Novel approaches to assess diet and kidney health risk

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Nederlandse samenvatting

Chronische nierschade is een wereldwijd probleem dat 8 tot 16% van de wereldbevolking treft. Chronische nierschade wordt vaak in de loop van de tijd erger, met uiteindelijk nierfalen als gevolg. Het is ook een belangrijke oorzaak van vroegtijdig overlijden en hart- en vaatziekten. Patiënten met nierfalen hebben nierfunctie vervangende therapie nodig, zoals dialyse of niertransplantatie, met slechte prognose en hoge kosten als gevolg. Hoewel verschillende medicijnen, zoals blokkers van het renine-angiotensine systeem en natriumglucose-cotransporter 2 (SGLT2) remmers, de achteruitgang in nierfunctieverlies bij patiënten met chronische nierschade vertragen, zijn er dringend betere preventieve strategieën nodig om het ontstaan van chronische nierschade te voorkomen of uit te stellen en hierdoor de ziektelast op bevolkingsniveau te verminderen. Het aanpassen van leefstijl, waaronder een gezond dieet, is een belangrijke preventieve strategie om chronische nierschade te voorkomen.

Van oudsher is voedingsonderzoek binnen de nefrologie met name gericht op individuele voedingsstoffen en voedingsmiddelen bij patiënten met (ernstige) chronische nierschade of bij niertransplantatiepatiënten. Tegenwoordig wordt er steeds meer nadruk gelegd op de mogelijke rol van voedingsfactoren, zoals nutriënten, voedingsgroepen en voedingspatronen, in de preventie van ziekten. Dit proefschrift beschrijft verschillende nieuwe benaderingen om de rol van voeding als beïnvloedbare determinant van nierfunctie te bepalen. Deze nieuwe benaderingen kunnen leiden tot betere preventie van chronische nierschade, omdat ze beter rekening houden met de complexiteit van voeding en voedingsinname in de praktijk.

Hoofdstuk 1 geeft een korte introductie over chronische nierschade, verschillende methodes om voedingsfactoren in de voedingsepidemiologie te beoordelen en beschrijft het doel van dit proefschrift.

Hoofdstuk 2 beschrijft de ruimtelijke clustering van nierfunctie op wijkniveau in Noord-Nederland. Deze ruimtelijke verschillen in nierfunctie kunnen op zijn minst gedeeltelijk verband houden met voedingspatronen op buurtniveau. Daarnaast bleek er een rol voor luchtverontreiniging. De clustering van nierfunctie binnen bepaalde regio's suggereert dat geografische factoren van belang zijn, ondanks universele toegang tot het gezondheidszorgsysteem in Nederland. Daarom is het belangrijk om rekening te houden met factoren op buurtniveau,

waaronder voedingsfactoren, bij het bepalen van public health strategieën. Uit onze analyse blijkt dat het relevant is om preventieprogramma's uit te breiden tot méér dan een "one size fits all' aanpak en om de gezondheidsverschillen op buurt niveau en de bijbehorende risicofactoren verder in kaart te brengen.

In **Hoofdstuk 3** ontdekten we dat een hoog kwalitatief dieet, gemeten aan de hand van de Lifelines Diet Score, geassocieerd was met een lager risico op het ontwikkelen van chronische nierschade of een afname in nierfunctie van ≥20% in de algemene bevolking. Deze resultaten suggereren dat een gezond dieet, zoals beschreven in de Nederlandse Voedingsrichtlijnen 2015, naast de chronische ziekten waarop de richtlijnen gebaseerd zijn ook mogelijk implicaties heeft voor de preventie van chronische nierschade. De Lifelines Diet Score kan een nuttig hulpmiddel zijn om de kwaliteit van een dieet te evalueren en kan worden aanbevolen als hulpmiddel bij de evaluatie van voedingsstrategieën voor de preventie van chronische nierschade.

