General Discussion
GENERAL DISCUSSION

Nutrition is of paramount importance for life and health, providing fuel sources to maintain energy-equilibrium, building blocks of cellular structures and a large variety of vitamins, minerals and other chemical compounds required for optimal cellular metabolism and homeostasis. Although guidelines state that a healthy diet is important in the management of kidney transplant recipients, this is mainly based on extrapolation of findings from high risk groups in the general population and patients with chronic kidney disease, while little is known about the specific population kidney transplant recipients. Accordingly, the evidence supporting recommendations for kidney transplants recipients is almost invariably rated as low, the majority being opinion-based.

In this thesis, we pursue to strengthen the empirical basis for dietary recommendations in kidney transplant recipients. To this purpose, we conducted a number of longitudinal association studies in available data, and moreover, for better future studies we designed and established a well-documented prospective cohort of kidney transplant recipients, that includes not only biomedical data, but also extensive data on nutrition and other lifestyle factors, and outcome data: the Transplantlines cohort.

The studies in the thesis in particular aimed to explore whether nutritional factors could serve as potential modifiable risk factors to improve long term outcome after kidney transplantation. Nutrition could be important for the prevention and management of a multitude of health-related problems that kidney transplant recipients experience (i.e. metabolic disorders, infections, cognitive dysfunction, gastro-intestinal complaints, malignancies etc.). Our studies mainly focused on cardiovascular disease, graft failure and mortality, as major components of the burden of disease in this population. To this purpose, we studied the associations of several aspects of nutrition, including dietary intake of individual food components, diet quality and malnutrition on these long-term outcomes in stable outpatient kidney transplant recipients. We focused on the intake of marine-derived omega-3 polyunsaturated fatty acids as well as fruit and vegetables, as these nutrients and foods have been postulated to be cardioprotective. We further investigated the role of diet quality by assessing dietary adherence to the Dietary Approaches to Stop Hypertension and...
the Mediterranean diet, which both favorably affect cardiovascular health\textsuperscript{22-25} and have also been associated with a lower risk of chronic kidney disease\textsuperscript{26}.

**Omega-3 Poly-Unsaturated Fatty Acids**

Both eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) are considered non-essential amino acids because they can be synthesized from alpha-linoleic acid (ALA). However this process is extremely limited in humans since less than 5\% of ALA is converted to EPA and less than 0.5\% of ALA is converted to DHA\textsuperscript{27}. Therefore, consumption of dietary sources rich in EPA and DHA, mainly fatty fish, is necessary to reach sufficient amounts of these fatty acids in human tissue.

In this thesis we examined EPA and DHA intake in 627 stable kidney transplant recipients and found that in more than 75\% of kidney transplant recipients intake of EPA and DHA below recommended intake of 250-500 mg/day\textsuperscript{28}. Importantly, in prospective analyses we observed that EPA and DHA intake was inversely associated with all-cause mortality in kidney transplant recipients and observed an association of similar magnitude, though non-significant, of EPA and DHA intake with cardiovascular mortality. These findings are in line with findings from Eide et al. who demonstrated in a cohort of 1990 kidney transplant recipients that higher plasma phospholipid EPA and DHA concentrations were independently associated with lower all-cause and cardiovascular mortality\textsuperscript{29}. Moreover, recently published results from the ORENTA trial showed that 44 weeks of omega-3 fatty acid supplementation in kidney transplant recipients lowered triglycerides and CRP concentrations and improved flow-mediated arterial dilation and orthostatic heart-rate variability, further supporting a beneficial role for EPA and DHA intake in optimizing cardiometabolic health of kidney transplant recipients\textsuperscript{30,31}.

