom du på spørsmål 3 har krysset av for ett av alternativene fra 2 til 6:

3a) Hvor lenge varer aktiviteten om gangen? (i gjennomsnitt)

1. Mindre enn 5 minutter
2. 5-9 minutter
3. 10-14 minutter
4. 15-19 minutter
5. 20-24 minutter
6. 25-29 minutter
7. 30-34 minutter
8. 35-39 minutter
9. 40-44 minutter
10. 45-49 minutter
11. 50-54 minutter
12. 55-59 minutter
13. 60 minutter eller mer

3b) Hvor slitsom er aktiviteten?

1. Svært lett
2. Veldig lett
3. Lett
4. Litt anstrengende
5. Anstrengende
6. Veldig anstrengende
7. Svært anstrengende

4) Hvilket av disse alternativene passer best for deg?

1. Jeg trener ikke, og jeg har ikke tenkt å begynne
2. Jeg trener ikke, men det er mulig jeg begynner
3. Jeg trener noen ganger, men ikke regelmessig
4. Jeg trener regelmessig, men har akkurat startet
5. Jeg har trent regelmessig i mer enn 6 måneder

5) Hva gjør du vanligvis i friminuttene?

1. Sitter (snakker/leser)
2. Står eller går rundt
3. Løper rundt og leker/spiller

6) Hva gjør du vanligvis i storefri (bortsett fra å spise)?

1. Sitter (snakker/leser)
2. Står eller går rundt
3. Løper rundt og leker/spiller

7) Hvordan kommer du deg vanligvis til skolen?

1. Med bil
2. Med buss, trikk, T-bane eller tog
3. Med sykkel
4. Går

8) Hvordan kommer du deg vanligvis hjem fra skolen?

1. Med bil
2. Med buss, trikk, T-bane eller tog
3. Med sykkel
4. Går

9) Hvor lang tid bruker du vanligvis til skolen (en vei)?

1. Mindre enn 5 minutter
2. 5 til 14 minutter
3. 15 til 29 minutter
4. 30 til 59 minutter
5. 60 minutter eller mer

10) Hvor mange timer ser du vanligvis på TV på en vanlig hverdag?

1. Mer enn 5 timer
2. 4-5 timer
3. 3-4 timer
4. 2-3 timer
5. 1-2 timer
6. Mindre enn 1 time

11) Hvor mange timer ser du vanligvis på TV på en vanlig helgedag eller fridag?

1. Mer enn 5 timer
2. 4-5 timer
3. 3-4 timer
4. 2-3 timer
5. 1-2 timer
6. Mindre enn 1 time

12) Hvor mange timer bruker du vanligvis til data, TV-spill eller andre spill på en vanlig hverdag? (F.eks. surfing på internett, Gameboy, Nintendo, Playstation)

1. Mer enn 5 timer
2. 4-5 timer
3. 3-4 timer
4. 2-3 timer
5. 1-2 timer
6. Mindre enn 1 time

13) Hvor mange timer bruker du vanligvis til data, TV-spill eller andre spill på en vanlig helgedag eller fridag? (F.eks. surfing på internett, Gameboy, Nintendo, Playstation)

1. Mer enn 5 timer
2. 4-5 timer
3. 3-4 timer
4. 2-3 timer
5. 1-2 timer
6. Mindre enn 1 time

14) Hvor lenge arbeider du med lekser i løpet av en dag? (i gjennomsnitt)

(Ta med tiden du bruker til lekser både på hverdager og helgedager)

1. Mindre enn 5 minutter
2. 5-19 minutter
3. 20-39 minutter
4. 40-59 minutter
5. 60-79 minutter
6. 80-99 minutter
7. 100-119 minutter
8. 2 timer (120 min) eller mer

15) Hvor lang tid bruker du vanligvis på å lese aviser, blader, romaner, noveller eller lignende på en vanlig hverdag?

1. Mindre enn 5 minutter
2. 5-19 minutter
3. 20-39 minutter
4. 40-59 minutter
5. 60-79 minutter
6. 80-99 minutter
7. 100-119 minutter
8. 2 timer (120 min) eller mer

16) Hvor lang tid bruker du vanligvis på å lese aviser, blader, romaner, noveller eller lignende på en vanlig helgedag eller fridag?

1. Mindre enn 5 minutter
2. 5-19 minutter
3. 20-39 minutter
4. 40-59 minutter
5. 60-79 minutter
6. 80-99 minutter
7. 100-119 minutter
8. 2 timer (120 min) eller mer

17) Hvor mange timer i døgnet sover du vanligvis på hverdager?

1. Mindre enn 7 timer
2. 7-9 timer
3. 9-11 timer
4. 11-13 timer
5. 13-15 timer
6. Mer enn 15 timer

18) Hvor mange timer i døgnet sover du vanligvis på helgedager og fridager?