Aangezien er een verband lijkt te bestaan tussen gezonde voeding en nierfunctie, is het interessant om te kijken of het dieet verder verfijnd kan worden door een specifiek voedingspatroon samen te stellen dat gunstig is voor de nieren. In **Hoofdstuk 4** hebben we de reduced rank regression (RRR) methode gebruikt om geslacht-specifieke voedingspatronen te identificeren die de variatie in nierfunctie in de algemene populatie kunnen verklaren. Vervolgens ontdekten we dat een hogere score op het nierfunctie-gebaseerde voedingspatroon geassocieerd was met een afname in nierfunctie van ≥20% of het ontwikkelen van chronische nierschade, zowel bij mannen als bij vrouwen. Vergeleken met traditionele onderzoeken die gericht zijn op individuele voedingsstoffen of voedingsmiddelen, zijn voedingspatronen informatiever omdat ze een breder beeld geven van het gebruikelijke voedingsgedrag en rekening houden met de complexe samenstelling van veel voedingsproducten en de interacties tussen voedingsstoffen in voedsel.

In **Hoofdstuk 5** hebben we de RRR-methode toegepast om een voedingspatroon te construeren dat de verklaarde variatie in de componenten van het metabool syndroom bij niertransplantatiepatiënten maximaliseert. Vervolgens vonden we dat ons metabool syndroom-gerelateerde voedingspatroon geassocieerd was met een hoger sterfterisico. Deze resultaten suggereren dat een voedingspatroon gekoppeld aan de componenten van het metabool syndroom het sterfterisico na niertransplantatie kan verhogen. Identificatie van ziekte specifieke voedingspatronen met behulp van de RRR-methode, zoals

geïllustreerd door onze studie voor het nierfunctie-gebaseerde voedingspatroon in de algemene bevolking en metabool syndroom gerelateerde voedingspatroon in niertransplantatiepatiënten, kan nieuwe mogelijkheden bieden voor voedingsinterventies om de niergezondheid te verbeteren.

Preventie van chronische nierschade kan bestaan uit een hogere inname van gezonde voedingsproducten, maar ook het vermijden van ongezonde voedingsmiddelen zoals ultra bewerkte voedingsmiddelen. In **Hoofdstuk 6** ontdekten we dat een hogere consumptie van ultra bewerkte voedingsmiddelen geassocieerd was met een hoger risico op chronische nierschade of een daling in nierfunctie van onafhankelijk van de algehele voedingskwaliteit en andere voedingsindexen. Het vermijden van ultra bewerkte voedingsmiddelen wordt dus beschouwd als een geschikte strategie voor het voorkomen van risico's voor de niergezondheid.

In dit proefschrift hebben we verschillende nieuwe benaderingen gebruikt om de invloed van het dieet op de niergezondheid te analyseren. Deze benaderingen bieden aanknopingspunten voor nieuwe strategieën die moeten leiden tot langer behoud van een goede nierfunctie. Hoewel er al enkele algemenere voedingsscores en voedingspatronen bekend waren, zijn deze niet specifiek voor de preventie van nierschade. Dit proefschrift laat zien dat de geografische verschillen in voedingsinname, kwalitatief goede voeding (afgemeten aan o.a. de Lifelines Diet Score), nierspecifieke voedingspatronen en ultra bewerkte voedingsmiddelen geassocieerd zijn met een betere of slechtere niergezondheid. Gezonde voedingsgewoonten zijn essentieel om chronische nierschade en de bijbehorende complicaties (waaronder hart- en vaatziekten) te voorkomen. Nieuwe methoden om de complexiteit van het dieet in de praktijk te benaderen geven belangrijke inzichten en bieden in de toekomst gelegenheid om gerichtere voedingsadviezen te geven als leidraad voor duurzaam behoud van niergezondheid.