In this thesis we found no association between EPA and DHA intake and mortality in kidney transplant recipients that were smokers. Smokers are known to have lower tissue levels of omega-3 fatty acids compared to non-smokers and these differences are independent of dietary intake\textsuperscript{32}. An altered EPA and DHA metabolism and increased omega-3 lipid peroxidation in smokers likely is responsible for these differences and might also explain the findings from our study\textsuperscript{32,33}. Furthermore, we observed that the favorable association between EPA and DHA intake was also affected by age and was most pronounced in the group
of older subjects. The exact mechanisms responsible for this interaction with age is not completely clear, however this might be attributable to favorable effects of EPA and DHA on anabolic resistance which may help prevent the development of age-related sarcopenia. Over the last decades, the role of EPA and DHA in cardiovascular disease have received great attention but remains controversial. The mechanisms by which EPA and DHA may benefit cardiovascular disease are considered to be multifactorial and are yet to be fully clarified, however it has been proposed that reducing susceptibility for ventricular arrhythmia, retarding growth of atherosclerotic plaques, reducing adhesion molecule expression, reducing platelet-derived growth factor, promoting nitric oxide-induced endothelial relaxation and anti-inflammatory effects may be mechanisms involved. Numerous observational studies in the general population have shown favorable associations omega-3 polyunsaturated fatty acids with cardiovascular outcomes and early trials including the DART, GISSI-P, JELIS and GISSI-HF studies showed favorable effects of omega-3 fatty acids on cardiovascular outcomes. Otherwise, more recent studies such as the Alpha Omega, OMEGA, SU.FO.OM3, ORIGIN, AREDS2, and Risk & Prevention Study reported neutral effects. The discrepancy between these findings may result from limitations, including short follow-up, a long event-to-enrollment interval in secondary prevention, low omega-3 dose, and high background fish intake. Additionally, a lower than expected event rate, likely due to improved standard care, has limited the statistical power in several studies to detect a beneficial effect of omega-3 fatty acids. Moreover, 3 recently published large trials demonstrated beneficial effects of omega-3 supplementation on vascular death in patients with type 2 diabetes, heart attacks and coronary heart disease in elderly, and cardiovascular disease in statin-treated patients with hypertriglyceridemia, adding to the evidence that omega-3 polyunsaturated fatty acids do provide additional benefit in the prevention of cardiovascular disease.

## FRUIT AND VEGETABLES

### Fruit and Vegetable consumption and Cardiovascular Mortality

Results from observational studies in the general population have consistently shown favorable associations of fruit and vegetable consumption with cardiovascular outcomes. In line with these studies performed, we showed
that vegetable consumption also is associated with lower risk of cardiovascular and all-cause mortality in kidney transplant recipients. We observed a ± 50% lower risk for cardiovascular mortality and a 25% lower risk for all-cause mortality per each increase in vegetable serving per day, independent of age, sex, income and education level. Additional adjustment for other potential confounders did not materially affect this association. Furthermore, we demonstrated that fruit intake is associated with cardiovascular and all-cause mortality risk in kidney transplant recipients with an eGFR > 45 ml/min/1.73m² or without proteinuria, but not in the subgroup of kidney transplant recipients with an eGFR < 45 ml/min/1.73m² or proteinuria. There are likely multiple mechanisms by which higher consumption of fruits and vegetables may exert protective effects, particularly, on cardiovascular mortality. For instance, beneficial effects of fruit and vegetable have been attributed to various bio-active compounds with anti-oxidant properties that may prevent oxidative modification of LDL and/or other oxidative events that play a key role in the development and progression of atherosclerosis.

