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Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands

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ABSTRACT

Purpose:

The ReLife study is set up to obtain insight in the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized renal cell cancer (RCC). Further, it aims to assess the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes including health-related quality of life.

Participants:

The ReLife study is a multicenter prospective cohort study including 369 patients with newly diagnosed stage I-III RCC recruited from January 2018-June 2021 from 18 hospitals in the Netherlands. At 3 months, 1 and 2 years after treatment, participants fill out a general questionnaire and questionnaires about their lifestyle habits (e.g. diet, physical activity, smoking, alcohol consumption), medical history, and health-related quality of life. At all 3 time points, patients wear an accelerometer (ActivPAL) and donate blood samples. CT scans for body composition analysis are collected. Permission is asked for collection of tumour samples for assessment of tumour characteristics and acquired genetic alterations. Information about disease characteristics, treatment of the primary tumour and clinical outcomes is collected from medical records by the Netherlands Cancer Registry.

Findings to date:

A total of 837 invited patients were eligible and 369 patients were willing to participate and included (response rate 44%). The mean age of patients was 62.5 ± 9.0 years and 70% was male. The majority had stage I (65%) disease and were treated with radical nephrectomy (57%).

Future plans:

Data collection at 3 months and 1 years after diagnosis has been finalized and data collection at 2 years after diagnosis is expected to be finalized in June 2023. Results of studies based on this cohort are essential to develop personalized evidence-based lifestyle advice for patients with localized RCC to enable them to get more control over their own disease course.

STRENGTHS AND LIMITATIONS

- The ReLife study is the first population-based prospective cohort study on lifestyle-related factors and clinical outcomes in patients with localized RCC.
- Comprehensive data on lifestyle-related factors and quality of life were collected at 3 months, 1 year and 2 years after diagnosis.
- Both self-reported and objective data on body composition and physical activity were collected.
- A limitation is that power for survival analyses is insufficient and future pooling with other studies is required.

INTRODUCTION

Incidence rates of kidney cancer are increasing (1), which is partly explained by the increased use of diagnostic imaging but also by the increased prevalence of obesity (2). The worldwide number of new kidney cancer cases was estimated to be over 430,000 in 2020 (3). More than 90% of kidney cancers are renal cell cancers (RCC) (4). Of all RCC patients, about 70-80% are diagnosed with localised disease (stage I-III) and about 20-30% with advanced or metastatic disease (stage IV) (2). Almost all RCC patients with localised disease are treated with partial or radical nephrectomy (5). Despite this treatment, 20-30% of patients with localised disease will have a relapse or develop metastatic RCC during follow-up (6). Five-year relative survival rates are approximately 90% (stage I and II), 65% (stage III), and 12% (stage IV) (2).

Classical prognostic factors for localised RCC include anatomical (e.g., TNM classification), histological (e.g., tumour grade, histological subtype), clinical (e.g., performance status, certain blood values), and molecular features (e.g., *BAP1* and *PBRM1* mutations), but the combination of these features does not have sufficient predictive accuracy (7). In order to provide tailored treatment and follow-up care, the identification of additional prognostic factors that predict the expected clinical course in each individual patient is subject of active scientific research.

Nowadays, more than 60% of RCC patients are overweight or obese at diagnosis (body mass index (BMI) ≥25 kg/m^2) (8). A meta-analysis of prospective observational studies showed a 24% increased risk of RCC for men and a 34% increased risk for women per 5 kg/m^2 increase in BMI (9). It is estimated that about 17% and 24% of RCC cases are attributable to overweight in the Netherlands and in the UK, respectively (10, 11). Paradoxically, meta-analyses on BMI and survival suggest that RCC patients who were overweight or obese at diagnosis have a significantly better overall, cancer-specific, and recurrence-free survival compared with normal weight patients (12, 13). The higher risk but better prognosis with higher BMI is counterintuitive. Possibly, body composition explains part of this paradox.

Body composition refers to the content of fat, lean tissue and bone in the human body. The amount and distribution of these tissues may be independent of BMI; subjects with similar

BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional areas and mean radiodensity of these tissues can be assessed by analysis of computed tomography (CT) scans at the level of the third lumbar vertebra (L3), using established Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and SM areas at L3 are linearly related to body TAT and SM mass (14-16).

High VAT mass, low SM index (SMI (SM/height^2)), and low SM radiodensity (SMD) have been associated with adverse postoperative (17) and survival outcomes (18-20) in several cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated with increased overall mortality in patients with metastatic RCC (21). No meta-analysis could be performed for localized RCC due to the limited number of studies and heterogeneity in body composition parameters and outcomes (21). One study also suggested an association of low vs. high SMI with higher overall and cancer-specific mortality (22) while other studies found that low vs. high VAT was associated with a higher risk of recurrence (23) or cancer-specific mortality (24, 25).

Body composition is known to differ by age, gender and race (26, 27). Studies on the association of tumour characteristics with body composition features are inconsistent (28, 29) and studies on the association of lifestyle habits and circulating biomarkers with body composition parameters are not available in patients with RCC. Smoking has been associated with increased RCC risk and RCC-specific mortality (30). Studies on dietary factors and physical activity are inconsistent for RCC risk (31) and not available for clinical outcomes including health-related quality of life (HRQoL). Some studies suggest that circulating biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size (32), invasion, progression or metastasis (32-34) and survival (35, 36) in patients with RCC but results are inconsistent.

Thus, the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized RCC needs to be clarified. Further, there is a clear need to obtain more insight in body composition features and lifestyle

habits and their relation with clinical outcomes in patients with localized RCC. This information is essential to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes.

COHORT DESCRIPTION

Setting

The ReLife study (**Re**nal cell cancer: **Life**style, prognosis, and quality of **Life**) is a prospective cohort study including patients with newly diagnosed pathologically confirmed primary stage I-III RCC. The study has been designed to evaluate 1) the association of patient and tumour characteristics, lifestyle habits, and circulating biomarkers with body composition features, and 2) the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including HRQOL. Patients were recruited in 18 hospitals in the East, South, and Central parts of the Netherlands. Before the start of the study, permission was asked from all urologists of the participating hospitals to select and invite eligible patients from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organisation (IKNL). Once every 2 weeks, newly diagnosed patients were identified through IKNL using notification lists of the Pathological Anatomical National Automate Archive (PALGA foundation) in the Netherlands. Approximately 10 weeks after treatment (surgery or ablation), patients were invited on behalf of their urologist to participate in this study (**Figure 1**). Patients who agreed to participate provided a written informed consent. Enrolment started in January 2018 and ended in June 2021 and collection of follow-up data is still ongoing.

Figure 1 Timeline and study design of the ReLife study

Patient and public involvement

Four patient representatives were asked for feedback on the grant proposal and one patient representative was involved in the design and set-up phase of the study. Patients were not involved in the conducting of this research, but will be involved in the reporting and dissemination plans regarding information provision to patients. Results from the study will be communicated to participants and urologists from the participating hospitals through the study website (www.radboudumc.nl/trials/relife), through newsletters and through the website of the patient society. Results will be submitted for publication in peer-reviewed journals and presented at

relevant (inter)national conferences.

Participants

Eligible participants were Dutch speaking patients between 18 and 75 years old who were newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who underwent a (partial) nephrectomy or ablation. Patients with a previous diagnosis of cancer in the five years before RCC diagnosis and those with a lymph node metastasis or distant metastasis were not eligible.

Data collection and management

Questionnaires

Participants are asked to complete self-administered web-based or paper-and-pencil-based questionnaires at 3 months (T3mo), 1 year (T1y) and 2 years (T2y) after treatment (**Figure 1, Table 1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone calls are made to non-responding participants and to respondents whose questionnaires have missing items.

The general questionnaire at T3mo contains questions on demographics (age, sex, ethnicity, education, living situation, occupation, marital status) and personal and family history of cancer. All questionnaires collect information about height, body weight, amount and frequency of alcohol consumption during week- and weekend days, smoking habits, comorbidities and the use of dietary supplements and medication. Information on smoking habits is collected in detail, including age or date of starting and stopping smoking, number of cigarettes smoked per day, and duration of smoking. Information about habitual physical activity is collected by using the previously validated Short Questionnaire to Assess Health (SQUASH) (37), which is fairly reliable and valid in an adult population (37-39). The SQUASH questionnaire assesses the average time, i.e. number of days per week and hours and minutes per day, spent in commuting activities, leisure time activities, household activities,

Table 1. Overview of data collection in ReLife at the three time points after treatment

	Measures	T3mo	T1y	T2y
Questionnaires				
Sociodemographic data	Date of birth, gender, country of birth of participant, father, mother, race, living situation, marital status, highest level of education, working history	X		
Anthropometry	Height at baseline, weight two years before diagnosis, weight loss 3-6 months before diagnosis, average weight during adult life	X		
	Current body weight, waist and hip circumference	X	X	X
Lifestyle	Current and past smoking behaviour including dose and duration, alcohol consumption, (reasons for) changes in eating habits, mobility	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity (29)	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days (32-34)	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X
Medical history	Previously diagnosed with cancer, family history of cancer	X		
	Comorbidities, medication use, dietary supplement use	X	X	X
Diet	163- item Food Frequency Questionnaire	X	X	X
Health-related quality of life	EORTC QLQ-C30 (36)	X	X	X
Accelerometer				
	Habitual physical (in)activity, sedentary behavior	X	X	X
Blood				
	EDTA whole blood for DNA isolation	X		
	EDTA plasma, serum	X	X	X
Tissue				
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X[a]		
CT scan				
	Diagnostic CT scan	X		
	Follow-up CT scans		X[b]	X[b]
Clinical data				
	Disease characteristics, treatment	X	X	X
	Postoperative outcomes, recurrence and progression	X	X	X

[a] To date only permission, no actual collection.; [b] Dependent on availability.

and activities at work in a normal week in the past month. At all three time points, patients are also asked to measure and report their waist and hip circumference.

Habitual dietary intake is collected at all three time points using a 163-item validated and reproducible self-administered food frequency questionnaire that was developed by Wageningen University (40-42). The questionnaire contains questions about the frequency of consumption of food products and the portion size during the previous month. Frequency and portion size of consumed food products are multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) (43).

Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-C30 (44). The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100 scale.