English Summary

Chronic kidney disease (CKD) is a global public health problem that affects 8 to 16% of the population worldwide. CKD is often progressive, ultimately resulting in kidney failure, and is an important cause of premature mortality and cardiovascular morbidity. Patients with kidney failure require kidney replacement therapy such as dialysis or transplantation, with poor outcomes and excessive cost. Although several pharmacological treatments, such as renin-angiotensin system inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors, slow the decline in kidney function in patients with CKD, better upstream preventive strategies to avoid or delay the onset of CKD are urgently needed to reduce the burden of this public health problem at the population level. Therefore, effective strategies for lifestyle modification, including a healthy diet, are the main priority to prevent CKD and estimated glomerular filtration rate (eGFR) decline.

In the nephrology field, nutritional epidemiologic studies have traditionally focused on nutrients and foods in patients with established, and particularly advanced CKD, or in kidney transplant recipients (KTRs). Currently, there is increasing emphasis on the possible role of dietary factors, such as nutrients, single food, food groups, and dietary patterns, for preventive purposes. This thesis describes several new approaches to assess the role of the dietary factors as a modifiable determinant in kidney health risk and to guide public health strategies for the prevention of CKD and kidney function decline, taking into account the complexity of overall diet and dietary intake in real life.

Chapter 1 comprises a brief introduction of CKD, several methodologies to assess dietary factors and diseases in the nutritional epidemiology, and the aim of this thesis.

Chapter 2 describes spatial clustering of kidney function at the neighborhood level in the Northern Netherlands. These spatial differences in kidney function may be related at least in part to the neighborhood-level dietary intake. The spatial disparity in kidney function within the region suggests that small-scale geographic factors still matter among individuals, despite similar and universal access to the health care system, a characteristic of the health care system in The Netherlands. Therefore, it is important to take neighborhood-level factors, including dietary factors, into account to guide strategies for the prevention of kidney function decline. Our analysis shows that it is relevant to extend prevention

programs beyond a one-size-fits-all approach and to pursue further identification of small-scale spatial health disparities and their corresponding risk factors.

In **Chapter 3**, we found that higher adherence to a high-quality diet assessed by Lifelines Diet Score (LLDS) was associated with a lower risk of incident CKD or ≥20% eGFR decline in the general population. These results suggest that a healthy diet, in line with the 2015 Dutch Dietary Guidelines, is beneficial to more than just the chronic diseases that the guidelines are based on, and may also have implications for the prevention of CKD. The LLDS can be a useful tool to evaluate overall diet quality and can be recommended as a tool in the evaluation of dietary strategies for the prevention of CKD.

Since there is apparently a link between a healthy diet and kidney outcomes, it would be interesting to see if the diet can be further refined by composing a kidney-specific dietary pattern. In **Chapter 4**, we used the reduced rank regression (RRR) method to identify sex-specific kidney dietary patterns explaining the maximum variation in eGFR in the general population. Subsequently, we found that a higher score on the eGFR-based dietary pattern (eGFR-DP) was associated with a lower risk of a ≥20% eGFR decline or incident CKD both in men and women. Compared with traditional studies targeting individual nutrients or food, dietary patterns are more informative because they provide a broader picture of habitual dietary behavior and consider the complex composition of many food products and the interactions among nutrients within foods.

In **Chapter 5**, we applied RRR to construct a dietary pattern that maximized the explained variation in the components of metabolic syndrome (MetS) in kidney transplant recipients (KTRs). Subsequently, we found that the higher metabolic syndrome-related dietary pattern (MetS-DP) score was associated with a higher all-cause mortality risk. Our results suggest that a dietary pattern linked to the components of metabolic syndrome may increase mortality risk after kidney transplantation. Identification of disease-specific dietary patterns using the RRR method, as illustrated by our study for eGFR-DP in the general population and MetS-DP in KTRs, may open novel avenues for dietary interventions to prevent kidney health risk.