Additionally, it has been postulated that other nutritional compounds including, fiber, potassium and magnesium may help reduce cardiovascular risk as well. Furthermore, in our study, kidney transplant recipients with higher intakes of fruits and vegetables had lower HOMA-IR scores compared to those with lower fruit and vegetable intake. HOMA-IR is a marker for insulin resistance and has been associated with increased risk of development of cardiovascular disease and mortality in the general population. Importantly, insulin resistance plays a central role in the development of diabetes, a condition that conveys a 2-3 higher risk of cardiovascular disease in kidney transplant recipients. However, we also demonstrated that the favorable associations of fruit intake were modified by kidney function, and we observed no significant associations in the subgroup of subjects with poor kidney function. The modifying effect by kidney function observed in the analyses regarding fruit intake but not in those with vegetable could originate from differences in nutrient content, such as the higher fructose content in fruits. Fructose is used as a substrate for gluconeogenesis, but via fructolysis can also lead to production of inflammatory mediators such as uric acid. Consequently, accumulation of uric acid due to impaired renal uric acid excretion may negate the favorable effects of fruit consumption in kidney transplant recipients with poor kidney function and explain the observed modifying effect by kidney function in our study.
Fruit and Vegetable consumption and Post-Transplant Diabetes Mellitus

In Chapter 4 we investigated the associations between fruit and vegetable intake and the development of post-transplantation diabetes mellitus after kidney transplantation. In this study we included 472 stable kidney transplant recipients without diabetes at baseline of whom 52 developed post-transplant diabetes mellitus during ± 5.2 years of follow-up. Similar to our previous findings, fruit and vegetable consumption was considerably lower than current guidelines in the general population. In this study, we did not observe a significant association of fruit intake with development of PTDM. Fruit intake has been described to reduce the risk of diabetes in the general population\textsuperscript{66,67}. It might be that in our study variation of fruit intake was too low or too few events of PTDM occurred, or a combination of both, for us to observe an otherwise existing association. Alternatively, it might be that kidney transplant recipients are particularly susceptible to the adverse effects of fructose, which is present in large amounts in fruits and may predispose patients to weight gain and the metabolic syndrome\textsuperscript{68}. We did, however, observe that vegetable intake was inversely associated with the development of post-transplant diabetes mellitus. In additional analyses we further demonstrated that in particular intake of cruciferous and green-leafy vegetables appears to reduce the risk to develop post-transplant diabetes mellitus. These findings are consistent with several meta-analyses of studies in the general population that have also demonstrated vegetable intake, or subcategories of vegetables, to be inversely associated with the risk for diabetes\textsuperscript{69–74}. In this thesis we also demonstrated that the favorable association between vegetable intake and diabetes development could be partially be attributed to a better metabolic profile (i.e., higher HDL-cholesterol and lower triglycerides and waist circumference). The underlying mechanisms underlying the favorable associations between vegetable intake with metabolic health and development of post-transplant diabetes mellitus are likely multifactorial. Bioactive compounds in vegetables, such as anti-oxidants and magnesium reduce pancreatic B-cell dysfunction induced by oxidative stress\textsuperscript{75} and improving insulin signaling\textsuperscript{76}. Also, since vegetables are rich sources of dietary fibers, favorable metabolic effects that have been attributed to dietary fibers such as improved satiety, post-prandial hyperglycemia and insulin sensitity\textsuperscript{77} are likely to contribute as well. In theory, the favorable associations on metabolic profile and risk of PTDM observed in our study might also result from food displacement of less-healthy foods\textsuperscript{78,79}, which we did not account for in this study.
Altogether our findings underline the importance of adequate fruit and vegetable intake to improve cardiovascular health in kidney transplant recipients. In the general population, consumption of 4-5 servings of fruits and vegetables per day each is recommended for the prevention of cardiovascular disease\textsuperscript{80}. In this thesis we used data from two cohorts of stable outpatient kidney transplant recipients and observed on average fruit and vegetable intake was considerably lower than current recommendations. Food choice, including consumption of fruit and vegetable, is determined by a variety of factors including personal, economic, cultural and environmental factors\textsuperscript{81–83}. Recently, in kidney transplant recipients several transplant-related factors have been identified that may further hinder the consumption of fruits and vegetables\textsuperscript{84}. Reported barriers included food-drug interactions, low priority in disease management and dietary restrictions to prevent food-borne infections, but also difficulties in diet transition were reported as important barriers to comply to recommended amounts of fruits and vegetables intake. A pro-active approach to identify and address these barriers may prove to be pivotal in attempts to improve fruit and vegetable intake and should be included in the nutritional counseling of kidney transplant recipients.