1. Mindre enn 7 timer
2. 7-9 timer
3. 9-11 timer
4. 11-13 timer
5. 13-15 timer
6. Mer enn 15 timer



TAKK FOR HJELPEN!!

Adult physical activity questionnaire

International physical activity questionnaire (IPAQ)

Vi vet i dag for lite om folks aktivitets- og mosjonsvaner, og om hva som gjør at noen er fysisk aktive og andre ikke. Ved å besvare dette spørreskjemaet bidrar du til å få frem nyttig kunnskap uansett om du er fysisk aktiv eller ikke.

Når du svarer på spørsmålene (1-4):

Meget anstrengende – er fysisk aktivitet som får deg til å puste *mye mer* enn vanlig

Middels anstrengende – er fysisk aktivitet som får deg til å puste *litt mer* enn vanlig

Husk: det er kun aktiviteter som varer *minst 10 minutter i strekk* som skal rapporteres.

- 1a Hvor mange dager i løpet av de siste 7 dager har du drevet med *meget anstrengende* fysiske aktiviteter som tunge løft, gravearbeid, aerobics eller sykle fort? Tenk bare på de aktiviteter som varer *minst 10 minutter i strekk*.

Dager per uke
 Ingen (gå til spørsmål 2a)

- 1b På en vanlig dag hvor du utførte *meget anstrengende* fysiske aktiviteter, hvor lang tid brukte du da på dette?

Timer Minutter

- 2a Tenk på de aktiviteter som varer *minst 10 minutter i strekk* som skal rapporteres. Hvor mange dager i løpet av de siste 7 dager har du drevet med *middels anstrengende* fysiske aktiviteter som å bære lette ting, sykle i moderat tempo eller mosjonstennis? Ikke ta med gange.

Dager per uke
 Ingen (gå til spørsmål 3a)

- 2b På en vanlig dag hvor du utførte *middels anstrengende* fysiske aktiviteter, hvor lang tid brukte du da på dette ?

Timer Minutter

- 3a Hvor mange dager i løpet av de siste 7 dager, *gikk du minst 10 minutter i strekk* for å komme deg fra et sted til et annet? Dette inkluderer gange på jobb og hjemme, gange til buss, eller gange som du gjør på tur eller som trening i fritiden.

Dager per uke
 Ingen (gå til spørsmål 4)

- 3b På en vanlig dag hvor du *gikk* for å komme deg fra et sted til et annet, hvor lang tid brukte du da totalt på å gå?

Timer Minutter

- 4 Dette spørsmålet omfatter all tid du tilbringer i ro (*sittende*) på jobb, hjemme, på kurs og på fritiden. Det kan være tiden du sitter ved et arbeidsbord, hos venner, mens du leser eller sitter eller ligger for å se på TV.

I løpet av de siste 7 dager, hvor lang tid brukte du vanligvis totalt på å sitte på en vanlig hverdag?

Timer

Minutter

APPENDIX B

The strenght and difficulties questionnaire (SDQ)

Sterke og svake sider (SDQ-Nor)

S 11-16

Vennligst kryss av for hvert utsagn: Stemmer ikke, Stemmer delvis eller Stemmer helt. Prøv å svare på alt selv om du ikke er helt sikker eller synes utsagnet virker rart. Svar på grunnlag av hvordan du har hatt det de siste 6 månedene.

Ditt navn

Gutt/Jente

Fødselsdato

	Stemmer ikke	Stemmer delvis	Stemmer helt
Jeg prøver å være hyggelig mot andre. Jeg bryr meg om hva de føler	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er rastløs. Jeg kan ikke være lenge i ro	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg har ofte hodepine, vondt i magen eller kvalme	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg deler gjerne med andre (mat, spill, andre ting)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg blir ofte sint og har kort lunte	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er ofte for meg selv. Jeg gjør som regel ting alene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg gjør som regel det jeg får beskjed om	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg bekymrer meg mye	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg stiller opp hvis noen er såret, lei seg eller føler seg dårlig	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er stadig urolig eller i bevegelse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg har en eller flere gode venner	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg slåss mye. Jeg kan få andre til å gjøre det jeg vil	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er ofte lei meg, nedfor eller på gråten	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg blir som regel likt av andre på min alder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg blir lett distrauert, jeg synes det er vanskelig å konsentrere meg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg blir nervøs i nye situasjoner. Jeg blir lett usikker	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er snill mot de som er yngre enn meg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg blir ofte beskyldt for å lyve eller jukse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Andre barn eller unge plager eller mobber meg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg tilbyr meg ofte å hjelpe andre (foreldre, lærere, andre barn/unge)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg tenker meg om før jeg handler (gjør noe)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg tar ting som ikke er mine hjemme, på skolen eller andre steder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg kommer bedre overens med voksne enn de på min egen alder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg er redd for mye, jeg blir lett skremt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Jeg fullfører oppgaver. Jeg er god til å konsentrere meg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Har du andre kommentarer eller bekymringer?