Prevention of kidney health risk may include a higher intake of healthy food products but also, importantly, avoiding unhealthy foods such as ultra-processed foods (UPF). In **Chapter 6**, we found that a higher UPF consumption was significantly associated with a higher risk of the composite kidney outcome

(incident CKD or a ≥20% eGFR decline relative to baseline) and with a stronger annual eGFR decline, independent of confounders including overall diet quality and other nutrition indices. Thus, avoiding UPF is deemed a suitable strategy for the prevention of kidney health risks.

In this thesis, we used several novel approaches to analyze the role of diet in kidney health risks. These novel approaches provide new insights into the nutritional prevention for kidney health risk. Current dietary guidelines are mainly focused on the role of single nutrients or foods against kidney diseases. Such an approach is helpful to understand the etiology and pathogenesis of kidney diseases. However, it is less efficient and valuable for policy formulation where some quantification of the overall diet quality and overall benefits of a dietary pattern for kidney health is required. Although some diet scores and dietary patterns already existed, these were not specific for preventing kidney health risk. Thus, new approaches revealing the association between diet and kidney health are needed to complement the prevention of kidney health risk and reduce the burden of kidney diseases. This thesis describes that geographic differences in dietary intake, a food-based healthy diet score, kidney-specific dietary patterns, and ultra-processed foods are associated with kidney health risk. In conclusion, achieving healthier dietary habits is a main strategy for the prevention of CKD and its complications. Novel approaches, addressing the complexity of diet in daily life provide important insights and opportunities to guide the prevention of CKD by dietary measures in the future.

中文摘要

慢性肾脏病（chronic kidney disease, CKD）是一种全球性的公共卫生问题，影响着全球8%至16%的人口。CKD通常是进展性的，最终将导致肾功能衰竭，并且是引起过早死亡和心血管疾病的重要因素。肾功能衰竭患者需要进行肾脏替代治疗，比如肾脏透析或移植，通常预后不佳且造成过高的医疗费用。尽管肾素-血管紧张素系统抑制剂和钠-葡萄糖协同转运蛋白2抑制剂等几种药物可以减缓CKD患者肾功能的下降，但是目前迫切的需要更好的上游预防策略来避免或者延迟CKD的发生。因此，改变生活方式的有效策略，包括健康饮食，是预防CKD和估计肾小球滤过率（estimated glomerular filtration rate, eGFR）下降的优先方式。

在肾脏病学领域，营养流行病学的研究传统上侧重于在已确诊的，尤其是晚期CKD患者或肾移植受者的营养素和食品的研究。目前，越来越强调饮食因素（例如营养素，单一食物，食物组和饮食模式）以用于预防目的可能作用。本论文描述了几种新方法来评估饮食因素对肾脏健康风险的作用，同时考虑到总体饮食的复杂性和现实生活的饮食摄入，可用于指导预防CKD和肾功能下降公共卫生策略。

第一章简要介绍了CKD，营养流行病学中评估饮食因素和疾病的几种方法，以及本论文目的。

第二章描述了在荷兰北部社区层面上的肾功能空间聚类。肾功能空间分布的差异可能至少部分与社区层面饮食摄入差异相关。尽管荷兰的医疗保健系统的特征是具有相似和普遍的可及性，同一个地区内肾功能空间分布出现差异表明了在个体中小规模的地理因素仍然很重要。因此，在指导预防肾功能下降上，考虑社区层面的因素包括饮食因素是很重要的。我们的研究表明，将预防计划扩展到一刀切的方法之外，以及进一步确定小规模空间健康差异及其相应的风险因素是相关的。

第三章描述了在一般人群中，对高质量饮食（Lifelines饮食评分来评估）的更高依从性与发生CKD或eGFR下降大于20%的风险较低相关。这些结果表明，符合2015年荷兰饮食指南的健康饮食不仅对指南所依据的慢性疾病有益，而且还可能对预防CKD有影响。Lifelines饮食评分可以作为评估整体饮食质量的有用工具，并且可以推荐作为评估预防CKD饮食策略的工具。