**Dietary Patterns**

Traditionally, research and dietary recommendations for patient with chronic kidney disease has predominantly been nutrient-based which focuses on quantities of single nutrient intake without specific emphasis on overall diet quality\textsuperscript{85}. Importantly, the nutrient-based approach does not allow for complex interactions among nutrients, or for cumulative effects of nutrients to be taken into account, and the high correlation between some nutrients in the diet makes it difficult to examine their separate effects\textsuperscript{86}. Although these limitations are less evident when studying single food products, it should be realized that people consume meals consisting of a variety of foods and studying the overall diet rather than single nutrients or foods may better encompass the total health potential of a diet\textsuperscript{87}.

**Dietary Approaches to Stop Hypertension**

In Chapter 5 we investigated the adherence to the Dietary Approaches to Stop Hypertension (DASH) and associations with kidney function decline and mortality in kidney transplant recipients. The DASH diet has been designed to lower blood
pressure and as expected kidney transplant recipients with better adherence to
the DASH diet exhibited lower blood pressure. Compared to subjects in the lowest
tertile of adherence to the DASH diet, both systolic and diastolic blood pressure were
approximately 5 mmHg lower in subjects in the highest tertile of adherence. More
or less effects of similar magnitude were also demonstrated in the original DASH
trial that reported a 5.5 and 3.0 mmHg lowering effect by the DASH diet on systolic
and diastolic blood pressure, respectively. Importantly, in our study the majority
received antihypertensive drugs which would suggest that the blood pressure
lowering effect of the DASH diet further adds to pharmacological interventions
to control blood pressure. Kidney transplant recipients with better adherence to
the DASH-diet also showed a more favorable lipid profile, demonstrated by higher
HDL-cholesterol levels and lower triglycerides levels at baseline. We showed that
compared to subjects in the lowest tertile of adherence to the DASH diet those in
the highest tertile had a significant lower risk to develop kidney function decline
(HR 0.46; 95%CI 0.28-0.76, P=0.002) and had significant lower mortality risk (HR
0.48; 95%CI 0.30-0.77, P=0.002). Additional adjustment for several potential
confounders did not materially affects these results. Furthermore, baseline eGFR
appeared to affect the associations between DASH adherence with outcomes and
favorable outcomes were most pronounced in kidney transplant recipients with
higher eGFR at baseline. Our findings are supported by studies in the general
population that showed adherence DASH diet to be associated lower risk of
rapid eGFR decline, lower mortality risk in hypertensive adults and lower risk
of ESKD in patients with moderate CKD and hypertension. High blood pressure
considerably increases the risk of graft failure and mortality in kidney transplant
recipients. It thus seems plausible that the favorable associations between
DASH adherence with kidney function preservation and mortality observed in our
study may be attributed to the blood lowering effect of the DASH diet. In addition,
the more favorable lipid profile and lower prevalence of proteinuria in kidney
transplant recipients with higher adherence to the DASH diet likely also have
contributed to the lower risk for kidney function decline and mortality risk.
Nevertheless, the favorable associations of adherence to the DASH diet and study
outcomes remained significant after adjustment for baseline blood pressure and
lipid profile, indicating other mechanisms are likely also involved that remain to
be elucidated.
Mediterranean Diet