Vær så snill å snu arket - det er noen få spørsmål til på den andre siden

Samlet, synes du at du har vansker på ett eller flere av følgende områder:
med følelser, konsentrasjon, oppførsel eller med å komme overens med andre mennesker ?

Nei	Ja- små vansker	Ja- tydelige vansker	Ja- alvorlige vansker
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Hvis du har svart "Ja", vennligst svar på følgende spørsmål:

- Hvor lenge har disse vanskene vært tilstede?

Mindre enn en måned	1-5 måneder	6-12 måneder	Mer enn ett år
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Forstyrrer eller plager vanskene deg?

Ikke i det hele tatt	Bare litt	En god del	Mye
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Virker vanskene inn på livet ditt på noen av disse områdene?

	Ikke i det hele tatt	Bare litt	En god del	Mye
HJEMME / I FAMILIEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FORHOLD TIL VENNER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LÆRING PÅ SKOLEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FRITIDSAKTIVITETER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Er vanskene en belastning for de rundt deg (familie, venner, lærere osv.) ?

Ikke i det hele tatt	Bare litt	En god del	Mye
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Din underskrift

Datoen i dag

Tusen takk for hjelpen

Sterke og svake sider (SDQ-Nor)

F 4-16

Vennligst kryss av for hvert utsagn: Stemmer ikke, Stemmer delvis eller Stemmer helt. Prøv å svare på alt selv om du ikke er helt sikker eller synes utsagnet virker rart. Svar på grunnlag av barnets oppførsel de siste 6 månedene.

Barnets navn

Gutt/Jente

Fødselsdato

	Stemmer ikke	Stemmer delvis	Stemmer helt
Omtenkksom, tar hensyn til andre menneskers følelser	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rastløs, overaktiv, kan ikke være lenge i ro	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Klager ofte over hodepine, vondt i magen eller kvalme	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Deler gjerne med andre barn (godter, leker, andre ting)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Har ofte raserianfall eller dårlig humør	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ganske ensom, leker ofte alene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Som regel lydig, gjør vanligvis det voksne ber om	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mange bekymringer, virker ofte bekymret	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hjelpsom hvis noen er såret, lei seg eller føler seg dårlig	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stadig urolig eller i bevegelse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Har minst en god venn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Slås ofte med andre barn eller mobber dem	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ofte lei seg, nedfor eller på gråten	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vanligvis likt av andre barn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lett avledet, mister lett konsentrasjonen	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nervøs eller klengete i nye situasjoner, lett utrygg	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Snill mot yngre barn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lyver eller jukser ofte	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Plaget eller mobbet av andre barn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tilbyr seg ofte å hjelpe andre (foreldre, lærere, andre barn)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tenker seg om før hun / han handler (gjør noe)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stjeler hjemme, på skolen eller andre steder	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kommer bedre overens med voksne enn med barn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Redd for mye, lett skremt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fullfører oppgaver, god konsentrasjonsevne	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Har du andre kommentarer eller bekymringer?

Vær så snill å snu arket - det er noen få spørsmål til på den andre siden

Samlet, synes du at barnet ditt har vansker på ett eller flere av følgende områder:
med følelser, konsentrasjon, oppførsel eller med å komme overens med andre mennesker?

Nei	Ja- små vansker	Ja- tydelige vansker	Ja- alvorlige vansker
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Hvis du har svart "Ja", vennligst svar på følgende spørsmål:

- Hvor lenge har disse vanskene vært tilstede?

Mindre enn en måned	1-5 måneder	6-12 måneder	Mer enn ett år
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Blir barnet selv forstyrret eller plaget av vanskene?

Ikke i det hele tatt	Bare litt	En god del	Mye
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Påvirker vanskene barnets dagligliv på noen av de følgende områder?

	Ikke i det hele tatt	Bare litt	En god del	Mye
HJEMME / I FAMILIEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FORHOLD TIL VENNER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
LÆRING PÅ SKOLEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FRITIDSAKTIVITETER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Er vanskene en belastning for deg eller familien som helhet?

Ikke i det hele tatt	Bare litt	En god del	Mye
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Underskrift

Dato

Mor / Far / Andre (vennligst beskriv):

Tusen takk for hjelpen

**The pediatric quality of life inventory
(PedsQL™ 4.0)**

ID#	_____
Dato:	_____

PedsQLTM

Livskvalitet hos barn

Versjon 4.0 – norwegian

Oversatt til norsk av
T. Reinfell og T.H. Diseth, 2002.
Tilbakeoversettelse ved E. M. Strømsland.
Godkjent av J. W Varni, 2003.