由于健康饮食和肾脏结果之间有着明显的相关性，是否可以制定肾脏特定的饮食模式来进一步完善饮食也会很有意义。在第四章中，我们使用降阶回归的方法来确定不同性别的肾脏特定的饮食模式，以解释一般人群中eGFR的最大变化。随后，我们发现基于eGFR的饮食模式的较高评分与发生CKD和eGFR下降大于20%的风险较低相关。与针对个别营养素的传统研究相比，饮食模式提供了更多的信息，因为它们提供了更广泛的习惯性饮食行为图，并考虑了许多食物的复杂成分以及食物中营养素的相互作用。

在第五章中，我们应用降阶回归的方法构建了一种饮食模式，该模式解释了肾移

植受者中代谢综合征组成成分的最大变化。随后，我们发现较高基于代谢综合征成分的饮食模式评分与较高的全因死亡风险相关。这个研究结果表明，与代谢综合征组成成分相关的饮食模式可能会增加肾移植后死亡的风险。正如本论文中描述对一般人群基于eGFR的饮食模式和对肾移植受者基于代谢综合成成分的饮食模式的研究所示，使用降阶回归的方法构建特定疾病相关的饮食模式可能会为预防肾脏健康风险的饮食干预开辟新途径。

预防肾脏健康风险可能包括增加健康食物的摄入量，但是避免不健康的食物也同样的重要，比如超加工食品。在第六章中，我们发现摄入较多的超加工食品与复合肾脏终点（发生CKD和eGFR相对于基线下降大于20%）或者与较快的年eGFR下降的较高风险显著相关，独立于包括总体饮食质量和其他营养指标的混杂因素。因此，避免摄入超加工食物可以认为是预防肾脏健康风险的合适策略。

在本论文中，我们使用了几种新方法来分析饮食在肾脏健康风险中的作用。这些新方法为肾脏健康风险的营养预防提供了新的见解。目前的饮食指南主要关注单一营养素或食物对肾脏疾病的作用。这样的方法有助于了解肾脏疾病的病因和发病机制，然而，对于需要对整体饮食质量和饮食模式对肾脏健康的整体益处进行一些量化的政策制定时，它的效率和价值较低。虽然一些饮食评分和饮食模式已经存在，但这些并不是专门用于预防肾脏健康风险。因此，需要新的方法来揭示饮食与肾脏健康之间的关系，以补充预防肾脏健康风险并减轻肾脏疾病的负担。本论文描述了饮食摄入的地理差异、基于食物的健康饮食评分、肾脏特定的饮食模式和超加工食品与肾脏健康风险相关。总之，养成更健康的饮食习惯是预防CKD及其并发症的主要策略。解决日常生活中饮食复杂性的新方法为指导未来通过饮食措施预防CKD 提供了重要的见解和机会。
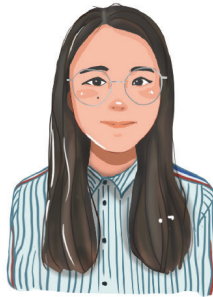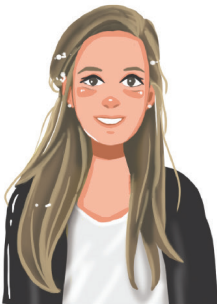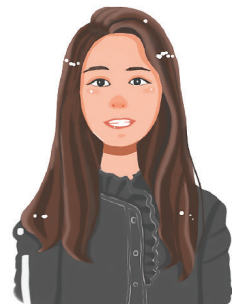
@ Gerjan

@ Martin

@ Louise

@ Qingqing

@ Anna-Sphoie

@ Xuelai

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Alice falls into a deep rabbit hole and emerges to a forest in a magic place called Wonderland. I fell into a fantastic low land and emerged to tulips and windmills in a flat place called Nederland. Nederland is my "Wonderland". The whole story began in the autumn of 2017. Now it is time to conclude my four-year life in this wonderful place and express my gratitude to all the people involved in my life during this period.

