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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066909
Article Type:	Cohort profile
Date Submitted by the Author:	26-Jul-2022
Complete List of Authors:	Maurits, Jake; Radboudumc, Department for Health Evidence Sedelaar, Michiel; Radboudumc, Department of Urology Aben, Katja; Netherlands Cancer Registry; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University & Research, Division of Human Nutrition and Health; Radboudumc, Department for Health Evidence Kiemeneij, Lambertus; Radboudumc, Department for Health Evidence Vrieling, Alina; Radboudumc, Department for Health Evidence
Keywords:	NUTRITION & DIETETICS, Kidney tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PREVENTIVE MEDICINE

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3 1 **Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life)**  
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5 2 **study in the Netherlands**  
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45 19 **Keywords:** renal cell cancer, diet, lifestyle, body composition, biomarkers, quality of life,  
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47 20 cohort profile  
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51 21  
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53 22 **Word count:** 2349  
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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  $62.5 \pm 9.0$  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.

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5 52 **STRENGTHS AND LIMITATIONS**

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7 53 - The ReLife study is the first population-based prospective cohort study on lifestyle-related  
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9 54 factors and clinical outcomes in patients with localized RCC.

10  
11 55 - Comprehensive data on lifestyle-related factors and quality of life were collected at 3 months,  
12  
13 56 1 year and 2 years after diagnosis.

14  
15 57 - Both self-reported and objective data on body composition and physical activity were  
16  
17 58 collected.

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19 59 - A limitation is that power for survival analyses is insufficient and future pooling with other  
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21 60 studies is required.  
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## 61 INTRODUCTION

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

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

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

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

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3 89 BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose  
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5 90 tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional  
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7 91 areas and mean radiodensity of these tissues can be assessed by analysis of computed  
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9 92 tomography (CT) scans at the level of the third lumbar vertebra (L3), using established  
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11 93 Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and  
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13 94 SM areas at L3 are linearly related to body TAT and SM mass (14-16).

15 95 High VAT mass, low SM index (SMI (SM/height<sup>2</sup>)), and low SM radiodensity (SMD) have  
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17 96 been associated with adverse postoperative (17) and survival outcomes (18-20) in several  
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19 97 cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated  
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21 98 with increased overall mortality in patients with metastatic RCC (21). No meta-analysis could  
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23 99 be performed for localized RCC due to the limited number of studies and heterogeneity in body  
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25 100 composition parameters and outcomes (21). One study also suggested an association of low  
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27 101 vs. high SMI with higher overall and cancer-specific mortality (22) while other studies found  
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29 102 that low vs. high VAT was associated with a higher risk of recurrence (23) or cancer-specific  
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31 103 mortality (24, 25).

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33  
34 104 Body composition is known to differ by age, gender and race (26, 27). Studies on the  
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36 105 association of tumour characteristics with body composition features are inconsistent (28, 29)  
37  
38 106 and studies on the association of lifestyle habits and circulating biomarkers with body  
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40 107 composition parameters are not available in patients with RCC. Smoking has been associated  
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42 108 with increased RCC risk and RCC-specific mortality (30). Studies on dietary factors and  
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44 109 physical activity are inconsistent for RCC risk (31) and not available for clinical outcomes  
45  
46 110 including health-related quality of life (HRQoL). Some studies suggest that circulating  
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48 111 biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size (32), invasion,  
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50 112 progression or metastasis (32-34) and survival (35, 36) in patients with RCC but results are  
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52 113 inconsistent.

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55 114 Thus, the association of patient and tumour characteristics, lifestyle habits and circulating  
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57 115 biomarkers with body composition features in patients with localized RCC needs to be clarified.  
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59 116 Further, there is a clear need to obtain more insight in body composition features and lifestyle