Accelerometer

Habitual physical (in)activity is objectively measured at all three time points using the activPAL physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to be an accurate tool for measuring daily physical activity levels (45). Participants are asked to wear the device continuously on the front right thigh for seven consecutive days. Data are uploaded using the activPAL software.

Blood samples

Non-fasting blood samples are collected at all three time points. At T3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At

the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory for Experimental Internal Medicine of Radboudumc using commercially available enzyme-linked immunosorbent assays is planned.

Tumour samples

From all patients, permission for collection of tumour specimens is requested for potential future assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic alterations (e.g. in the *BAP1* or *PBRM1* genes) (5). Tumour blocks can be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories.

CT scans

CT scans are retrieved from medical records of all patients for the assessment of body composition. Diagnostic CT scans are available from almost all RCC patients as they are used for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well. From these CT scans, cross-sectional areas (cm^2) and mean radiodensity of SM, VAT, SAT and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).

Clinical data

Information about disease characteristics and treatment for the initial tumour and subsequent recurrences is collected from the medical records by data managers of the Netherlands Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage, tumour grade and histology. With respect to therapy, information is collected on type of treatment (type of nephrectomy, type of ablation), operation time, blood

loss, complications (Clavien-Dindo classification) and length of hospital stay. Furthermore, data on performance status (e.g. WHO performance status, ASA score) are collected.

Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and Fuhrman grade, is also collected.

Power calculation and data analyses

The power calculation of this study is based on our initial research question, i.e. the cross-sectional association of patient and tumour characteristics, lifestyle habits, and circulating concentrations of biomarkers with body composition features. With 369 patients, we will have sufficient power (≥80%) to detect a multiple correlation coefficient of 0.30 (Cohen's f^2=0.10 for patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations of biomarkers with body composition features), corresponding to a small (f^2=0.02) to medium (f^2=0.15) effect size (46). This power calculation is based on 276 stage I-III patients (assuming 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition features as outcome variables (cross-sectional area and radiodensity of SM and cross-sectional area of VAT). For the power calculation, we correct for multiplicity (3 body composition features) by using the Bonferroni corrected alpha of 0.05/3.

Multiple linear regression analyses will be used to estimate the cross-sectional association of patient and tumor characteristics, lifestyle habits, and biomarkers with body composition features. Longitudinal associations of body composition features, lifestyle habits and biomarkers with HRQoL will be assessed using linear mixed models. Logistic regression and Cox proportional hazard analyses will be used to estimate the association of body composition features, lifestyle habits and biomarkers with other clinical outcomes.

FINDINGS TO DATE

Characteristics of study participants

Figure 2 Flowchart of the ReLife study

From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19 measures. In total, 837 patients were eligible and 369 patients agreed to participate and filled out the first or second questionnaires (response rate 44%) (**Figure 2**). The number of questionnaires, ActivPal measurements and blood samples available at T3mo are also shown in **Figure 2**. The collection of CT scans and data at T1y and T2y are is still ongoing.

In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients was 62.5 ± 9.0 years and 70% was male. Most patients had stage I (65%) and Fuhrman grade 2 (50%) disease. The majority has been treated with radical (57%) or partial nephrectomy (42%). Participants were comparable to non-participants with respect to age, sex, tumour stage, tumour grade and type of treatment. The majority of participants was overweight (44%) or obese (25%) and was a former smoker (50%).

Table 2. Baseline characteristics of 369 patients with renal cell cancer included in the ReLife study

Age at diagnosis (y), mean ± SD	62.5 ± 9.0
Sex, n (%)	
Male	258 (70)
Female	111 (30)
Educational level, n (%)[a]	
Low	151 (41)
Medium	116 (31)
High	98 (27)
Missing	4 (1)
BMI (kg/m^2), mean ± SD	27.5 ± 4.6
BMI (kg/m^2), n (%)	
Underweight (≤18.5)	1 (0.3)
Normal weight (18.5-25)	111 (30)
Overweight (25-≤30)	163 (44)
Obese (>30)	91 (25)
Missing	3 (1)
Waist circumference (cm), mean ± SD[b]	101.2 ± 12.1
Hip circumference (cm), mean ± SD[b]	102.0 ± 9.5
Cigarette smoking status, n (%)	
Current	43 (12)
Former	186 (50)
Never	137 (37)
Missing	3 (1)
Tumor stage, n (%)	
I	239 (65)
II	55 (15)
III	75 (20)
Fuhrman grade, n (%)	
1	49 (13)
2	185 (50)
3	67 (18)
4	23 (6)
unknown	45 (12)
Treatment, n (%)	
Radical nephrectomy	210 (57)
Partial nephrectomy	153 (42)
Ablation[c]	6 (2)
Comorbidities, n (%)	
0	54 (15)
1	85 (23)
≥2	227 (62)
Missing	3 (1)

[a] Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university)

[b] Values for 8 participants were missing

[c] Other treatment consisted of cryoablation (n=2), radiofrequency ablation (n=3) and microwave ablation (n=1)

Abbreviations

BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal; IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue; NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT: subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health; TAT: total adipose tissue; T1y: 1 year after treatment; T2y: 2 years after treatment; T3mo: three months after treatment; VAT: visceral adipose tissue.

DECLARATIONS

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Authors' contributions

AV, EK, JPM, JSFM, KKHA, and LALMK contributed to the conception and design of the study. AV provides overall study management and coordinates the project. JSFM contributed to data collection. AV and JSFM drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol has been approved on March 2, 2017 by the Committee for Human Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in the study provided a written informed consent.

Consent for publication

Not applicable.

Availability of data and material

Data and material are not yet available since data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

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Figure 1. Timeline and study design of the ReLife study

Figure 2. Flow chart of the ReLife study

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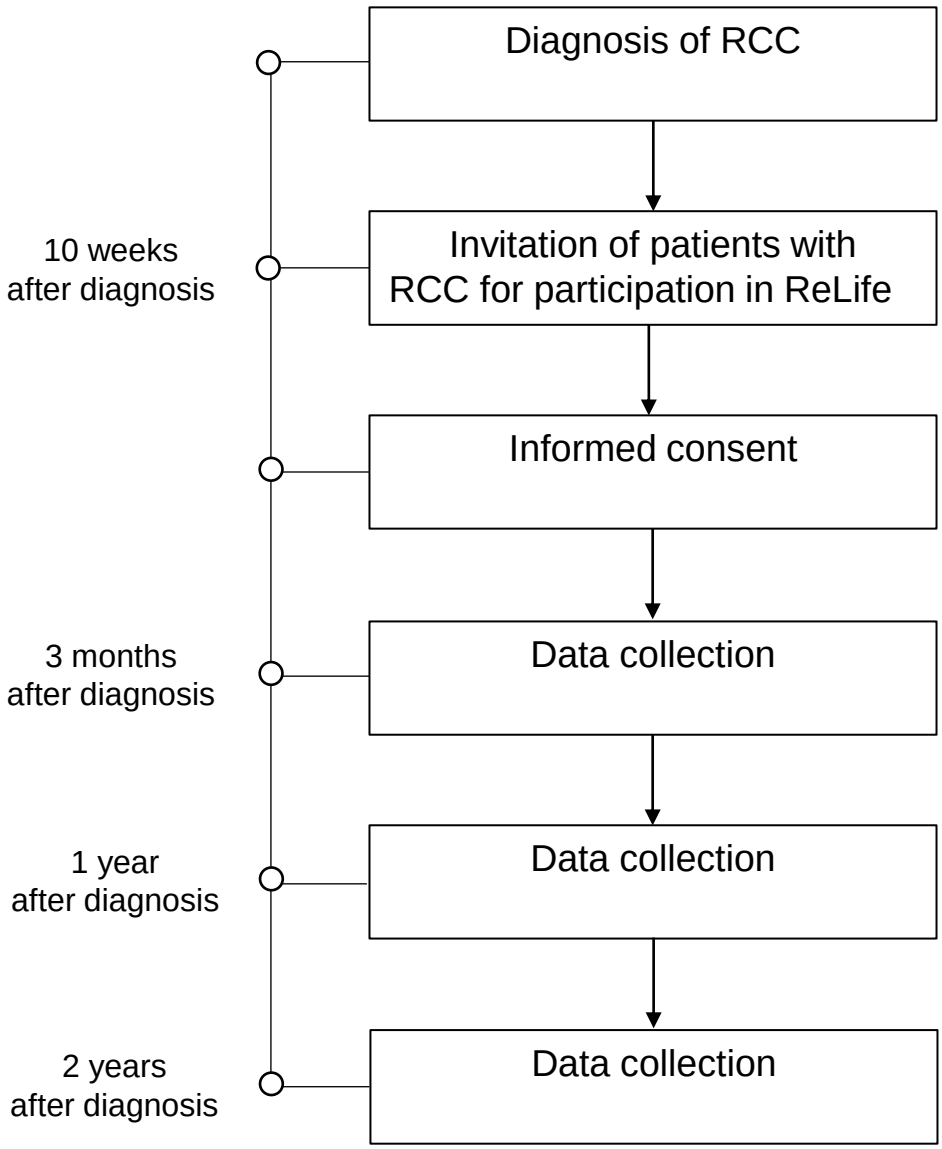
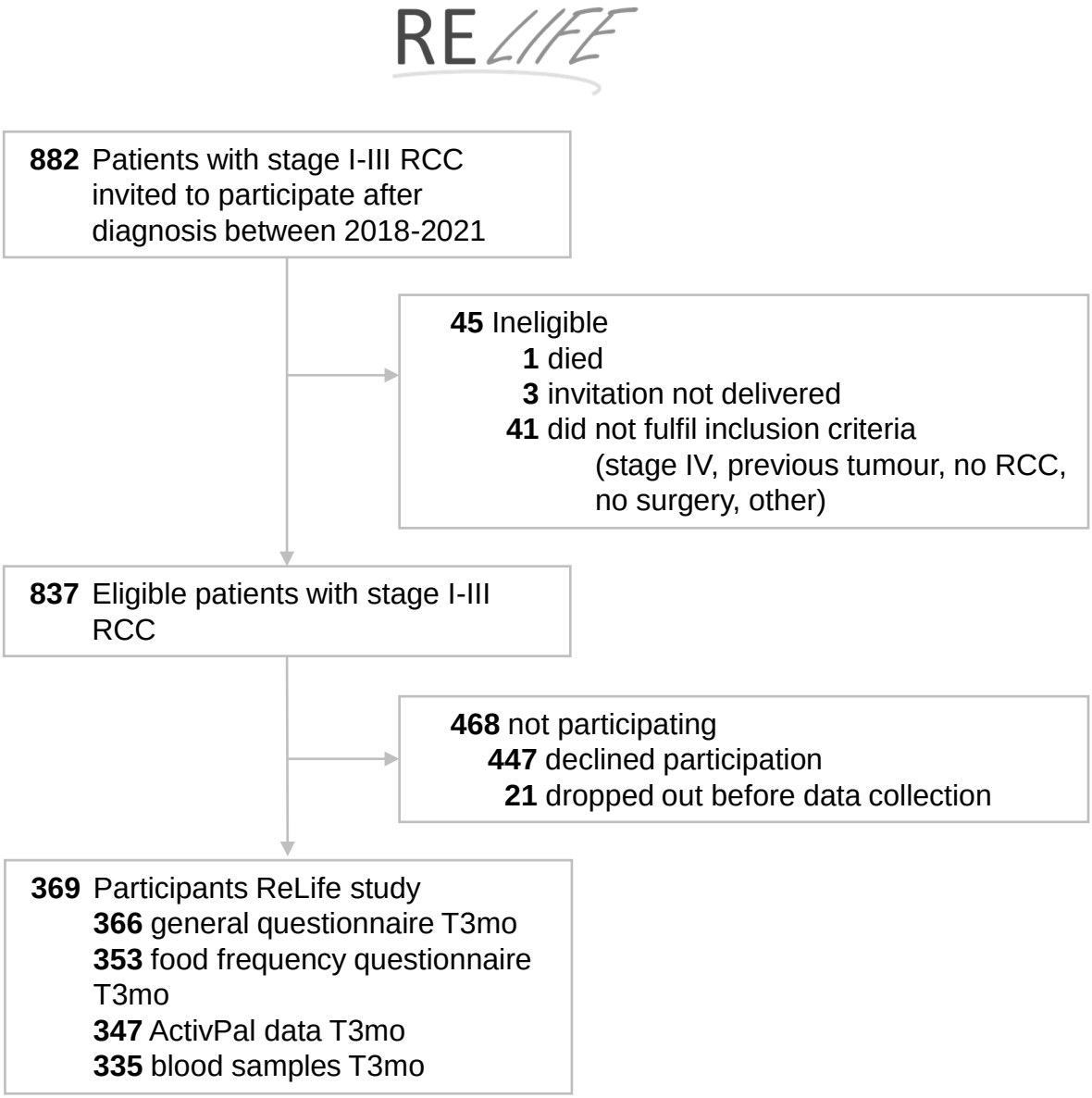
Overview ReLife study