My researches

Oft expectation fails, and most oft there where most it promises; and oft it hits where hope is coldest, and despair most fits.

William Shakespeare

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My life with nefronerds

If you are lucky enough to have lived in Paris as a young man, then wherever you go for the rest of your life, it stays with you, for Paris is a moveable feast.

Ernest Hemingway

I would say If you are lucky enough to have lived in Groningen as a young man, then wherever you go for the rest of your life, it stays with you, for Groningen is a moveable feast. Looking back on the past four years, I still can't imagine that I stayed in this "Wonderland" for four years. There is happiness and joy, but also sadness and sorrow. I appreciate and cherish all the experiences here and they will stay in my memory and influence me for the rest of my life.

I would like to thank all the Nefronerds. We together moved from Triade to Dialysis Center, and eventually landed in the Zusterhuis. We together had Friday borrel and parties at the city center, Sinterklaas celebration and wrote English poems to each other, Volleyball tournament of UMCG (We won the best costume prize once!), ASN conferences in San Diego and Washington in the US, California self-driving trips and New York city tour, ERA-EDTA conference in Paris, European nutrition conference in Dublin, Nefroweekend in the Netherlands, KCM every week, CMC lunchtime every day. There are so many beautiful memories with you. Dear colleagues, the followings are your deepest impressions in my mind. **Lyanne**, we sat together at the Triade building; you warmly helped me practice Dutch using the tea bag tag, and you are the volleyball queen! Special thanks for helping me with the Dutch summary at the last minute. **Joelle**, we sat together at the Triade building as well; we celebrated your birthday in Las Vegas and it seemed I ruined your best day in the end, but you definitely my good friend here! **Stanley**, we enrolled in the Nephrology Department in the same year and possibly graduate in the same year; your Asian face helped me quickly merge myself into Nefronerds.

Maryse, your laughter enlivens the atmosphere; you wrote a beautiful English poem to introduce Dutch culture to me at my first Sinterklaas; we quarreled at Las Vegas because of a door card, but in the end, we hugged each other and our friendship was restored. **Antonio**, I would never forget the song you sang, *Chain of Fools*, "chain....chain....Chaaaaaaaain"; we tried the delicious Chinese food in San Francisco with Maryse and Joelle and we shot a nice movie there called *One Day in San Francisco (Fuller House)*. **Camilo**, you are different from other colleagues to me because you are my first non-Dutch colleague here; you are a passionate South American, and your passion has infected me; we and your cousin spent a nice time in Rotterdam and Maastricht. **Bart**, you are a cultural man and you know Chinese people more than me; my first impression of you was that you looked like Harry Potter. **Marieke**, you were an ADPKD girl; your smile and enthusiasm for the research have infected me. **Amber**, we spent a lot of time together at the Zusterhuis; you are a fantasy girl who loves fantasy books, manga, movies, and dancing, and I love your bookshelf with fantasy books on the whole wall. Many thanks for helping me with the Dutch summary at the last minute. **Anna-Sophie**, you are a hard-working girl and you are always the last one who leaves the Zusterhuis; you are justice and willing to take care of our feelings. I appreciate that you are willing to be my paranymph and help me a lot with my promotion. **Mingjie**, you are my first Chinese colleague in our department; we went to Paris and Dublin together to attend the conferences; thanks a lot to help me solve many methodology problems of my research and your perspective from the nutrition field help me a lot. **Yinjie**, you are a sweet Chinese girl and we shared a lot of memories together; you, Mingjie, Louise, and I had a Monday meeting every week which supported me going through the most difficult pandemic lockdown. **Yusof**, you are knowledgeable and there is nothing you don't know; we were the non-alcohol drinkers at the borrel. **Marco**, you are a tall guy and you took me to watch my first improvised comedy show in Groningen (Stranger Things Have Happened). **Suzanne**, you are a sweet girl and always willing to offer help; we shared many stories together at the Zusterhuis. **Lianne**, when I just arrived, you were about to graduate; now I am about to leave and you are back. My first experience at the party in the city center was led by you and Stanley. **Rianne**, I could not distinguish your name from Lianne at first, but now I can; you like cycling regardless of wind and rain. **Jip**, you are my tallest female friend; you are so kind to allow me to take care of your cat; Siep and Janneke are so cute! **Bernardo**, we met each