FORELDRE RAPPORT FOR SMÅ BARN (alder 2-4)

INSTRUKSJONER

På følgende side er det en liste med ting som kanskje er et problem for **barnet ditt**. Vennligst fortell oss **hvor stort problem** dette har vært for **barnet ditt** i løpet av **den SISTE måneden** ved å sette en ring rundt:

- 0** hvis det **aldri** er et problem
- 1** hvis det **nesten aldri** er et problem
- 2** hvis det **noen ganger** er et problem
- 3** hvis det **ofte** er et problem
- 4** hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.
Hvis du ikke forstår et av spørsmålene, vennligst spør om hjelp.

Hvor stort *problem* har dette vært for barnet ditt i løpet av den *SISTE* måneden...

FYSISK FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Gå en tur	0	1	2	3	4
2. Løpe	0	1	2	3	4
3. Delta i aktiviteter og lek	0	1	2	3	4
4. Løfte tunge ting	0	1	2	3	4
5. Bade eller dusje	0	1	2	3	4
6. Hjelpe til med å rydde lekene sine	0	1	2	3	4
7. Har vondt eller smerter (Hvor?)	0	1	2	3	4
8. Har lite overskudd og energi	0	1	2	3	4

FØLELSESMESSIG FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Føler seg redd eller skremt	0	1	2	3	4
2. Føler seg nedfor og trist	0	1	2	3	4
3. Føler seg sint eller sur/gretten	0	1	2	3	4
4. Har problemer med å sove	0	1	2	3	4
5. Bekymrer seg over hva som vil skje med ham/henne	0	1	2	3	4

SOSIAL FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Kommer ikke overens med andre barn	0	1	2	3	4
2. Andre barn vil ikke være hans/hennes venn	0	1	2	3	4
3. Blir plaget eller ertet av andre barn	0	1	2	3	4
4. Kan ikke gjøre ting som andre barn på hans eller hennes alder kan gjøre	0	1	2	3	4
5. Holde følge med andre barn i lek	0	1	2	3	4

FUNGERING I BARNEHAGEN (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Følge med i barnehagen	0	1	2	3	4
2. Glemmer ting	0	1	2	3	4
3. Gjøre aktiviteter i barnehagen	0	1	2	3	4
4. Borte fra barnehagen fordi han/hun føler seg i dårlig form	0	1	2	3	4
5. Borte fra barnehagen for å gå til legen eller sykehus	0	1	2	3	4

ID# _____
Dato: _____

PedsQLTM

Livskvalitet hos barn

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Godkjent av J. W Varni, 2003

BARNERAPPORT FOR YNGRE BARN (alder 5-7)

Instruksjon for intervjuer:

Jeg kommer til å stille deg noen spørsmål om ting som kan være et problem for noen barn. Jeg ønsker å vite hvor mye problem disse tingene kan være for deg.




Vis barnet svarmuligheten og pek deretter på alternative svar mens du leser spørsmålene for barnet.

Hvis dette ikke i det hele tatt er noe problem for deg, pek på ansiktet som smiler

Hvis det noen ganger er et problem for deg, pek på ansiktet som er i midten

Hvis dette veldig ofte er et problem for deg, pek på det sinte ansiktet

Jeg vil lese hvert spørsmål for deg. Pek på det bildet som viser meg hvor mye dette er vanskelig for deg. La oss først prøve et eksempel.

	Aldri	Noen Ganger	Veldig Mye
1. Det er vanskelig for deg å knipse med fingrene			

Spør barnet om å vise deg knipsingen med fingrene for å avgjøre i hvilken grad spørsmålet har blitt korrekt besvart. Gjenta spørsmålet hvis barnet gir et svar som er forskjellig fra hans eller hennes handling.

Hvor stort problem er dette for deg?

Aldri



Noen
Ganger



Veldig
Mye



ID#

Dato: _____

PedsQLTM

Livskvalitet hos barn

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T. Reinfell og T.H. Diseth, 2002
Tilbakeoversettelse ved E. M. Strømmland
Godkjent av J. W Varni, 2003

FORELDRERAPPORT FOR SMÅ BARN (ALDER 5-7)

INSTRUKSJONER

På følgende side er det en liste med ting som kanskje er et problem for **barnet ditt**. Vennligst fortell oss **hvor stort problem** dette har vært for **barnet ditt** i løpet av **den SISTE måneden** ved å sette en ring rundt..

- 0 hvis det **aldri** er et problem
- 1 hvis det **nesten aldri** er et problem
- 2 hvis det **noen ganger** er et problem
- 3 hvis det **ofte** er et problem
- 4 hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.

Hvis du ikke forstår et av spørsmålene, vennligst spør om hjelp..