RELIFE
882 Patients with stage I-III RCC invited to participate after diagnosis between 2018-2021
45 Ineligible
1 died
3 invitation not delivered
41 did not fulfil inclusion criteria
(stage IV, previous tumour, no RCC, no surgery, other)
837 Eligible patients with stage I-III RCC
468 not participating
447 declined participation
21 dropped out before data collection
369 Participants ReLife study
366 general questionnaire T3mo
353 food frequency questionnaire T3mo
347 ActivPal data T3mo
335 blood samples T3mo

BMJ Open

Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands

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Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands

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Keywords: renal cell cancer, diet, lifestyle, body composition, biomarkers, quality of life, cohort profile

Word count: 2349

ABSTRACT

Purpose:

The ReLife study is set up to obtain insight into the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized renal cell cancer (RCC). Further, it aims to assess the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes including health-related quality of life.

Participants:

The ReLife study is a multicenter prospective cohort study involving 368 patients with newly diagnosed stage I-III RCC recruited from January 2018-June 2021 from 18 hospitals in the Netherlands. At 3 months, 1 and 2 years after treatment, participants fill out a general questionnaire and questionnaires about their lifestyle habits (e.g. diet, physical activity, smoking, alcohol consumption), medical history, and health-related quality of life. At all 3 time points, patients wear an accelerometer and have blood samples taken. CT scans for body composition analysis are being collected. Permission is asked for collection of tumour samples. Information about disease characteristics, treatment of the primary tumour and clinical outcomes is being collected from medical records by the Netherlands Cancer Registry.

Findings to date:

A total of 836 invited patients were eligible and 368 patients were willing to participate and were included (response rate 44%). The mean age of patients was 62.5 ± 9.0 years and 70% was male. The majority had stage I (65%) disease and were treated with radical nephrectomy (57%). Data collection at 3 months and 1 years after treatment has been finalized.

Future plans:

Data collection at 2 years after treatment is expected to be finalized in June 2023 and longitudinal clinical data will continue to be collected. Results of studies based on this cohort are important to develop personalized evidence-based lifestyle advice for patients with localized RCC to enable them to get more control over their disease course.

STRENGTHS AND LIMITATIONS

- The ReLife study is the first population-based prospective cohort study on lifestyle-related factors and clinical outcomes in patients with localized RCC worldwide.
- Comprehensive data on lifestyle-related factors and quality of life are collected at 3 months, 1 year and 2 years after treatment.
- Both self-reported and objective data on body composition and physical activity are collected.
- A limitation is that power for survival analyses is likely to be insufficient and future pooling with other studies may be required.

INTRODUCTION

Incidence rates of kidney cancer are increasing (1), which is partly explained by the increased use of diagnostic imaging but also by the increased prevalence of obesity (2). The worldwide number of new kidney cancer cases was estimated to be over 430,000 in 2020 (3). In the Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 (4). More than 90% of kidney cancers are renal cell cancers (RCC) (5). Of all RCC patients, about 70-80% are diagnosed with localised disease (stage I-III) and about 20-30% with advanced or metastatic disease (stage IV) (2). Almost all RCC patients with localised disease are treated with partial or radical nephrectomy (6). Despite this treatment, 20-30% of patients with localised disease will have a relapse or develop metastatic RCC during follow-up (7). Five-year relative survival rates are approximately 90% (stage I and II), 65% (stage III), and 12% (stage IV) (2).

Classical prognostic factors for localised RCC include anatomical (e.g., TNM classification), histological (e.g., tumour grade, histological subtype), clinical (e.g., performance status, certain blood values), and molecular features (e.g., *BAP1* and *PBRM1* mutations), but the combination of these features does not have sufficient predictive accuracy (8). In order to provide tailored treatment and follow-up care, the identification of additional prognostic factors that predict the expected clinical course in each individual patient is subject of active scientific research.

Nowadays, more than 60% of RCC patients are overweight or obese at diagnosis (body mass index (BMI) ≥25 kg/m^2) (9). A meta-analysis of prospective observational studies showed a 24% increased risk of RCC for men and a 34% increased risk for women per 5 kg/m^2 increase in BMI (10). It is estimated that about 17% and 24% of RCC cases are attributable to overweight in the Netherlands and in the UK, respectively (11, 12). Paradoxically, meta-analyses on BMI and survival suggest that RCC patients who were overweight or obese at diagnosis have a significantly better overall, cancer-specific, and recurrence-free survival compared with normal weight patients (13, 14). The higher risk but better prognosis with higher BMI is counterintuitive. Possibly, body composition explains part of this paradox.

Body composition refers to the content of fat, lean tissue and bone in the human body. The amount and distribution of these tissues may be independent of BMI; subjects with similar BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional areas and mean radiodensity of these tissues can be assessed by analysis of computed tomography (CT) scans at the level of the third lumbar vertebra (L3), using established Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and SM areas at L3 are linearly related to body TAT and SM mass (15-17).

High VAT mass, low SM index (SMI (SM/height^2)), and low SM radiodensity (SMD) have been associated with adverse postoperative (18) and survival outcomes (19-21) in several cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated with increased overall mortality in patients with metastatic RCC (22). No meta-analysis could be performed for localized RCC due to the limited number of studies and heterogeneity in body composition parameters and outcomes (22). Studies also suggested an association of low vs. high SMI with higher overall and cancer-specific mortality (23) and of lower SMD with higher overall mortality (24). Other studies found that low vs. high VAT was associated with a higher risk of recurrence (25), cancer-specific (26, 27), and overall mortality (24).

Body composition is known to differ by age, gender and race (28, 29). Studies on the association of tumour characteristics with body composition features are inconsistent (30, 31) and studies on the association of lifestyle habits and circulating biomarkers with body composition parameters are not available in patients with RCC. Smoking has been associated with increased RCC risk and RCC-specific mortality (32). Studies on dietary factors and physical activity are inconsistent for RCC risk (33) and not available for clinical outcomes including health-related quality of life (HRQoL). Some studies suggest that circulating biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size (34), invasion, progression or metastasis (34-36) and survival (37, 38) in patients with RCC but results are inconsistent.

Thus, the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized RCC needs to be clarified. Further, there is a clear need to obtain more insight in body composition features and lifestyle habits and their relation with clinical outcomes in patients with localized RCC. This information is important to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes. Therefore, the objectives of this study are to evaluate 1) the association of patient and tumour characteristics, lifestyle habits, and circulating biomarkers with body composition features, and 2) the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQOL.

COHORT DESCRIPTION

Setting

The ReLife study (**Re**nal cell cancer: **Life**style, prognosis, and quality of **Life**) is a prospective cohort study involving patients with newly diagnosed pathologically confirmed primary stage I-III RCC. Patients were recruited in 18 hospitals in the East, South, and Central parts of the Netherlands. Before the start of the study, permission was asked from all urologists of the participating hospitals to select and invite eligible patients from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organisation (IKNL). Once every 2 weeks, newly diagnosed patients were identified by IKNL personnel using notification lists of the Pathological Anatomical National Automate Archive (PALGA foundation) in the Netherlands. Approximately 10 weeks after treatment (surgery or ablation), patients were invited by IKNL personnel on behalf of their urologist to participate in this study (**Figure 1**). Patients who agreed to participate provided a written informed consent. Enrolment started in January 2018 and ended in June 2021 and collection of follow-up data is still ongoing.

Figure 1 Timeline and study design of the ReLife study

Patient and public involvement

Four patient representatives were asked for feedback on the grant proposal and one patient representative was involved in the design and set-up phase of the study. Patients were not involved in the conduction of this research, but will be involved in the reporting and dissemination plans regarding information provision to patients. Results from the study will be communicated to participants and urologists from the participating hospitals through the study website (www.radboudumc.nl/trials/relife), through newsletters and through the website of the patient society. Results will be submitted for publication in peer-reviewed journals and presented at relevant (inter)national conferences.