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

For peer review only

## 120 COHORT DESCRIPTION

### 121 Setting

122 The ReLife study (**Renal cell cancer: Lifestyle, prognosis, and quality of Life**) is a prospective  
123 cohort study including patients with newly diagnosed pathologically confirmed primary stage I-  
124 III RCC. The study has been designed to evaluate 1) the association of patient and tumour  
125 characteristics, lifestyle habits, and circulating biomarkers with body composition features, and  
126 2) the association of body composition features, lifestyle habits and circulating biomarkers with  
127 clinical outcomes, including HRQOL. Patients were recruited in 18 hospitals in the East, South,  
128 and Central parts of the Netherlands. Before the start of the study, permission was asked from  
129 all urologists of the participating hospitals to select and invite eligible patients from the  
130 Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer  
131 Organisation (IKNL). Once every 2 weeks, newly diagnosed patients were identified through  
132 IKNL using notification lists of the Pathological Anatomical National Automate Archive (PALGA  
133 foundation) in the Netherlands. Approximately 10 weeks after treatment (surgery or ablation),  
134 patients were invited on behalf of their urologist to participate in this study (**Figure 1**). Patients  
135 who agreed to participate provided a written informed consent. Enrolment started in January  
136 2018 and ended in June 2021 and collection of follow-up data is still ongoing.

137

138 **Figure 1** Timeline and study design of the ReLife study

139

### 140 Patient and public involvement

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

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2  
3 148 relevant (inter)national conferences.  
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## 7 150 **Participants**

9 151 Eligible participants were Dutch speaking patients between 18 and 75 years old who were  
11 152 newly diagnosed with a histologically confirmed primary stage I-III RCC tumour and who  
13 153 underwent a (partial) nephrectomy or ablation. Patients with a previous diagnosis of cancer in  
15 154 the five years before RCC diagnosis and those with a lymph node metastasis or distant  
17 155 metastasis were not eligible.  
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## 22 157 **Data collection and management**

### 24 158 *Questionnaires*

26 159 Participants are asked to complete self-administered web-based or paper-and-pencil-based  
28 160 questionnaires at 3 months (T3mo), 1 year (T1y) and 2 years (T2y) after treatment (**Figure 1,**  
30 161 **Table 1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone  
32 162 calls are made to non-responding participants and to respondents whose questionnaires have  
34 163 missing items.

36 164 The general questionnaire at T3mo contains questions on demographics (age, sex, ethnicity,  
38 165 education, living situation, occupation, marital status) and personal and family history of  
40 166 cancer. All questionnaires collect information about height, body weight, amount and  
42 167 frequency of alcohol consumption during week- and weekend days, smoking habits,  
44 168 comorbidities and the use of dietary supplements and medication. Information on smoking  
46 169 habits is collected in detail, including age or date of starting and stopping smoking, number of  
48 170 cigarettes smoked per day, and duration of smoking. Information about habitual physical  
50 171 activity is collected by using the previously validated Short Questionnaire to Assess Health  
52 172 (SQUASH) (37), which is fairly reliable and valid in an adult population (37-39). The SQUASH  
54 173 questionnaire assesses the average time, i.e. number of days per week and hours and  
56 174 minutes per day, spent in commuting activities, leisure time activities, household activities,  
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175 **Table 1.** Overview of data collection in ReLife at the three time points after treatment

	Measures	T3mo	T1y	T2y
<b>Questionnaires</b>				
<i>Sociodemographic data</i>	Date of birth, gender, country of birth of participant, father, mother, race, living situation, marital status, highest level of education, working history	X		
<i>Anthropometry</i>	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
<i>Lifestyle</i>	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
<i>Medical history</i>	Previously diagnosed with cancer, family history of cancer	X		
	Comorbidities, medication use, dietary supplement use	X	X	X
<i>Diet</i>	163- item Food Frequency Questionnaire	X	X	X
<i>Health-related quality of life</i>	EORTC QLQ-C30 (36)	X	X	X
<b>Accelerometer</b>				
	Habitual physical (in)activity, sedentary behavior	X	X	X
<b>Blood</b>				
	EDTA whole blood for DNA isolation	X		
	EDTA plasma, serum	X	X	X
<b>Tissue</b>				
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X <sup>a</sup>		
<b>CT scan</b>				
	Diagnostic CT scan	X		
	Follow-up CT scans		X <sup>b</sup>	X <sup>b</sup>
<b>Clinical data</b>				
	Disease characteristics, treatment	X	X	X
	Postoperative outcomes, recurrence and progression	X	X	X

176 <sup>a</sup> To date only permission, no actual collection.; <sup>b</sup> Dependent on availability.