Hvor stort **problem** har dette vært for barnet ditt i løpet av den **SISTE måneden...**

FYSISK FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Gå en tur	0	1	2	3	4
2. Løpe	0	1	2	3	4
3. Delta i idrettsaktiviteter eller i lek	0	1	2	3	4
4. Løfte tunge ting	0	1	2	3	4
5. Bade eller dusje alene	0	1	2	3	4
6. Delta i husarbeid / rydde opp i lekene sine	0	1	2	3	4
7. Har vondt eller smerter (Hvor?)	0	1	2	3	4
8. Har lite overskudd og energi	0	1	2	3	4

FØLELSESMESSIG FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Føler seg redd eller skremt	0	1	2	3	4
2. Føler seg nedfor og trist	0	1	2	3	4
3. Føler seg sint	0	1	2	3	4
4. Har problemer med å sove	0	1	2	3	4
5. Bekymrer seg over hva som vil skje med ham/henne	0	1	2	3	4

SOSIAL FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Kommer ikke overens med andre barn	0	1	2	3	4
2. Andre barn vil ikke være hans/hennes venn	0	1	2	3	4
3. Blir plaget eller ertet av andre barn	0	1	2	3	4
4. Kan ikke gjøre ting som andre barn på hans eller hennes alder kan gjøre	0	1	2	3	4
5. Holde følge i lek med andre barn	0	1	2	3	4

SKOLE FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Følge med i klassen	0	1	2	3	4
2. Glemmer ting	0	1	2	3	4
3. Gjøre skolearbeidet sitt	0	1	2	3	4
4. Borte fra skolen fordi han/hun føler seg i dårlig form.	0	1	2	3	4
5. Borte fra skolen for å gå til legen eller sykehuset	0	1	2	3	4

ID# _____

Dato: _____

PedsQLTM

Livskvalitet hos barn

Versjon 4.0 – norwegian

Oversatt til norsk av
T. Reinfjell og T.H. Diseth, 2002
Tilbakeoversettelse ved E. M. Strømstrand
Godkjent av J. W Varni, 2003

FORELDRERAPPORT FOR BARN (alder 8-12)

INSTRUKSJONER

På følgende side er det en liste med ting som kanskje er et problem for **barnet ditt**. Vennligst fortell oss **hvor stort problem** dette har vært for **barnet ditt** i løpet av **den SISTE måneden** ved å sette en ring rundt..

- 0 hvis det **aldri** er et problem
- 1 hvis det **nesten aldri** er et problem
- 2 hvis det **noen ganger** er et problem
- 3 hvis det **ofte** er et problem
- 4 hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.

Hvis du ikke forstår et av spørsmålene, vennligst spør om hjelp..

Hvor stort problem har dette vært for deg i løpet av den SISTE måneden...

MIN HELSE OG AKTIVITETER (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Det er vanskelig for meg å gå en tur	0	1	2	3	4
2. Det er vanskelig for meg å løpe	0	1	2	3	4
3. Det er vanskelig for meg å delta i sport eller lek	0	1	2	3	4
4. Det er vanskelig for meg å løfte tunge ting	0	1	2	3	4
5. Det er vanskelig for meg å bade eller dusje alene	0	1	2	3	4
6. Det er vanskelig for meg å hjelpe til hjemme	0	1	2	3	4
7. Jeg har vondt eller smerter (Hvor?)	0	1	2	3	4
8. Jeg har lite overskudd eller energi	0	1	2	3	4

FØLELSENE MINE (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Jeg føler meg redd eller skremt	0	1	2	3	4
2. Jeg føler meg nedfor og trist	0	1	2	3	4
3. Jeg føler meg sint eller sur/gretten	0	1	2	3	4
4. Jeg har problemer med å sove	0	1	2	3	4
5. Jeg bekymrer meg over hva som vil skje med meg	0	1	2	3	4

HVORDAN JEG KOMMER OVERENS MED ANDRE (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Jeg har problemer med å komme overens med andre barn	0	1	2	3	4
2. Andre barn vil ikke være venner med meg	0	1	2	3	4
3. Andre barn plager eller erter meg	0	1	2	3	4
4. Jeg kan ikke gjøre ting som andre barn på min alder kan	0	1	2	3	4
5. Det er vanskelig for meg å holde følge med andre barn	0	1	2	3	4

SKOLEN (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Det er vanskelig for meg å følge med i klassen	0	1	2	3	4
2. Jeg glemmer ting	0	1	2	3	4
3. Jeg har problemer med å gjøre skolearbeidet mitt	0	1	2	3	4
4. Jeg er borte fra skolen fordi jeg ikke føler meg i form	0	1	2	3	4
5. Jeg er borte fra skolen for å gå til legen eller sykehuset	0	1	2	3	4

ID#

Dato:

PedsQLTM

Livskvalitet hos barn

Versjon 4.0 – Oversatt til norsk av
T. Reinjell og T.H. Diseth, 2002
Tilbakeoversettelse ved E. M. Strømsland
Godkjent av J. W Varni, 2003

BARNERAPPORT (alder 8-12)

INSTRUKSJONER

På den følgende siden er det en liste med ting som kanskje er et problem for deg. Vennligst fortell oss **hvor stort problem** dette har vært for deg i løpet av **den SISTE måneden** ved å sette en ring rundt.....