Participants

Eligible participants were between 18 and 75 years old who were newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who underwent a (partial) nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since all study materials and questionnaires were only available in Dutch. Patients with a previous diagnosis of cancer in the five years before RCC diagnosis and those with a lymph node metastasis or distant metastasis were not eligible.

Data collection and management

Questionnaires

Participants are asked to complete self-administered web-based or paper-and-pencil-based questionnaires at 3 months (3mo), 1 year (1y) and 2 years (2y) after treatment (**Figure 1, Table 1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone calls are made to non-responding participants and to respondents whose questionnaires have missing items.

The general questionnaire at 3mo contains questions on demographics (age, sex, ethnicity, education, living situation, occupation, marital status) and personal and family history of cancer. All questionnaires collect information about height, body weight, amount and frequency of alcohol consumption during week- and weekend days, smoking habits, comorbidities and the use of dietary supplements and medication. Information on smoking habits is collected in detail, including age or date of starting and stopping smoking, number of cigarettes smoked per day, and duration of smoking. Information about habitual physical activity is collected by using the validated short questionnaire to assess health-enhancing physical activity (SQUASH) (39). The SQUASH questionnaire assesses the average time, i.e. number of days per week and hours and minutes per day, spent in commuting activities, leisure time activities, household activities, and activities at work in a normal week in the past month. At all three time points, patients are also asked to measure and report their waist and hip circumference.

Table 1. Overview of data collection in ReLife at the three time points after treatment

	Measures	3mo	1y	2y
Questionnaires				
Sociodemographic data	Date of birth, gender, country of birth of participant, father, mother, race, living situation, marital status, highest level of education, working history	X		
Anthropometry	Height at baseline, weight two years before diagnosis, weight loss 3-6 months before diagnosis, average weight during adult life	X		
	Current body weight, waist and hip circumference	X	X	X
Lifestyle	Current and past smoking behaviour including dose and duration, alcohol consumption, (reasons for) changes in eating habits, mobility	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity (29)	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days (32-34)	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X
Medical history	Previously diagnosed with cancer, family history of cancer	X		
	Comorbidities, medication use, dietary supplement use	X	X	X
Diet	163- item Food Frequency Questionnaire	X	X	X
Health-related quality of life	EORTC QLQ-C30 (44)	X	X	X
Accelerometer				
	Habitual physical (in)activity, sedentary behavior	X	X	X
Blood				
	EDTA whole blood for DNA isolation	X		
	EDTA plasma, serum	X	X	X
Tissue				
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X[a]		
CT scan				
	Diagnostic CT scan	X		
	Follow-up CT scans		X[b]	X[b]
Clinical data				
	Disease characteristics, treatment	X	X	X
	Postoperative outcomes, recurrence and progression	X	X	X

[a] To date only permission, no actual collection.; [b] Dependent on availability.

Habitual dietary intake is collected at all three time points using a 163-item validated and reproducible self-administered food frequency questionnaire that was developed by Wageningen University (40-42). The questionnaire contains questions about the frequency of consumption of food products and the portion size during the previous month. Frequency and portion size of consumed food products are multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) (43).

Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-C30 (44). The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100 scale.

Accelerometer

Habitual physical (in)activity is objectively measured at all three time points using the activPAL physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to be an accurate tool for measuring daily physical activity levels (45). Participants are asked to wear the device continuously on the front right thigh for seven consecutive days. Data are uploaded using the activPAL software.

Blood samples

Non-fasting blood samples are collected at all three time points. At 3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank.

The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory for Experimental Internal Medicine of Radboudumc using commercially available enzyme-linked immunosorbent assays is planned.

Tumour samples

From all patients, permission for collection of tumour specimens is requested for future assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic alterations (e.g. in the *BAP1* or *PBRM1* genes) (6). Formalin-fixed paraffin-embedded tumour blocks can be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories.

CT scans

CT scans are retrieved from medical records of all patients for the assessment of body composition. Diagnostic CT scans are available from almost all RCC patients as they are used for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well. From these CT scans, cross-sectional areas (cm^2) and mean radiodensity of SM, VAT, SAT and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).

Clinical data

Information about disease characteristics and treatment for the initial tumour and subsequent recurrences is collected from the medical records by data managers of the Netherlands Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage, Fuhrman grade and morphology. With respect to therapy, information is collected on type of treatment (type of nephrectomy, type of ablation), operation time, blood loss, complications (Clavien-Dindo classification) and length of hospital stay. Furthermore, data on performance status (e.g. WHO performance status, ASA score) are collected.

Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and Fuhrman grade, and survival, are also collected. We will continue to collect further information on these clinical outcomes in the future to evaluate their association with body composition features, lifestyle habits and circulating biomarkers.

Power calculation and data analyses

The power calculation of this study is based on our initial research question, i.e. the cross-sectional association of patient and tumour characteristics, lifestyle habits, and circulating concentrations of biomarkers with body composition features. With 369 patients, we will have sufficient power (≥80%) to detect a multiple correlation coefficient of 0.30 (Cohen's f^2=0.10 for patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations of biomarkers with body composition features), corresponding to a small (f^2=0.02) to medium (f^2=0.15) effect size (46). This power calculation is based on 276 stage I-III patients (assuming 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition features as outcome variables (cross-sectional area and radiodensity of SM and cross-sectional area of VAT). For the power calculation, we correct for multiplicity (3 body composition features) by using the Bonferroni corrected alpha of 0.05/3.

Patient characteristics were described using means and standard deviations (SD), medians and interquartile ranges (IQR), or total numbers and percentages where appropriate. Differences in sociodemographic and clinical characteristics between participants and non-participants were evaluated with chi-squared tests. Two-sided p-values <0.05 were considered statistically significant. Multiple linear regression analyses will be used to estimate the cross-sectional association of patient and tumor characteristics, lifestyle habits, and biomarkers with body composition features. Longitudinal associations of body composition features, lifestyle habits and biomarkers with HRQoL will be assessed using linear mixed models. Logistic regression and Cox proportional hazard analyses will be used to estimate the association of

body composition features, lifestyle habits and biomarkers with other clinical outcomes. All statistical analyses will be conducted in R.

FINDINGS TO DATE

Characteristics of study participants

From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19 measures. In total, 836 patients were eligible and 368 patients agreed to participate and filled out the first or second questionnaires (response rate 44%) (**Figure 2**). The median time between time of treatment and time of the 3mo questionnaire completion was 13 weeks (interquartile range 12-14 weeks). The number of questionnaires, ActivPal measurements and blood samples available at 3mo are also shown in **Figure 2**.

Figure 2 Flowchart of the ReLife study

In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients was 62.4 ± 9.0 years and 70% was male. Most patients had stage I (65%) and Fuhrman grade 2 (50%) disease. The majority was treated with radical (57%) or partial nephrectomy (42%). The majority of participants were overweight (44%) or obese (25%) and 50% were former smokers. Participants were more likely to be female than non-participants but were comparable with respect to age, tumour stage, tumour grade, morphology and type of treatment (**Table 3**).

Table 2. Baseline characteristics of 368 patients with renal cell cancer included in the ReLife study

Age at diagnosis (y)	62.4 ± 9.0
Sex	
Male	257 (70)
Female	111 (30)
Race	
White	356 (97)
Black	1 (0.3)
Asian	3 (1)
Other	5 (1)
Missing	3 (1)
Educational level[a]	
Low	151 (41)
Medium	115 (31)
High	98 (27)
Missing	4 (1)
Paid occupation	
Yes	170 (46)
No	195 (53)
Missing	3 (1)
Living situation	
Alone	48 (13)
With partner	228 (62)
With partner and kids	81 (22)
Alone, but with kids	8 (2)
Missing	3 (1)
BMI (kg/m^2)	27.6 ± 4.7
BMI (kg/m^2)	
Underweight (≤18.5)	1 (0.3)
Normal weight (18.5-25)	110 (30)
Overweight (25-≤30)	163 (44)
Obese (>30)	91 (25)
Missing	3 (1)
Waist circumference (cm)[b]	101.2 ± 12.1
Hip circumference (cm)[b]	102.1 ± 9.5
Cigarette smoking status	
Current	43 (12)
Former	185 (50)
Never	137 (37)
Missing	3 (1)
Alcohol consumption (g/d)	
0	104 (28)
>0-10	145 (39)
>10	101 (27)
Missing	18 (5)
Total moderate-to-vigorous physical activity (min/wk)	
<75	27 (7)
75-150	142 (39)
≥150	193 (52)
Missing	6 (2)
Tumor stage	
I	238 (65)
II	55 (15)

III	75 (20)
Fuhrman grade	
1	49 (13)
2	185 (50)
3	67 (18)
4	23 (6)
unknown	44 (12)
Treatment	
Radical nephrectomy	210 (57)
Partial nephrectomy	152 (41)
Ablation[c]	6 (2)
Comorbidities	
0	54 (15)
1	85 (23)
≥2	226 (61)
Missing	3 (1)

Values are mean ± SD or n (%).

[a] Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university)

[b] Values for 8 participants were missing

[c] Other treatment consists of cryoablation (n=2), radiofrequency ablation (n=3) and microwave ablation (n=1)

Table 3. Comparison of demographic and clinical characteristics of 368 patients with renal cell cancer included in the ReLife study and 468 invited non-participants

	Participants	Non-participants	P-value[a]
N	368	468	
Age category (y)			
18-44	14 (4)	28 (6)	0.34
45-64	180 (49)	218 (47)	
65-75	174 (47)	222 (47)	
Sex			
Male	257 (70)	360 (77)	0.02
Female	111 (30)	108 (23)	
Tumor stage			
I	238 (65)	298 (64)	0.51
II	55 (15)	61 (13)	
III	75 (20)	109 (23)	
Fuhrman grade			
1	49 (13)	86 (18)	0.32
2	185 (50)	219 (47)	
3	67 (18)	74 (16)	
4	23 (6)	33 (7)	
unknown	44 (12)	56 (12)	
Morphology			0.97
Clear cell renal tumour	260 (71)	338 (72)	
Papillary renal tumour	48 (13)	58 (12)	
Chromophobe renal tumour	25 (7)	30 (6)	
Other[b]	35 (9)	42 (9)	
Treatment			
Radical nephrectomy	210 (57)	272 (58)	0.76
Partial nephrectomy	152 (41)	191 (41)	
Ablation[c]	6 (2)	5 (1)	

Values are n (%).