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3 177 and activities at work in a normal week in the past month. At all three time points, patients  
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5 178 are also asked to measure and report their waist and hip circumference.  
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9 180 Habitual dietary intake is collected at all three time points using a 163-item validated and  
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11 181 reproducible self-administered food frequency questionnaire that was developed by  
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13 182 Wageningen University (40-42). The questionnaire contains questions about the frequency of  
14  
15 183 consumption of food products and the portion size during the previous month. Frequency and  
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17 184 portion size of consumed food products are multiplied to obtain their intake in grams per day.  
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19 185 Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) (43).  
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24 187 Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-  
25  
26 188 C30 (44). The EORTC QLQ-C30 contains five function scales (physical, role, cognitive,  
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28 189 emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting)  
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30 190 and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial  
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32 191 impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with  
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34 192 ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100  
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36 193 scale.  
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#### 40 195 *Accelerometer*

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43 196 Habitual physical (in)activity is objectively measured at all three time points using the activPAL  
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45 197 physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to  
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47 198 be an accurate tool for measuring daily physical activity levels (45). Participants are asked to  
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49 199 wear the device continuously on the front right thigh for seven consecutive days. Data are  
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51 200 uploaded using the activPAL software.  
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#### 54 202 *Blood samples*

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57 203 Non-fasting blood samples are collected at all three time points. At T3mo, 10 ml EDTA  
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59 204 whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At  
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3 205 the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood  
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5 206 samples are collected, processed and stored at -80°C locally in the participating hospitals  
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7 207 according to a standard protocol before transportation on dry ice to the Radboud Biobank.  
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9 208 The blood samples are stored in the Radboud Biobank at -80°C for future analyses of  
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11 209 genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory  
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13 210 for Experimental Internal Medicine of Radboudumc using commercially available  
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15 211 enzyme-linked immunosorbent assays is planned.  
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### 19 213 *Tumour samples*

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22 214 From all patients, permission for collection of tumour specimens is requested for potential  
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24 215 future assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic  
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26 216 alterations (e.g. in the *BAP1* or *PBRM1* genes) (5). Tumour blocks can be identified by using  
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28 217 the PALGA foundation and retrieved using the Dutch National Tissuebank Portal (DNTP) from  
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30 218 the local pathology laboratories.  
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### 34 220 *CT scans*

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36 221 CT scans are retrieved from medical records of all patients for the assessment of body  
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38 222 composition. Diagnostic CT scans are available from almost all RCC patients as they are used  
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40 223 for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well.  
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42 224 From these CT scans, cross-sectional areas (cm<sup>2</sup>) and mean radiodensity of SM, VAT, SAT  
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44 225 and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).  
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### 48 227 *Clinical data*

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51 228 Information about disease characteristics and treatment for the initial tumour and subsequent  
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53 229 recurrences is collected from the medical records by data managers of the Netherlands Cancer  
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55 230 Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and  
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57 231 post-surgical (pTNM) stage, tumour grade and histology. With respect to therapy, information  
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59 232 is collected on type of treatment (type of nephrectomy, type of ablation), operation time, blood

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3 233 loss, complications (Clavien-Dindo classification) and length of hospital stay. Furthermore,  
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5 234 data on performance status (e.g. WHO performance status, ASA score) are collected.  
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9 236 Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and  
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11 237 Fuhrman grade, is also collected.  
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### 15 239 *Power calculation and data analyses*

17 240 The power calculation of this study is based on our initial research question, i.e. the cross-  
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19 241 sectional association of patient and tumour characteristics, lifestyle habits, and circulating  
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21 242 concentrations of biomarkers with body composition features. With 369 patients, we will have  
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23 243 sufficient power ( $\geq 80\%$ ) to detect a multiple correlation coefficient of 0.30 (Cohen's  $f^2=0.10$  for  
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25 244 patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations  
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27 245 of biomarkers with body composition features), corresponding to a small ( $f^2=0.02$ ) to medium  
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29 246 ( $f^2=0.15$ ) effect size (46). This power calculation is based on 276 stage I-III patients (assuming  
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31 247 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition  
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33 248 features as outcome variables (cross-sectional area and radiodensity of SM and cross-  
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35 249 sectional area of VAT). For the power calculation, we correct for multiplicity (3 body  
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37 250 composition features) by using the Bonferroni corrected alpha of 0.05/3.  
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40 251 Multiple linear regression analyses will be used to estimate the cross-sectional association of  
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42 252 patient and tumor characteristics, lifestyle habits, and biomarkers with body composition  
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44 253 features. Longitudinal associations of body composition features, lifestyle habits and  
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46 254 biomarkers with HRQoL will be assessed using linear mixed models. Logistic regression and  
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48 255 Cox proportional hazard analyses will be used to estimate the association of body composition  
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50 256 features, lifestyle habits and biomarkers with other clinical outcomes.  
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## 54 258 **FINDINGS TO DATE**