We extended our research on potential benefits of diet quality on preservation of kidney function in Chapter 6, where we focused on the Mediterranean diet. In contrast to the DASH-diet, the Mediterranean diet is not designed, but is a dietary pattern traditionally consumed by inhabitants of the Mediterranean region. The Mediterranean diet is one of the most extensively studied dietary patterns and has demonstrated to reduce the risk of diabetes, cardiovascular disease, and mortality in the general population\textsuperscript{96,97}. Moreover, epidemiological studies in the general population Mediterranean diet indicate that the Mediterranean diet may also benefit kidney function preservation\textsuperscript{98-101}. In this thesis we demonstrated that better adherence to the Mediterranean diet is inversely associated with graft failure (HR 0.68; 95%CI 0.50-0.91, \textit{p}=0.01), kidney function decline (HR 0.68; 95%CI 0.55-0.85, \textit{p}=0.001) and graft loss (HR 0.74; 95%CI 0.63-0.88, \textit{p}=0.001) independent of potential confounders, including age, sex, body surface area, primary kidney disease, eGFR, 24-hr protein excretion, time after transplantation, HLA-mismatches, living donor kidney, pre-emptive transplantation. Additional adjustment for other potential confounders including immunosuppressive drug use, cardiovascular risk factors, antihypertensive treatment and other lifestyle related parameters did not materially alter these results. We also observed that the magnitude of these associations was modified by severity of proteinuria and time after transplantation. For example, we estimated that each 2-point increase in kidney transplant recipients with proteinuria of 3g/24h conveyed a 50% risk reduction on graft failure while in those with milder proteinuria, i.e. 0.5g/24h, a risk reduction of 26% was observed. Considering proteinuria is a major risk factor for graft failure\textsuperscript{95}, it seems likely that factors that potentially attenuate or delay progression of proteinuria could be particularly beneficial in those exhibiting severe proteinuria. Previously, a higher incidence of albuminuria was observed in Greek adolescent with poor adherence to the Mediterranean Diet and it was postulated that the Mediterranean diet may alleviate albuminuria through beneficial effects on endothelium, atherosclerosis and inflammation\textsuperscript{102}. Also, kidney transplant recipients who were more recently transplanted appeared to benefit the most of better adherence to the Mediterranean diet in our study and suggest that interventions to improve adherence to the Mediterranean diet should be made sooner rather than later following kidney transplantation.
Overall, the DASH and Mediterranean diet are very similar, and both diets are nutritionally balanced because no foods groups are explicitly prohibited. Hence, the question arises which diet kidney transplant recipients should follow. Recently, the European Renal Nutrition Working Group proposed the Mediterranean diet as the diet of choice for patients with chronic kidney disease due to its favorable effects on cardiovascular and kidney health\textsuperscript{103}. When we compare the associations between the DASH and Mediterranean diet on kidney function decline provided in \textbf{Chapter 5} and \textbf{6}, it appears that the Mediterranean diet is more significantly associated with kidney function decline. Food components that we accounted for in scoring adherence to the Mediterranean diet but not to the DASH diet, such as fish and the ratio monosaturated to saturated fatty acids, could be responsible for this difference. Recently, supplementation with EPA and DHA was shown to protect against chronic allograft damage and graft fibrosis in kidney transplant recipients\textsuperscript{30} and also experimental studies demonstrate beneficial effects of high monounsaturated and low saturated fatty acids intake on kidney structure and function\textsuperscript{104,105}. Nevertheless, it remains difficult to draw firm conclusions on the best diet for kidney transplant recipients based on these observational studies that shows both adherence to the DASH and Mediterranean diet to be inversely associated with kidney function decline. Moreover, the interaction between kidney function parameters and dietary adherence observed in our studies indicate that nutritional requirements may differ across different stages of kidney disease severity and warrant further investigation.