[a] From chi-squared test.

[b] Other morphology consists of adenocarcinoma with mixed subtypes (n=4 and n=5), eosinophilic solid and cystic renal cell carcinoma (n=1 and n=0), renal cell carcinoma not otherwise specified (n=28 and n=29), sarcomatoid renal cell carcinoma (n=2 and n=6), collecting duct carcinoma (n=0 and n=1), and clear cell papillary renal cell tumour (n=0 and n=1) for participants and non-participants, respectively.
[c] Other treatment consists of cryoablation (n=2 and n=2), radiofrequency ablation (n=3 and n=2), and microwave ablation (n=1 and n=1) for participants and non-participants, respectively.

FUTURE PLANS

We have already started and will first continue to work on the statistical analyses and writing of manuscripts addressing our main study objectives, i.e. 1) the association of patient and tumour characteristics, lifestyle habits, and circulating biomarkers with body composition features, and 2) the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications, length of hospital stay), and HRQOL. Statistical analyses for recurrence, progression, and survival will be conducted once follow-up is more mature or pooling with similar cohorts becomes possible.

STRENGHTS AND LIMITATIONS

To our knowledge, the ReLife study is the first population-based prospective longitudinal study on lifestyle-related factors and clinical outcomes in patients with localized RCC worldwide. Comprehensive data on lifestyle-related factors and HRQOL are collected at 3 months, 1 year and 2 years after treatment. Besides questionnaire data on lifestyle-related factors, also objective data on body composition and physical activity are collected. Data on sociodemographic variables and comorbidity is available as well. Information on several clinical outcomes is collected, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQOL. Moreover, blood samples are collected to measure lifestyle-related, disease-related and genetic biomarkers. Permission is available from participants to use their tumour tissue blocks for assessment of tumour characteristics and acquired genetic alterations.

However, there are also some limitations to this study. As is the case for all longitudinal studies, participants may drop out during the course of the study, potentially leading to selection bias. Some variables have missing values which will be addressed using multiple imputation when applicable. No information on lifestyle-related factors and HRQOL after the two-years follow-up measurement is available. Power for survival analyses is likely to be

insufficient and future pooling with other studies may be necessary. Lastly, we did not use RCC-specific measures of HRQOL in our study.

Results that can be obtained from this study are important to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes.

COLLABORATION

The ReLife study group is open for collaborations with national and international colleagues. Any person interested in collaborating on the ReLife study or in getting access to ReLife data for data analyses can contact the corresponding author. Requests for data will be discussed and decided by the ReLife study group and will require a Data Transfer Agreement.

Abbreviations

BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal; IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue; NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT: subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health; TAT: total adipose tissue; 1y: 1 year after treatment; 2y: 2 years after treatment; 3mo: three months after treatment; VAT: visceral adipose tissue.

DECLARATIONS

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Authors' contributions

AV, EK, JPM, JSFM, KKHA, and LALMK contributed to the conception and design of the study. AV provides overall study management and coordinates the project. JSFM contributed to data collection. AV and JSFM drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol has been approved on March 2, 2017 by the Committee for Human Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in the study provided a written informed consent.

Consent for publication

Not applicable.

Availability of data and material

Data and material are not yet available since data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

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Figure 1. Timeline and study design of the ReLife study

Figure 2. Flow chart of the ReLife study

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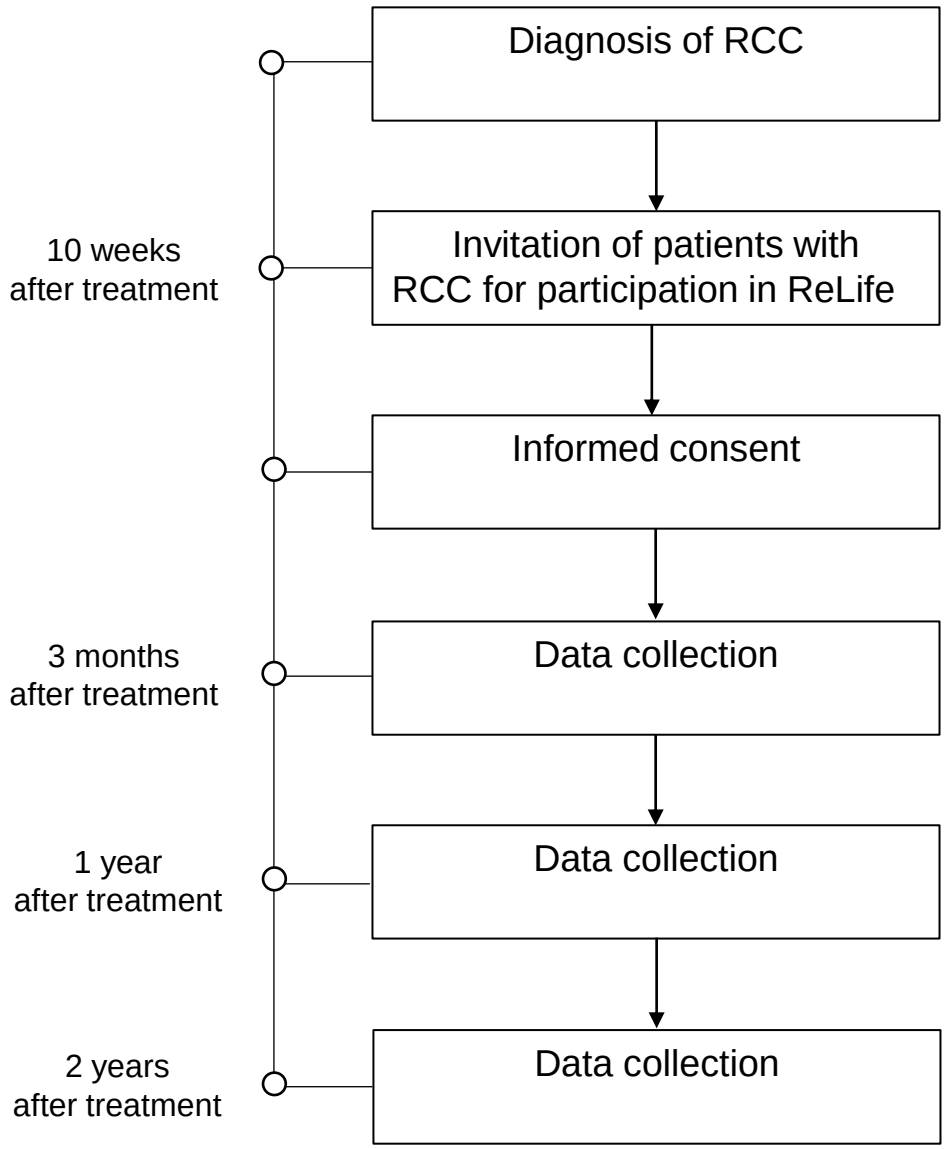
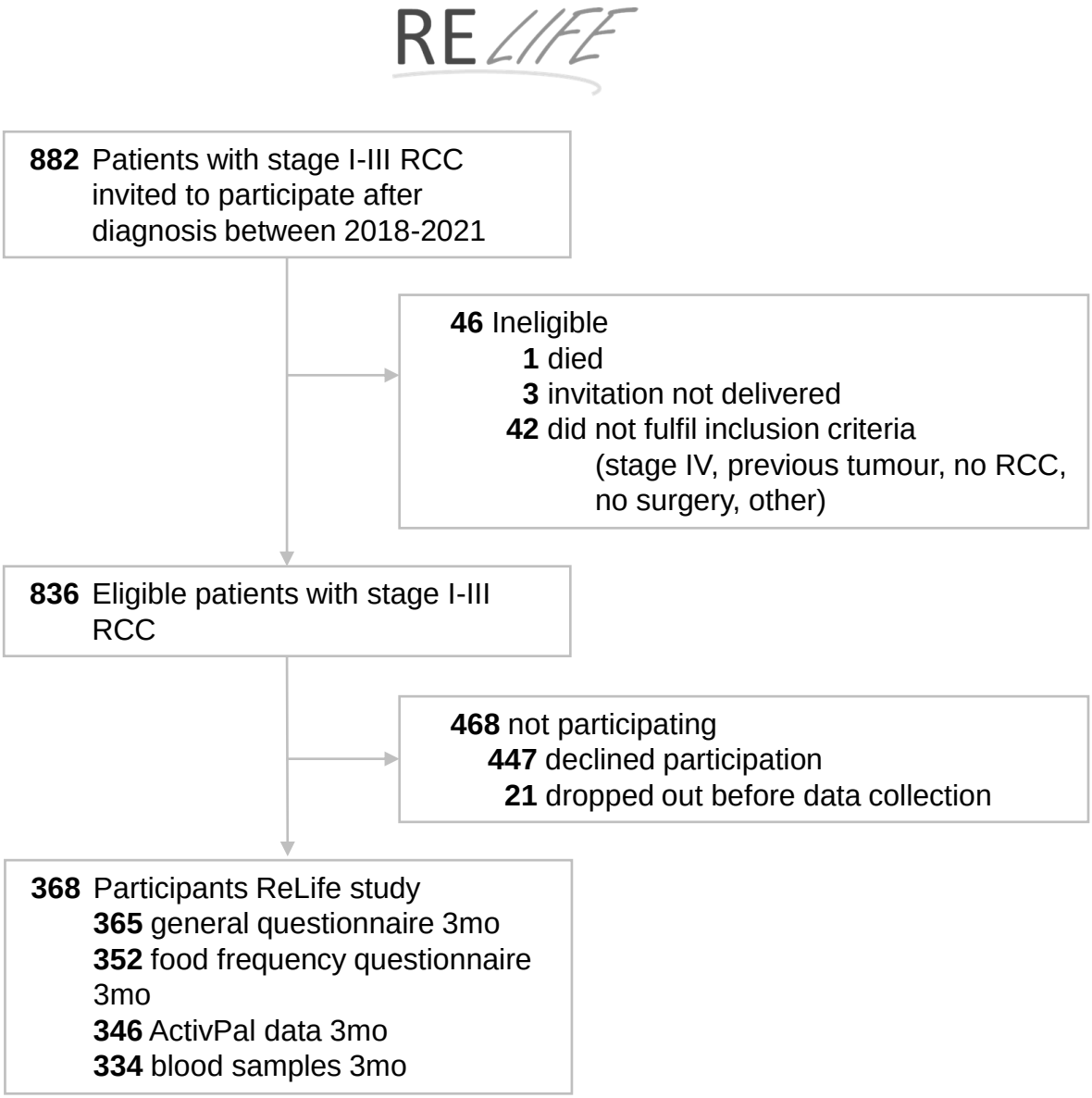