- 0 hvis det **aldri** er et problem
- 1 hvis det **nesten aldri** er et problem
- 2 hvis det **noen ganger** er et problem
- 3 hvis det **ofte** er et problem
- 4 hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.

Hvis du ikke forstår et av spørsmålene, vær så snill spør om hjelp.

Hvor stort **problem** har dette vært for barnet ditt i løpet av den **SISTE måneden**...

FYSISK FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Gå en tur	0	1	2	3	4
2. Løpe	0	1	2	3	4
3. Delta i drettsaktiviteter eller trening	0	1	2	3	4
4. Løfte tunge ting	0	1	2	3	4
5. Bade eller dusje alene	0	1	2	3	4
6. Delta i husarbeid / rydde opp i lekene sine	0	1	2	3	4
7. Har vondt eller smerter (Hvor?)	0	1	2	3	4
8. Har lite overskudd og energi	0	1	2	3	4

FØLELSMESSIG FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Føler seg redd eller skremt	0	1	2	3	4
2. Føler seg nedfor og trist	0	1	2	3	4
3. Føler seg sint	0	1	2	3	4
4. Har problemer med å sove	0	1	2	3	4
5. Bekymrer seg over hva som vil skje med ham/henne	0	1	2	3	4

SOSIAL FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Komme overens med andre barn	0	1	2	3	4
2. Andre barn vil ikke være hans/hennes venn	0	1	2	3	4
3. Blir plaget eller ertet av andre barn	0	1	2	3	4
4. Kan ikke gjøre ting som andre barn på hans eller hennes alder kan gjøre	0	1	2	3	4
5. Holde følge i lek med andre barn	0	1	2	3	4

SKOLE FUNGERING (problemer med...)	Aldri	Nesten Aldri	Noen Ganger	Ofte	Nesten Alltid
1. Følge med i klassen	0	1	2	3	4
2. Glemmer ting	0	1	2	3	4
3. Gjøre skolearbeidet sitt	0	1	2	3	4
4. Borte fra skolen fordi han/hun føler seg i dårlig form.	0	1	2	3	4
5. Borte fra skolen for å gå til legen eller sykehuset	0	1	2	3	4

ID# _____
Dato: _____

PedsQLTM

Livskvalitet hos barn

Version 4.0 – norwegian

Oversatt til norsk av
T. Reinfeill og T.H. Diseth, 2002.
Tilbakeoversettelse ved E. M. Strømmland.
Godkjent av J. W. Varni, 2003.

TENÅRINGSRAPPORT (alder 13-18)

INSTRUKSJONER

På den følgende siden er det en liste med ting som kanskje er et problem for deg. Vennligst fortell oss **hvor stort problem** dette har vært for deg i løpet av **den SISTE måneden** ved å sette en ring rundt:

- 0** hvis det **aldri** er et problem
- 1** hvis det **nesten aldri** er et problem
- 2** hvis det **noen ganger** er et problem
- 3** hvis det **ofte** er et problem
- 4** hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.
Hvis du ikke forstår et av spørsmålene, vær så snill spør om hjelp.

Hvor stort **problem** har dette vært for deg i løpet av **den SISTE måneden**...

HELSE OG AKTIVITETER (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Det er vanskelig for meg å gå en tur	0	1	2	3	4
2. Det er vanskelig for meg å løpe	0	1	2	3	4
3. Det er vanskelig for meg å delta i idrettsaktiviteter eller trening	0	1	2	3	4
4. Det er vanskelig for meg å løfte noe tungt	0	1	2	3	4
5. Det er vanskelig for meg å bade eller å dusje alene	0	1	2	3	4
6. Det er vanskelig for meg å delta i husarbeid	0	1	2	3	4
7. Jeg har vondt eller smerter (Hvor?.....)	0	1	2	3	4
8. Jeg har lite overskudd og energi	0	1	2	3	4

FØLELSENE MINE (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Jeg føler meg redd eller skremt	0	1	2	3	4
2. Jeg føler meg nedfor og trist	0	1	2	3	4
3. Jeg føler meg sint	0	1	2	3	4
4. Jeg har problemer med å sove	0	1	2	3	4
5. Jeg bekymrer meg over hva som vil skje med meg	0	1	2	3	4

HVORDAN JEG KOMMER OVERENS MED ANDRE (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Jeg har problemer med å komme overens med andre tenåringer	0	1	2	3	4
2. Andre tenåringer vil ikke være venner med meg	0	1	2	3	4
3. Andre tenåringer erter meg	0	1	2	3	4
4. Jeg kan ikke gjøre ting som andre tenåringer på min alder kan	0	1	2	3	4
5. Det er vanskelig å holde følge med vennene mine	0	1	2	3	4