other because of IgA nephropathy; you called me IgA girl and I am so glad we can have a nice collaboration. **Pragyi**, you are a lab girl and I am astonished by your wonderful researches; you have many plants at the Zusterhuis, and as a deskmate, I am responsible to take care of them and I love them. **Firas**, you are a complement boy; we quickly knew each other because of the complement stain and C1q can be successfully stained now. **Sara**, you are my first Iranian friend and I like talking about the cultural differences with you. **Jose**, you are my first Mexican friend; our PhD trajectories are at the same pace, so we discussed many practical things about our PhD life. **Arno**, you were an ANCA boy and I am surprised that we have common connections with the nephrology department at Peking University First Hospital in China. **Judith**, you are a committee of KCM and thank you for arranging the presentations every week; we shared nice memories at the Winter School Dutch Kidney Foundation. **Tim,** you were a master student when I first met you and now you are one member of the Nefronerds; we spend a good time in New York with Amber, Stanley, and Bart. **Arwin,** you are so energetic with all the things and thanks for your accompany when we sat at the Triade building**.** I would also like to thank **Anna, Amarens, Cas, Coby, Daan, Di, Dion, Gerald, Iris, Jessica, Jolin, Josie, Laura, Li, Lucia, Maarten, Manuela, Mariana, Marie, Michele, Niek, Paula, Paul, Rob-Jan, Rosa, Shuqi, Sophie, Tomas, Winie** and **Yvonne** for your accompany and help during my PhD life. Thank you all again for those memorable moments together!

My families and friends

海阔凭鱼跃，天高任鸟飞。*(Boundless is the sea for fish to dive at will, unlimited is the sky for birds to fly at ease.)*

Chinese proverb

When I was graduated from primary school, the headteacher wrote this Chinese proverb to me as a blessing. I am now flying outside of China to see the world. I appreciate that my parents always support me and encourage me to explore the world. Although our distance is far away, I feel that they have always been with me. (亲爱的爸爸妈妈，感谢你们支持和鼓励我探索这个世界，你们永远与我同在。).

It is not easy to start a new life in an unfamiliar city, especially without any friends at the beginning. I would like to thank my best Chinese friend **Xuelai** in Groningen. We together explored many places in this wonderful country. We are all

art lovers and your encouragement and compliment for my artworks support me to continue to develop my artistic talents. You set up a Chinese PhD dance group in Groningen and I met many talented friends here. Thus, many beautiful dance videos were born and they are one of my best memories here! I also appreciate that you are willing to be my paranymph and help me a lot with my promotion. A special thanks to **Mingjie, Yinjie, Zheng,** and **Senshuang**, you are like my family here. We spent almost every Chinese festival together and we had a wonderful trip to Gottingen together. Your special preparation for my 30th birthday party really touched me and I will never forget it. I would like to thank my best friend **Yuchen** in China, you updated me on many important Chinese news and you were my connection between Europe and China. I would also like to thank **Huwan**, you offered the accommodations to me in Amsterdam and we spent a wonderful time talking about art and books. I would also like to thank all the Chinese members of the book club in the Netherlands who accompanied me to spend the hard time during the corona pandemic.

It is time to finish this wonderful and fantasy journey in Nederland and start a new journey in China. I wholeheartedly thank all the people involved in my life during my PhD life in the Netherland. You and Groningen stay with me forever!