Overview ReLife study
Diagnosis of RCC
10 weeks after treatment
Invitation of patients with RCC for participation in ReLife
Informed consent
3 months after treatment
Data collection
1 year after treatment
Data collection
2 years after treatment
Data collection


RE LIFE
882 Patients with stage I-III RCC invited to participate after diagnosis between 2018-2021
46 Ineligible
1 died
3 invitation not delivered
42 did not fulfil inclusion criteria
(stage IV, previous tumour, no RCC, no surgery, other)
836 Eligible patients with stage I-III RCC
468 not participating
447 declined participation
21 dropped out before data collection
368 Participants ReLife study
365 general questionnaire 3mo
352 food frequency questionnaire 3mo
346 ActivPal data 3mo
334 blood samples 3mo

BMJ Open

Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Oncology
Keywords:	NUTRITION & DIETETICS, Kidney tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PREVENTIVE MEDICINE

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Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life) study in the Netherlands

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Keywords: renal cell cancer, diet, lifestyle, body composition, biomarkers, quality of life, cohort profile

Word count: 2349

ABSTRACT

Purpose:

The ReLife study is set up to obtain insight into the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized renal cell cancer (RCC). Further, it aims to assess the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes including health-related quality of life.

Participants:

The ReLife study is a multicenter prospective cohort study involving 368 patients with newly diagnosed stage I-III RCC recruited from January 2018-June 2021 from 18 hospitals in the Netherlands. At 3 months, 1 and 2 years after treatment, participants fill out a general questionnaire and questionnaires about their lifestyle habits (e.g. diet, physical activity, smoking, alcohol consumption), medical history, and health-related quality of life. At all 3 time points, patients wear an accelerometer and have blood samples taken. CT scans for body composition analysis are being collected. Permission is asked for collection of tumour samples. Information about disease characteristics, treatment of the primary tumour and clinical outcomes is being collected from medical records by the Netherlands Cancer Registry.

Findings to date:

A total of 836 invited patients were eligible and 368 patients were willing to participate and were included (response rate 44%). The mean age of patients was 62.5 ± 9.0 years and 70% was male. The majority had stage I (65%) disease and were treated with radical nephrectomy (57%). Data collection at 3 months and 1 years after treatment has been finalized.

Future plans:

Data collection at 2 years after treatment is expected to be finalized in June 2023 and longitudinal clinical data will continue to be collected. Results of studies based on this cohort are important to develop personalized evidence-based lifestyle advice for patients with localized RCC to enable them to get more control over their disease course.

STRENGTHS AND LIMITATIONS

- The ReLife study is the first population-based prospective cohort study on lifestyle-related factors and clinical outcomes in patients with localized RCC worldwide.
- Comprehensive data on lifestyle-related factors and quality of life are collected at 3 months, 1 year and 2 years after treatment.
- Both self-reported and objective data on body composition and physical activity are collected.
- A limitation is that power for survival analyses is likely to be insufficient and future pooling with other studies may be required.

INTRODUCTION

Incidence rates of kidney cancer are increasing [1], which is partly explained by the increased use of diagnostic imaging but also by the increased prevalence of obesity [2]. The worldwide number of new kidney cancer cases was estimated to be over 430,000 in 2020 [3]. In the Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 [4]. More than 90% of kidney cancers are renal cell cancers (RCC) [5]. Of all RCC patients, about 70-80% are diagnosed with localised disease (stage I-III) and about 20-30% with advanced or metastatic disease (stage IV) [2]. Almost all RCC patients with localised disease are treated with partial or radical nephrectomy [6]. Despite this treatment, 20-30% of patients with localised disease will have a relapse or develop metastatic RCC during follow-up [7]. Five-year relative survival rates are approximately 90% (stage I and II), 65% (stage III), and 12% (stage IV) [2].

Classical prognostic factors for localised RCC include anatomical (e.g., TNM classification), histological (e.g., tumour grade, histological subtype), clinical (e.g., performance status, certain blood values), and molecular features (e.g., *BAP1* and *PBRM1* mutations), but the combination of these features does not have sufficient predictive accuracy [8]. In order to provide tailored treatment and follow-up care, the identification of additional prognostic factors that predict the expected clinical course in each individual patient is subject of active scientific research.

Nowadays, more than 60% of RCC patients are overweight or obese at diagnosis (body mass index (BMI) ≥25 kg/m^2) [9]. A meta-analysis of prospective observational studies showed a 24% increased risk of RCC for men and a 34% increased risk for women per 5 kg/m^2 increase in BMI [10]. It is estimated that about 17% and 24% of RCC cases are attributable to overweight in the Netherlands and in the UK, respectively [11, 12]. Paradoxically, meta-analyses on BMI and survival suggest that RCC patients who were overweight or obese at diagnosis have a significantly better overall, cancer-specific, and recurrence-free survival compared with normal weight patients [13, 14]. The higher risk but better prognosis with higher BMI is counterintuitive. Possibly, body composition explains part of this paradox.

Body composition refers to the content of fat, lean tissue and bone in the human body. The amount and distribution of these tissues may be independent of BMI; subjects with similar BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional areas and mean radiodensity of these tissues can be assessed by analysis of computed tomography (CT) scans at the level of the third lumbar vertebra (L3), using established Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and SM areas at L3 are linearly related to body TAT and SM mass [15-17].

High VAT mass, low SM index (SMI (SM/height^2)), and low SM radiodensity (SMD) have been associated with adverse postoperative [18] and survival outcomes [19-21] in several cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated with increased overall mortality in patients with metastatic RCC [22]. No meta-analysis could be performed for localized RCC due to the limited number of studies and heterogeneity in body composition parameters and outcomes [22]. Studies also suggested an association of low vs. high SMI with higher overall and cancer-specific mortality [23] and of lower SMD with higher overall mortality [24]. Other studies found that low vs. high VAT was associated with a higher risk of recurrence [25], cancer-specific [26, 27], and overall mortality [24].

Body composition is known to differ by age, gender and race [28, 29]. Studies on the association of tumour characteristics with body composition features are inconsistent [30, 31] and studies on the association of lifestyle habits and circulating biomarkers with body composition parameters are not available in patients with RCC. Smoking has been associated with increased RCC risk and RCC-specific mortality [32]. Studies on dietary factors and physical activity are inconsistent for RCC risk [33] and not available for clinical outcomes including health-related quality of life (HRQoL). Some studies suggest that circulating biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size [34], invasion, progression or metastasis [34-36] and survival [37, 38] in patients with RCC but results are inconsistent.

Thus, the association of patient and tumour characteristics, lifestyle habits and circulating biomarkers with body composition features in patients with localized RCC needs to be clarified. Further, there is a clear need to obtain more insight in body composition features and lifestyle habits and their relation with clinical outcomes in patients with localized RCC. This information is important to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes. Therefore, the objectives of this study are to evaluate 1) the association of patient and tumour characteristics, lifestyle habits, and circulating biomarkers with body composition features, and 2) the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQoL.

COHORT DESCRIPTION

Setting

The ReLife study (**Re**nal cell cancer: **Life**style, prognosis, and quality of **Life**) is a prospective cohort study involving patients with newly diagnosed pathologically confirmed primary stage I-III RCC. Patients were recruited in 18 hospitals in the East, South, and Central parts of the Netherlands. Before the start of the study, permission was asked from all urologists of the participating hospitals to select and invite eligible patients from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organisation (IKNL). Once every 2 weeks, newly diagnosed patients were identified by IKNL personnel using notification lists of the Pathological Anatomical National Automate Archive (PALGA foundation) in the Netherlands. Approximately 10 weeks after treatment (surgery or ablation), patients were invited by IKNL personnel on behalf of their urologist to participate in this study (**Figure 1**). Patients who agreed to participate provided a written informed consent. Enrolment started in January 2018 and ended in June 2021 and collection of follow-up data is still ongoing.

Figure 1 Timeline and study design of the ReLife study

Patient and public involvement

Four patient representatives were asked for feedback on the grant proposal and one patient representative was involved in the design and set-up phase of the study. Patients were not involved in the conduction of this research, but will be involved in the reporting and dissemination plans regarding information provision to patients. Results from the study will be communicated to participants and urologists from the participating hospitals through the study website (www.radboudumc.nl/trials/relife), through newsletters and through the website of the patient society. Results will be submitted for publication in peer-reviewed journals and presented at relevant (inter)national conferences.

Participants

Eligible participants were between 18 and 75 years old who were newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who underwent a (partial) nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since all study materials and questionnaires were only available in Dutch. Patients with a previous diagnosis of cancer in the five years before RCC diagnosis and those with a lymph node metastasis or distant metastasis were not eligible.

Data collection and management

Questionnaires

Participants are asked to complete self-administered web-based or paper-and-pencil-based questionnaires at 3 months (3mo), 1 year (1y) and 2 years (2y) after treatment (**Figure 1, Table 1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone calls are made to non-responding participants and to respondents whose questionnaires have missing items.

The general questionnaire at 3mo contains questions on demographics (age, sex, ethnicity, education, living situation, occupation, marital status) and personal and family history of cancer. All questionnaires collect information about height, body weight, amount and frequency of alcohol consumption during week- and weekend days, smoking habits, comorbidities and the use of dietary supplements and medication. Information on smoking habits is collected in detail, including age or date of starting and stopping smoking, number of cigarettes smoked per day, and duration of smoking. Information about habitual physical activity is collected by using the validated short questionnaire to assess health-enhancing physical activity (SQUASH) [39]. The SQUASH questionnaire assesses the average time, i.e. number of days per week and hours and minutes per day, spent in commuting activities, leisure time activities, household activities, and activities at work in a normal week in the past month. At all three time points, patients are also asked to measure and report their waist and hip circumference.