SKOLEN (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Det er vanskelig for meg å følge med i klassen	0	1	2	3	4
2. Jeg glemmer ting	0	1	2	3	4
3. Jeg har problemer med å gjøre skolearbeidet mitt	0	1	2	3	4
4. Jeg er borte fra skolen fordi jeg ikke føler meg i form	0	1	2	3	4
5. Jeg er borte fra skole fordi jeg skal til legen/sykehuset	0	1	2	3	4

ID# _____
Dato: _____

PedsQLTM

Livskvalitet hos barn

Versjon 4.0 – norwegian

Oversatt til norsk av
T. Reinjfell og T.H. Diseth, 2002.
Tilbakeoversettelse ved E. M. Strømsland.
Godkjent av J. W Varni, 2003.

FORELDRERAPPORT FOR TENÅRINGER (alder 13-18)

INSTRUKSJONER

På følgende side er det en liste med ting som kanskje er et problem for **tenåring**er.. Vennligst fortell oss **hvor stort problem** dette har vært for **din tenåring** i løpet av **den SISTE måneden** ved å sette en ring rundt:

- 0** hvis det **aldri** er et problem
- 1** hvis det **nesten aldri** er et problem
- 2** hvis det **noen ganger** er et problem
- 3** hvis det **ofte** er et problem
- 4** hvis det **nesten alltid** er et problem

Det er ingen riktige eller gale svar.

Hvis du ikke forstår et av spørsmålene, vennligst spør om hjelp.

Hvor stort problem har dette vært for din tenåring i løpet av den *SISTE* måneden...

FYSISK FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Gå en tur	0	1	2	3	4
2. Løpe	0	1	2	3	4
3. Delta i idrettsaktiviteter eller trening	0	1	2	3	4
4. Løfte tunge ting	0	1	2	3	4
5. Bade eller dusje alene	0	1	2	3	4
6. Delta i husarbeid	0	1	2	3	4
7. Har vondt eller smerter (Hvor?)	0	1	2	3	4
8. Har lite overskudd og energi	0	1	2	3	4

FØLELSESMESSIG FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Føler seg redd eller skremt	0	1	2	3	4
2. Føler seg nedfor og trist	0	1	2	3	4
3. Føler seg sint	0	1	2	3	4
4. Har problemer med å sove	0	1	2	3	4
5. Bekymrer seg over hva som vil skje med ham/henne	0	1	2	3	4

SOSIAL FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Kommer ikke overens med andre tenåring	0	1	2	3	4
2. Andre tenåring vil ikke være hans/hennes venn	0	1	2	3	4
3. Blir plaget eller ertet av andre tenåring	0	1	2	3	4
4. Kan ikke gjøre ting som andre tenåring på hans eller hennes alder kan gjøre	0	1	2	3	4
5. Holde følge i aktiviteter med andre tenåring	0	1	2	3	4

SKOLE FUNGERING (problemer med...)	Aldri	Nesten aldri	Noen ganger	Ofte	Nesten alltid
1. Følge med i klassen	0	1	2	3	4
2. Glemmer ting	0	1	2	3	4
3. Gjøre skolearbeidet sitt	0	1	2	3	4
4. Borte fra skolen fordi han/hun føler seg i dårlig form	0	1	2	3	4
5. Borte fra skolen for å gå til legen eller sykehuset	0	1	2	3	4

General health questionnaire (GHQ)

Dato: ___/___/90

Vi vil gjerne vite hvordan din helse har vært de siste 2 ukene.

Vær vennlig å besvare alle spørsmålene ved å streke under det svaret du vurderer som den beste beskrivelsen av deg selv.

Husk at vi ønsker å vite om de eventuelle besvår du har nå eller har hatt gjennom de siste par ukene før innleggelsen/ denne undersøkelsen.

Det er viktig at du besvarer alle spørsmålene.

Har du i løpet av de siste par ukene:

1. Vært i stand til å konsentrere deg (fullt ut) om alt du har gjort?	Bedre enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
2. Ligget våken på grunn av bekymringer?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
3. Hatt lett for å våkne etter at du har sovnet?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
4. Vært i stand til å holde deg selv engasjert og i virksomhet?	Bedre enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
5. Vært ute blant andre så mye som du pleier?	Mer enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
6. Klart deg like bra som folk flest i samme situasjon?	Bedre enn de fleste	Omtrent som vanlig	Heller mindre enn vanlig	Mye mindre enn vanlig
7. Føler du at du i det store og hele greier deg bra?	Bedre enn vanlig	Omtrent som vanlig	Mindre bra enn vanlig	Mye mindre bra
8. Vært fornøyd med den måten du fungerer på?	Mer fornøyd	Omtrent som vanlig	Mindre enn vanlig	Mye mindre fornøyd
9. Vært i stand til å føle varme og hengivenhet for dine nærmeste?	Bedre enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
10. Funnet det lett å komme ut av det det med andre mennesker?	Bedre enn vanlig	Omtrent som vanlig	Mindre bra enn vanlig	Mye mindre enn vanlig
11. Brukt mye tid på å hygge deg med andre?	Mer tid enn vanlig	Omtrent som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
12. Følt at du tar del i ting på en nyttig måte?	Mer enn vanlig	Som vanlig	Mindre enn vanlig	Mye mindre brukbart