Qingqing
Groningen
June 17, 2021

List of publications

Cai Q, Xie X, Wang J, Shi S, Liu L, Chen Y, Lv J, Zhang H. Severe adverse effects associated with corticosteroid treatment in patients with IgA nephropathy. *Kidney Int Rep*. 2017;2(4):603-9.

He Y, Liu J, **Cai Q**, Lv J, Yu F, Chen Q, Zhao M. The pregnancy outcomes in patients with stage 3–4 chronic kidney disease and the effects of pregnancy in the long-term kidney function. *J Nephrol*. 2018;31(6):953-60.

Cai Q, Shi S, Wang S, Ren Y, Hou W, Liu L, Lv J, Haas M, Zhang H. Microangiopathic lesions in IgA nephropathy: a cohort study*. Am J Kidney Dis*. 2019;74(5):629-39

Cai Q, Dekker LH, Bakker SJ, de Borst MH, Navis G. Intraregional differences in renal function in the Northern Netherlands: The Lifelines Cohort Study. *PloS one*. 2019;14(10):e0223908.

Cai Q, Dekker LH, Bakker SJ, de Borst MH, Navis GJ. Dietary Patterns Based on Estimated Glomerular Filtration Rate and Kidney Function Decline in the General Population: The Lifelines Cohort Study. *Nutrients*. 2020;12(4):1099.

Faria B, Canão P, **Cai Q**, Henriques C, Matos AC, Poppelaars F, da Costa MG, Daha MR, Silva R, Pestana M, Seelen MA. Arteriolar C4d in IgA nephropathy: a cohort study. *Am J Kidney Dis*. 2020;76(5):669-78.

Cai Q, Osté MC, Gomes-Neto AW, Dekker LH, Borgonjen-van den Berg KJ, Geleijnse JM, Bakker SJ, de Borst MH, Navis GJ. Metabolic syndrome-related dietary pattern and risk of mortality in kidney transplant recipients. *Nutr Metab Cardiovasc Dis*. 2021;31(4):1129-36.

Cai Q, Dekker LH, Vinke PC, Corpeleijn E, Bakker SJ, de Borst MH, Navis GJ. Diet quality and incident chronic kidney disease in the general population: the Lifelines Cohort Study. *Clinical Nutrition. In revision*

Cai Q, Duan M, Dekker LH, Carrero JJ, Avesani CM, Bakker SJ, de Borst MH, Navis GJ. Ultra-processed food consumption and kidney function decline in the general population. *Submitted*

Appendix

About the author

Qingqing Cai was born in Jiangsu Province, China, on March 8th in 1991. In 2009, she finished high school at Jiangsu Jinhu High School. In September 2009, she studied clinical medicine at Fujian Medical University in Fujian Province, China. From 2013 to 2014, she did her internship at Zhongshan Hospital Xiamen University, Xiamen, China. In July 2014, she received her Bachelor of Medicine degree. From 2014 to 2017, Qingqing did her master at Peking University Health Science Center, Beijing, China. She studied IgA nephropathy under the supervision of Prof. Jicheng Lv at the Department of Internal Medicine, Division of Nephrology, the Peking University First Hospital. In July 2017, Qingqing obtained her Master of Science degree in the specialization of Internal Medicine. In 2017, she participated in the summer program at the School of Population and Public Health of the University of British Columbia, Vancouver, Canada.

From 2017 to 2021, Qingqing was financially supported by the China Scholarship Council (CSC) to do her PhD under the supervision of Prof. G.J. Navis, Prof. M.H. de Borst, and Dr. L.H. Dekker at the Department of Internal Medicine, Division of Nephrology, the University Medical Center Groningen, Groningen, The Netherlands. Her study was focus on the diet and kidney health risk in the general population and kidney transplant recipients. The work of this thesis led to several oral and poster presentations at international conferences both in the nephrology field and in the nutrition field.

After finishing her PhD, Qingqing will continue her research and clinical career performing as a post-doctoral researcher and internal medicine resident at National Clinical Research Center for Kidney Disease, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.