Table 1. Overview of data collection in ReLife at the three time points after treatment

	Measures	3mo	1y	2y
Questionnaires				
Sociodemographic data	Date of birth, gender, country of birth of participant, father, mother, race, living situation, marital status, highest level of education, working history	X		
Anthropometry	Height at baseline, weight two years before diagnosis, weight loss 3-6 months before diagnosis, average weight during adult life	X		
	Current body weight, waist and hip circumference	X	X	X
Lifestyle	Current and past smoking behaviour including dose and duration, alcohol consumption, (reasons for) changes in eating habits, mobility	X	X	X
	Short Questionnaire to Assess Health-enhancing physical activity (29)	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days (32-34)	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X
Medical history	Previously diagnosed with cancer, family history of cancer	X		
	Comorbidities, medication use, dietary supplement use	X	X	X
Diet	163- item Food Frequency Questionnaire	X	X	X
Health-related quality of life	EORTC QLQ-C30 [40]	X	X	X
Accelerometer				
	Habitual physical (in)activity, sedentary behavior	X	X	X
Blood				
	EDTA whole blood for DNA isolation	X		
	EDTA plasma, serum	X	X	X
Tissue				
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X[a]		
CT scan				
	Diagnostic CT scan	X		
	Follow-up CT scans		X[b]	X[b]
Clinical data				
	Disease characteristics, treatment	X	X	X
	Postoperative outcomes, recurrence and progression	X	X	X

[a] To date only permission, no actual collection.; [b] Dependent on availability.

Habitual dietary intake is collected at all three time points using a 163-item validated and reproducible self-administered food frequency questionnaire that was developed by Wageningen University [41-43]. The questionnaire contains questions about the frequency of consumption of food products and the portion size during the previous month. Frequency and portion size of consumed food products are multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) [44].

Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-C30 [45]. The EORTC QLQ-C30 contains five function scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100 scale.

Accelerometer

Habitual physical (in)activity is objectively measured at all three time points using the activPAL physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to be an accurate tool for measuring daily physical activity levels [46]. Participants are asked to wear the device continuously on the front right thigh for seven consecutive days. Data are uploaded using the activPAL software.

Blood samples

Non-fasting blood samples are collected at all three time points. At 3mo, 10 ml EDTA whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood samples are collected, processed and stored at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank.

The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory for Experimental Internal Medicine of Radboudumc using commercially available enzyme-linked immunosorbent assays is planned.

Tumour samples

From all patients, permission for collection of tumour specimens is requested for future assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic alterations (e.g. in the *BAP1* or *PBRM1* genes) [6]. Formalin-fixed paraffin-embedded tumour blocks can be identified by using the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from the local pathology laboratories.

CT scans

CT scans are retrieved from medical records of all patients for the assessment of body composition. Diagnostic CT scans are available from almost all RCC patients as they are used for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well. From these CT scans, cross-sectional areas (cm^2) and mean radiodensity of SM, VAT, SAT and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).

Clinical data

Information about disease characteristics and treatment for the initial tumour and subsequent recurrences is collected from the medical records by data managers of the Netherlands Cancer Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and post-surgical (pTNM) stage, Fuhrman grade and morphology. With respect to therapy, information is collected on type of treatment (type of nephrectomy, type of ablation), operation time, blood loss, complications (Clavien-Dindo classification) and length of hospital stay. Furthermore, data on performance status (e.g. WHO performance status, ASA score) are collected.

Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and Fuhrman grade, and survival, are also collected. We will continue to collect further information on these clinical outcomes in the future to evaluate their association with body composition features, lifestyle habits and circulating biomarkers.

Power calculation and data analyses

The power calculation of this study is based on our initial research question, i.e. the cross-sectional association of patient and tumour characteristics, lifestyle habits, and circulating concentrations of biomarkers with body composition features. With 369 patients, we will have sufficient power (≥80%) to detect a multiple correlation coefficient of 0.30 (Cohen's f^2=0.10 for patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations of biomarkers with body composition features), corresponding to a small (f^2=0.02) to medium (f^2=0.15) effect size [47]. This power calculation is based on 276 stage I-III patients (assuming 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition features as outcome variables (cross-sectional area and radiodensity of SM and cross-sectional area of VAT). For the power calculation, we correct for multiplicity (3 body composition features) by using the Bonferroni corrected alpha of 0.05/3.

Patient characteristics were described using means and standard deviations (SD), medians and interquartile ranges (IQR), or total numbers and percentages where appropriate. Differences in sociodemographic and clinical characteristics between participants and non-participants were evaluated with chi-squared tests. Two-sided p-values <0.05 were considered statistically significant. Multiple linear regression analyses will be used to estimate the cross-sectional association of patient and tumor characteristics, lifestyle habits, and biomarkers with body composition features. Longitudinal associations of body composition features, lifestyle habits and biomarkers with HRQoL will be assessed using linear mixed models. Logistic regression and Cox proportional hazard analyses will be used to estimate the association of

body composition features, lifestyle habits and biomarkers with other clinical outcomes. All statistical analyses will be conducted in R.

FINDINGS TO DATE

Characteristics of study participants

From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19 measures. In total, 836 patients were eligible and 368 patients agreed to participate and filled out the first or second questionnaires (response rate 44%) (**Figure 2**). The median time between time of treatment and time of the 3mo questionnaire completion was 13 weeks (interquartile range 12-14 weeks). The number of questionnaires, ActivPal measurements and blood samples available at 3mo are also shown in **Figure 2**.

Figure 2 Flowchart of the ReLife study

In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients was 62.4 ± 9.0 years and 70% was male. Most patients had stage I (65%) and Fuhrman grade 2 (50%) disease. The majority was treated with radical (57%) or partial nephrectomy (42%). The majority of participants were overweight (44%) or obese (25%) and 50% were former smokers. Compared to non-participants, participants were less likely to be male but were comparable with respect to age, tumour stage, tumour grade, morphology and type of treatment (**Table 3**).

Table 2. Baseline characteristics of 368 patients with renal cell cancer included in the ReLife study

Age at diagnosis (y)	62.4 ± 9.0
Sex	
Male	257 (70)
Female	111 (30)
Race	
White	356 (97)
Black	1 (0.3)
Asian	3 (1)
Other	5 (1)
Missing	3 (1)
Educational level[a]	
Low	151 (41)
Medium	115 (31)
High	98 (27)
Missing	4 (1)
Paid occupation	
Yes	170 (46)
No	195 (53)
Missing	3 (1)
Living situation	
Alone	48 (13)
With partner	228 (62)
With partner and kids	81 (22)
Alone, but with kids	8 (2)
Missing	3 (1)
BMI (kg/m^2)	27.6 ± 4.7
BMI (kg/m^2)	
Underweight (≤18.5)	1 (0.3)
Normal weight (18.5-25)	110 (30)
Overweight (25-≤30)	163 (44)
Obese (>30)	91 (25)
Missing	3 (1)
Waist circumference (cm)[b]	101.2 ± 12.1
Hip circumference (cm)[b]	102.1 ± 9.5
Cigarette smoking status	
Current	43 (12)
Former	185 (50)
Never	137 (37)
Missing	3 (1)
Alcohol consumption (g/d)	
0	104 (28)
>0-10	145 (39)
>10	101 (27)
Missing	18 (5)
Total moderate-to-vigorous physical activity (min/wk)	
<75	27 (7)
75-150	142 (39)
≥150	193 (52)
Missing	6 (2)
Tumor stage	
I	238 (65)
II	55 (15)

III	75 (20)
Fuhrman grade	
1	49 (13)
2	185 (50)
3	67 (18)
4	23 (6)
unknown	44 (12)
Treatment	
Radical nephrectomy	210 (57)
Partial nephrectomy	152 (41)
Ablation[c]	6 (2)
Comorbidities	
0	54 (15)
1	85 (23)
≥2	226 (61)
Missing	3 (1)

Values are mean ± SD or n (%).

[a] Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university)

[b] Values for 8 participants were missing

[c] Other treatment consists of cryoablation (n=2), radiofrequency ablation (n=3) and microwave ablation (n=1)

Table 3. Comparison of demographic and clinical characteristics of 368 patients with renal cell cancer included in the ReLife study and 468 invited non-participants

	Participants	Non-participants	P-value[a]
N	368	468	
Age category (y)			
18-44	14 (4)	28 (6)	0.34
45-64	180 (49)	218 (47)	
65-75	174 (47)	222 (47)	
Sex			
Male	257 (70)	360 (77)	0.02
Female	111 (30)	108 (23)	
Tumor stage			
I	238 (65)	298 (64)	0.51
II	55 (15)	61 (13)	
III	75 (20)	109 (23)	
Fuhrman grade			
1	49 (13)	86 (18)	0.32
2	185 (50)	219 (47)	
3	67 (18)	74 (16)	
4	23 (6)	33 (7)	
unknown	44 (12)	56 (12)	
Morphology			0.97
Clear cell renal tumour	260 (71)	338 (72)	
Papillary renal tumour	48 (13)	58 (12)	
Chromophobe renal tumour	25 (7)	30 (6)	
Other[b]	35 (9)	42 (9)	
Treatment			
Radical nephrectomy	210 (57)	272 (58)	0.76
Partial nephrectomy	152 (41)	191 (41)	
Ablation[c]	6 (2)	5 (1)	

Values are n (%).

[a] From chi-squared test.

[b] Other morphology consists of adenocarcinoma with mixed subtypes (n=4 and n=5), eosinophilic solid and cystic renal cell carcinoma (n=1 and n=0), renal cell carcinoma not otherwise specified (n=28 and n=29), sarcomatoid renal cell carcinoma (n=2 and n=6), collecting duct carcinoma (n=0 and n=1), and clear cell papillary renal cell tumour (n=0 and n=1) for participants and non-participants, respectively.
[c] Other treatment consists of cryoablation (n=2 and n=2), radiofrequency ablation (n=3 and n=2), and microwave ablation (n=1 and n=1) for participants and non-participants, respectively.

FUTURE PLANS

We have already started and will first continue to work on the statistical analyses and writing of manuscripts addressing our main study objectives, i.e. 1) the association of patient and tumour characteristics, lifestyle habits, and circulating biomarkers with body composition features, and 2) the association of body composition features, lifestyle habits and circulating biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications, length of hospital stay), and HRQoL. Statistical analyses for recurrence, progression, and survival will be conducted once follow-up is more mature or pooling with similar cohorts becomes possible.