**MALNUTRITION**

In \textbf{Chapter 7}, we studied the prevalence of malnutrition in outpatient kidney transplant recipients and its relation with Quality of Life and mortality risk. In 593 kidney transplant recipients with a functioning graft $\geq$ 1 year, we observed that 9% of all kidney transplant recipients were malnourished. The prevalence of malnutrition in our cohort is comparable, though somewhat lower, with findings from Westland et al who reported a 11% prevalence in non-dialysis dependent patients with CKD stage 3-5 in the Netherlands\textsuperscript{106}. On the other hand, the few studies that have investigated nutritional status in outpatient kidney transplant recipients have reported higher prevalence rates varying from 28% to 51%\textsuperscript{107-109}. The discrepancy in these prevalence rates could be attributed to regional
differences or to variation of tools used to assess malnutrition. However the higher albumin levels, a nutritional biomarker, in our kidney transplant recipients compared to those included in the studies by Malgorzewich et al\textsuperscript{108} and Molnar et al\textsuperscript{109} suggests that kidney transplant recipients in our study overall had a better nutritional status. Yet, the prevalence of malnutrition in these stable outpatients – with a mean age of 55 ± 14 years - is markedly higher than in the general population in the Netherlands. A malnutrition prevalence of ~10% corresponds to the population that received some form of home care, and to primary care populations over 70-75 years of age\textsuperscript{110}.

In this thesis we demonstrated that malnutrition was more frequently present in kidney transplant recipients who were female, widowed or had diabetes. We observed no differences in body weight or body mass index between kidney transplant recipients with and with malnutrition, although body weight and body mass index are often used in malnutrition screening tools. However, our data does show that body composition of kidney transplant recipients with malnutrition was different from those without malnutrition, as we observed that that lean body mass and creatinine excretion, a surrogate marker for muscle mass\textsuperscript{111}, was markedly lower in malnourished kidney transplant recipients. It therefore seems that body weight or body mass index are not appropriate measures to identify malnutrition in kidney transplant recipients, which might be explained by the inability of body mass index to distinguish between different types of body tissue. Furthermore, we observed that malnutrition in kidney transplant recipients was independently associated with lower Quality of Life and was most pronounced in the physical domain of Quality of Life ($\beta$ -11.5; 95%CI -14.3 to -8.7, P<0.001) and to a lesser extent with the mental domain of Quality of Life ($\beta$ -5.9; 95%CI -8.8 to -3.0, P<0.001). Importantly, malnutrition was associated with a >3 times higher mortality risk in kidney transplant recipients (HR 3.23; 95%CI 1.35 – 7.73, P=0.008), which was comparable with findings of Molnar et al. who used the Malnutrition-Inflammation Score to define malnutrition (MIS >3: HR 3.32; 95%CI 1.99 - 5.54)\textsuperscript{109}. Due to the observational nature of this study we were not able to investigate whether improving nutritional status improved quality of life or survival although results from studies in other populations do support this notion. Beneficial effects of nutritional interventions on quality of life have been demonstrated in malnourished subjects with Parkinson’s disease\textsuperscript{112} and elderly\textsuperscript{113}.
and nutritional intervention reduces mortality risk by 48% in malnourished medical inpatients\textsuperscript{114}. Therefore, attempts to increase vigilance and counteract malnutrition in kidney transplant recipients are warranted and systematically screening for undernutrition at the outpatient clinic should be considered.

**OVERALL CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE**

As illustrated throughout the chapters of this thesis, the relevance of nutrition in the management of kidney transplant recipients should not be overlooked as it could offer a great opportunity to improve long-term outcome. In this thesis we have investigated several aspects of nutrition, including dietary intake of individual ‘healthy’ nutrients, and foods, overall diet quality and malnutrition, and have linked them with long-term outcomes following transplantation. Consistently, we showed that kidney transplant recipients scoring poorly on nutritional indices had a considerably poorer prognosis underlining its importance.

Hence, efforts should be made to increase awareness of the importance of nutrition on health in health-care providers and importantly also in patients. Moreover, attention should be directed toward creating effective and efficient strategies to detect patients with poor dietary intake and/or malnutrition that require nutritional treatment. Implementation of such screening strategies can be challenging as the population of kidney transplant recipients continues to grow and healthcare resources are limited. However, the ongoing digitization of healthcare and electronic health records that allow patients to fill out screening questionnaires could provide excellent possibilities to accommodate a systematic nutritional screening strategy and should be explored.