13. Følt at du er i stand til å ta bestemmelser?	Mer enn vanlig	Som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
14. Følt deg stadig under press?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
15. Følt deg ute av stand til å mestre dine vanskeligheter?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
16. Følt livet som en kamp hele tiden?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
17. Vært i stand til å glede deg over dine daglige gjøremål?	Mer enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
18. Tatt tingene tungt?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
19. Blitt engstelig eller panisk uten grunn?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
20. Vært i stand til å møte dine problemer?	Mer enn vanlig	Samme som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
21. Synes at alt vokser over hodet på deg?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
22. Følt deg ulykkelig og nedtrykt (deprimert)?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
23. Mistet selvtilliten?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
24. Tenkt på deg selv som en verdiløs person?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
25. Følt at livet er helt håpløst?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
26. Sett lyst på din framtid?	Bedre enn vanlig	Omtrent som vanlig	Mindre enn vanlig	Mye mindre enn vanlig
27. Stort sett følt deg tilfreds, alt tatt i betraktning?	Mer enn vanlig	Som vanlig	Heller mindre enn vanlig	Mye mindre enn vanlig
28. Stadig følt deg nervøs og anspent/ oppjaget?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
29. Følt at livet ikke er verdt å leve?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig
30. Følt at du til tider ikke var i stand til å gjøre det minste fordi nervene dine var i ulage?	Ikke i det hele tatt	Ikke mer enn vanlig	Heller mer enn vanlig	Mye mer enn vanlig

The quality of life scale (QOLS)

ID.NR.
 MOR:
 FAR:

Spørsmål vedrørende din egen vurdering av tilfredshet med livet QOLS

Vennligst les gjennom hvert punkt og sett en ring rundt det tallet som best beskriver hvor fornøyd du er for tiden.

NB! Selv om du for tiden ikke deltar i noen aktivitet eller har noe forhold, ber vi deg besvare hvert punkt.

Du kan være fornøyd eller misfornøyd med ikke å delta i aktiviteten eller ha noe forhold.

	Svært fornøyd	Fornøyd	Stort sett fornøyd	Blandet	Stort sett misfornøyd	Misfornøyd	Svært misfornøyd
1. <u>Materielle goder</u> ; slik som hjem, mat, bekvemmeligheter, økonomisk trygghet	7	6	5	4	3	2	1
2. <u>Helse</u> ; slik som fysisk i form og energisk	7	6	5	4	3	2	1
3. <u>Forholdet til foreldre, søsken og andre slektninger</u> ; slik som kontakt, besøk, hjelp	7	6	5	4	3	2	1
4. <u>Ha og oppdra barn</u>	7	6	5	4	3	2	1
5. <u>Forholdet til ektefelle/samboer eller tilsvarende</u>	7	6	5	4	3	2	1
6. <u>Nære venner</u>	7	6	5	4	3	2	1
7. <u>Hjelpe og gi oppmuntring til andre, delta i frivillig engasjement, gi råd</u>	7	6	5	4	3	2	1
8. <u>Deltakelse i organisasjoner eller offentlig virksomhet</u>	7	6	5	4	3	2	1
9. <u>Studier</u> ; slik som skolegang, øke din forståelse, utvide dine kunnskaper	7	6	5	4	3	2	1
10. <u>Egenforståelse</u> ; slik som å kjenne dine sterke sider og dine begrensninger – vite hva livet dreier seg om	7	6	5	4	3	2	1
11. <u>Arbeid</u> ; slik som yrkeslivet eller i hjemmet	7	6	5	4	3	2	1
12. <u>Skapende aktiviteter</u> ; slik som musikk, kunst, poesi etc	7	6	5	4	3	2	1

13. <u>Sosial omgang</u> ; slik som å møte andre mennesker, gjøre ting, festligheter etc	7	6	5	4	3	2	1
14. <u>Les, lytte til musikk eller se på underholdning</u>	7	6	5	4	3	2	1
15. <u>Fysisk aktiv fritid</u> ; slik som sport, reiser, dans, turer	7	6	5	4	3	2	1
16. <u>Uavhengighet, gjøre noe på egenhånd</u>	7	6	5	4	3	2	1