STRENGTHS AND LIMITATIONS

To our knowledge, the ReLife study is the first population-based prospective longitudinal study on lifestyle-related factors and clinical outcomes in patients with localized RCC worldwide. Comprehensive data on lifestyle-related factors and HRQoL are collected at 3 months, 1 year and 2 years after treatment. Besides questionnaire data on lifestyle-related factors, also objective data on body composition and physical activity are collected. Data on sociodemographic variables and comorbidity is available as well. Information on several clinical outcomes is collected, including postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression, survival, and HRQoL. Moreover, blood samples are collected to measure lifestyle-related, disease-related and genetic biomarkers. Permission is available from participants to use their tumour tissue blocks for assessment of tumour characteristics and acquired genetic alterations.

However, there are also some limitations to this study. As is the case for all longitudinal studies, participants may drop out during the course of the study, potentially leading to selection bias. Some variables have missing values which will be addressed using multiple imputation when applicable. No information on lifestyle-related factors and HRQoL after the two-years follow-up measurement is available. Power for survival analyses is likely to be

insufficient and future pooling with other studies may be necessary. Lastly, we did not use RCC-specific measures of HRQoL in our study.

Results that can be obtained from this study are important to develop personalized evidence-based lifestyle advice for patients with localized RCC to improve their clinical outcomes.

COLLABORATION

The ReLife study group is open for collaborations with national and international colleagues. Any person interested in collaborating on the ReLife study or in getting access to ReLife data for data analyses can contact the corresponding author. Requests for data will be discussed and decided by the ReLife study group and will require a Data Transfer Agreement.

Abbreviations

BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal; IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue; NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT: subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health; TAT: total adipose tissue; 1y: 1 year after treatment; 2y: 2 years after treatment; 3mo: three months after treatment; VAT: visceral adipose tissue.

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Authors' contributions

AV, EK, JPMS, JSFM, KKHA, and LALMK contributed to the conception and design of the study. AV provides overall study management and coordinates the project. JSFM contributed to data collection. AV and JSFM drafted the manuscript. All authors have critically read and revised the manuscript. All authors approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study protocol has been approved on March 2, 2017 by the Committee for Human Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in the study provided a written informed consent.

Consent for publication

Not applicable.

Availability of data and material

Data and material are not yet available since data collection has not been completed yet. After completion of data collection, data will be made available by the corresponding author upon reasonable request.

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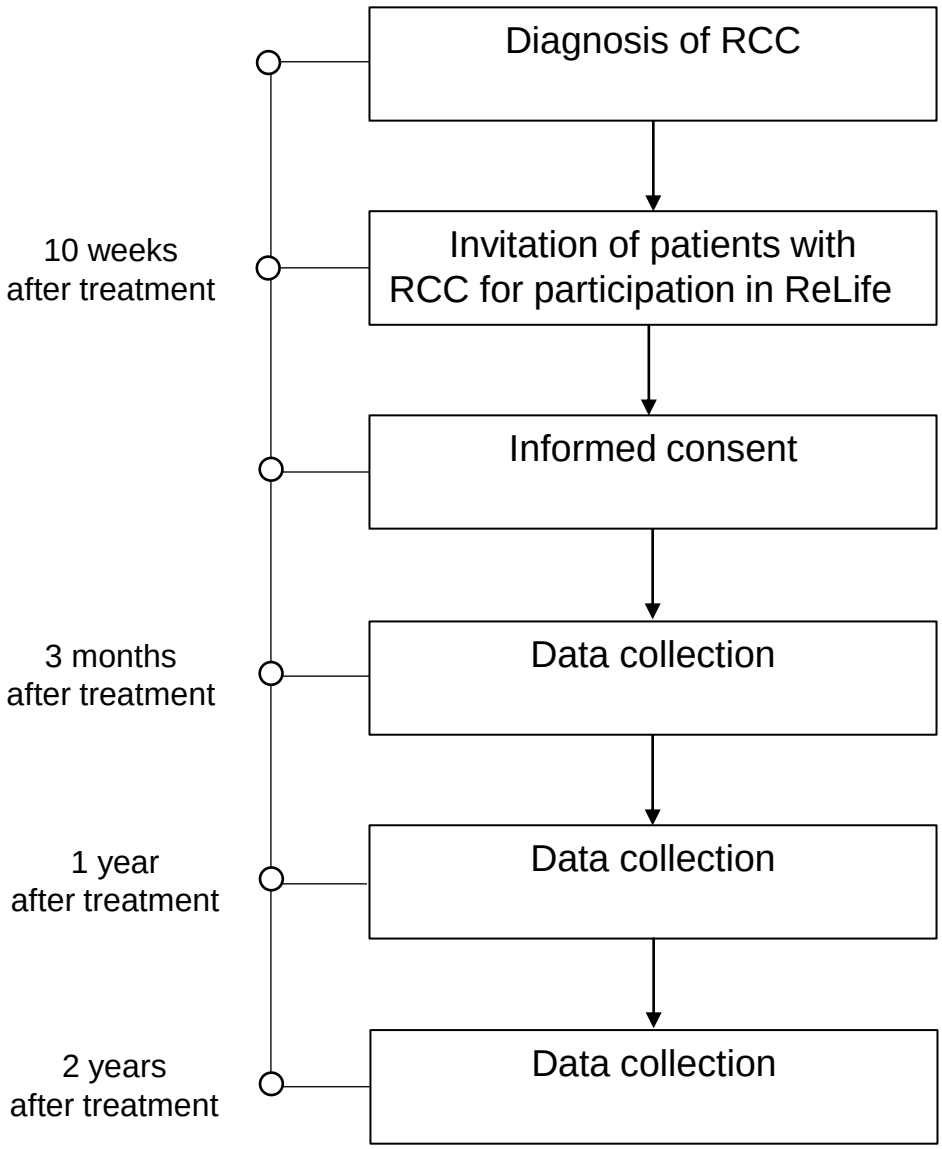
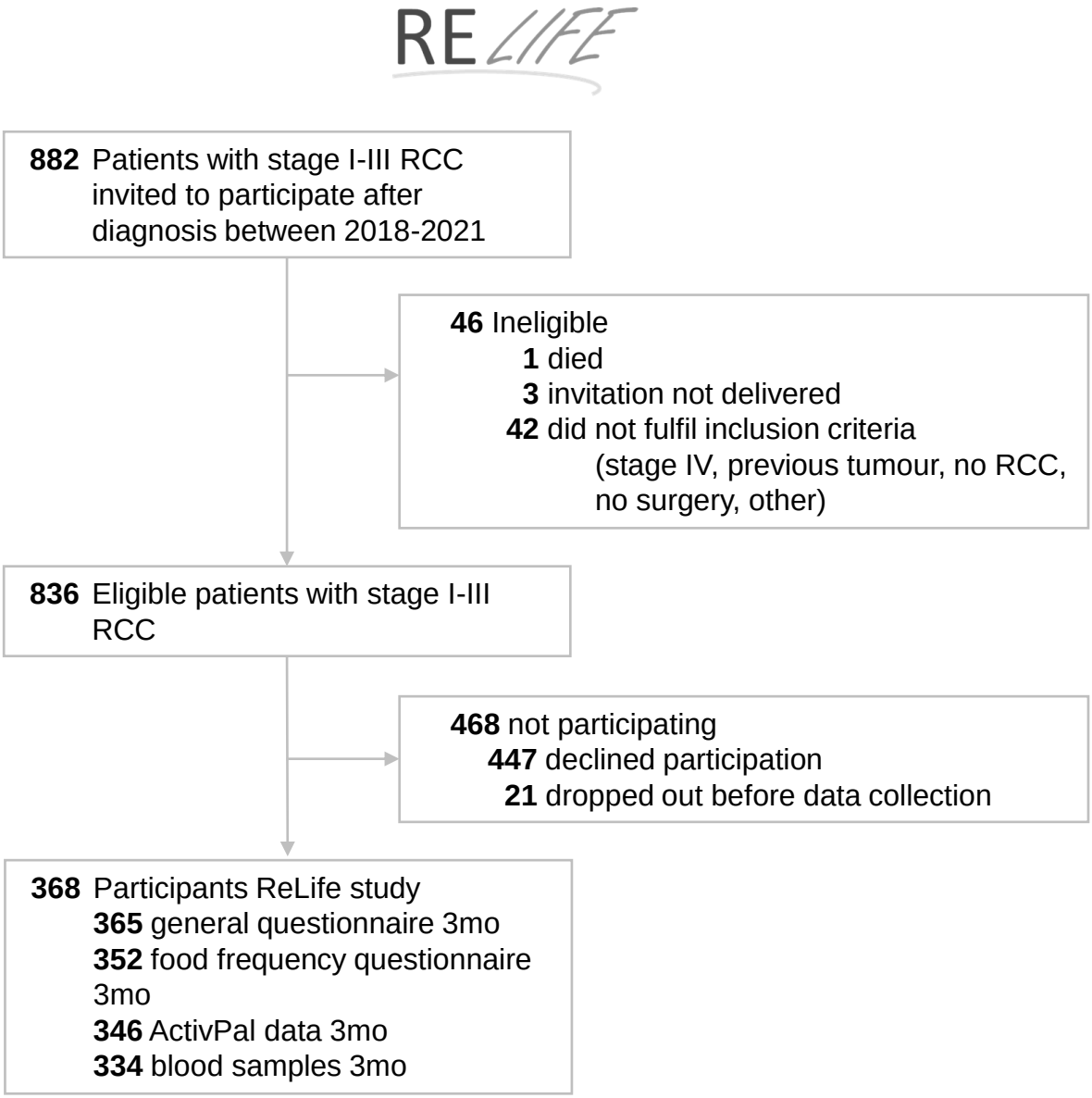
Figure 1. Timeline and study design of the ReLife study

Figure 2. Flow chart of the ReLife study

Overview ReLife study




RELIFE
882 Patients with stage I-III RCC invited to participate after diagnosis between 2018-2021
46 Ineligible
1 died
3 invitation not delivered
42 did not fulfil inclusion criteria
(stage IV, previous tumour, no RCC, no surgery, other)
836 Eligible patients with stage I-III RCC
468 not participating
447 declined participation
21 dropped out before data collection
368 Participants ReLife study
365 general questionnaire 3mo
352 food frequency questionnaire 3mo
346 ActivPal data 3mo
334 blood samples 3mo