Of note, our aim to reinforce the empirical basis for nutritional management in kidney transplant recipients can be considered part of a broader expressed need for better data and better strategies on lifestyle management in patients with chronic disease, resulting in the emergence of what is now called Lifestyle Medicine\textsuperscript{115}. In this context, the kidney transplant population represents a small niche. Yet, by the combination of a high burden of lifestyle-associated morbidity and mortality, and a well-documented routine follow-up infrastructure, rapid progress can be generated, as demonstrated by the studies in this thesis. This provides an excellent starting point for observational cohort studies beyond the
routinely available data, both for evaluation of non-routine outcome parameters, and for exploration of underlying mechanisms.

**DESIGN OF TRANSPANTLINES AND FUTURE PERSPECTIVES**

In the last chapter of this thesis, Chapter 8, the design of the TransplantLines Study is described. Over the years, organ transplantation has developed into an established treatment option for patients with end-organ dysfunction. Nevertheless, many challenges remain in the field of transplantation as transplant recipients are often affected by a multitude of cardiovascular-, renal-, neurological- and gastro-intestinal complications, and are prone to infections and malignancies, contributing to a high morbidity and mortality. To provide a better understanding of the causative factors driving these manifestations and their impact, we designed the TransplantLines study. The TransplantLines Study is a multidisciplinary longitudinal observational cohort that has the capacity to address a wide range of research topics and can provide hypothesis-generating discoveries to drive future research in the field of transplantation. Importantly, the TransplantLines Study is not restricted by narrow inclusion and exclusion criteria, as often seen in randomized controlled trials that hinder generalizability, and provides data reflecting the clinical reality which can also be used to evaluate current and future policies of care.

The TransplantLines Study will contain a large biobank containing tissue, blood, feces and urine samples of transplant recipients and living organ donors of all solid-organ transplant programs at the University Medical Center Groningen. Additionally, the biobank will be complemented with routine collected health data and detailed information regarding body composition, physical performance, cognitive functioning, experienced symptom burden, socioeconomic status, lifestyle factors and quality of life. By investigating a wide range of clinical, social/psychological and biochemical parameters, the TransplantLines Study allows for a better understanding of causal and modifiable risk factors involved in the development of comorbidities, graft failure and mortality following solid-organ transplantation. Moreover, by incorporating Patient Related Outcomes Measures, the TransplantLines Study adds to the development of more patient-centered approach to transplant care with emphasis on improving quality of life.
The TransplantLines Study also allows us to continue and extend our research regarding nutritional aspects of health in the field of transplantation. It would seem tempting to suggest that a randomized controlled trial would be the next step to consolidate the findings of this thesis, however several findings in this thesis warrant further investigation to determine the feasibility of such a study. For example, in this thesis we observed that the inverse association between EPA and DHA and mortality was modified by age and smoking behavior, suggesting EPA and DHA requirements may vary among smokers and younger subjects. It would be interesting to combine data on dietary EPA and DHA intake with measurements on functional biomarkers of EPA and DHA to determine whether this could be explained by age- and smoking-related alterations in metabolic handling of EPA and DHA. Additional measurements on dietary and kidney damage biomarkers could also help to better understand why favorable associations between fruit intake and adherence to the DASH diet were not observed in patients with an eGFR $< 45 \text{ ml/min/}1.73\text{m}^2$. Furthermore, in this thesis we mainly focused on patient and graft survival as study endpoints of interest. Nevertheless, there are likely various less definitive health-related problems in kidney transplant recipients (e.g. infections, non-fatal cardiovascular events, malignancies, gastro-intestinal complaints, cognitive dysfunction, sarcopenia, osteoporosis etc.) that could be affected by nutritional factors which remain to be investigated and could serve as intermediate endpoints.

All-in-all, we hope that with these efforts on improving nutritional care and dietary recommendations in renal transplant recipients, next steps can be made towards further improvement of long-term outcomes, in terms of fewer complications, better patient and graft survival and higher quality of life after kidney transplantation.
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