### 55 259 **Characteristics of study participants**

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3 261 **Figure 2** Flowchart of the ReLife study

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7 263 From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to  
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9 264 participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19  
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11 265 measures. In total, 837 patients were eligible and 369 patients agreed to participate and filled  
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13 266 out the first or second questionnaires (response rate 44%) (**Figure 2**). The number of  
14  
15 267 questionnaires, ActivPal measurements and blood samples available at T3mo are also shown  
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17 268 in **Figure 2**. The collection of CT scans and data at T1y and T2y are is still ongoing.

18  
19 269 In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients  
20  
21 270 was  $62.5 \pm 9.0$  years and 70% was male. Most patients had stage I (65%) and Fuhrman grade  
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23 271 2 (50%) disease. The majority has been treated with radical (57%) or partial nephrectomy  
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25 272 (42%). Participants were comparable to non-participants with respect to age, sex, tumour  
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27 273 stage, tumour grade and type of treatment. The majority of participants was overweight (44%)  
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29 274 or obese (25%) and was a former smoker (50%).  
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275 **Table 2.** Baseline characteristics of 369 patients with renal cell cancer included in the ReLife  
276 study

Age at diagnosis (y), mean $\pm$ SD	62.5 $\pm$ 9.0
Sex, n (%)	
Male	258 (70)
Female	111 (30)
Educational level, n (%) <sup>a</sup>	
Low	151 (41)
Medium	116 (31)
High	98 (27)
Missing	4 (1)
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	27.5 $\pm$ 4.6
BMI (kg/m <sup>2</sup> ), n (%)	
Underweight ( $\leq$ 18.5)	1 (0.3)
Normal weight (18.5-25)	111 (30)
Overweight (25- $\leq$ 30)	163 (44)
Obese ( $>$ 30)	91 (25)
Missing	3 (1)
Waist circumference (cm), mean $\pm$ SD <sup>b</sup>	101.2 $\pm$ 12.1
Hip circumference (cm), mean $\pm$ SD <sup>b</sup>	102.0 $\pm$ 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 <sup>c</sup>	6 (2)
Comorbidities, n (%)	
0	54 (15)
1	85 (23)
$\geq$ 2	227 (62)
Missing	3 (1)

277 <sup>a</sup> Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general  
278 secondary education, pre-university education), high (university of vocational education, university)

279 <sup>b</sup> Values for 8 participants were missing

280 <sup>c</sup> Other treatment consisted of cryoablation (n=2), radiofrequency ablation (n=3) and microwave ablation (n=1)

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3 281 **Abbreviations**  
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5 282 BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal;  
6  
7 283 IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue;  
8  
9 284 NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National  
10  
11 285 Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT:  
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13 286 subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal  
14  
15 287 muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health;  
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17 288 TAT: total adipose tissue; T1y: 1 year after treatment; T2y: 2 years after treatment; T3mo:  
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19 289 three months after treatment; VAT: visceral adipose tissue.  
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3 290 **DECLARATIONS**

4  
5 291 **Acknowledgements**

6  
7 292 We are grateful to all the patients who participate in this study and we thank the following  
8  
9 293 hospitals for their involvement in recruitment for the ReLife study: Amphia Ziekenhuis,  
10  
11 294 Breda/Oosterhout (D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (A.Q.H.J. Niemer);  
12  
13 295 Canisius-Wilhelmina Ziekenhuis, Nijmegen (D.M. Somford); Catharina Ziekenhuis,  
14  
15 296 Eindhoven (W.A. Scheepens); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (P.J.M.  
16  
17 297 Kil, B.P. Wijsman); Elkerliek Ziekenhuis, Helmond (P.J. van Hest); Gelre Ziekenhuizen,  
18  
19 298 Apeldoorn/Zutphen (D.M. Bochove-Overgaauw); Jeroen Bosch Ziekenhuis, 's-  
20  
21 299 Hertogenbosch (S. van der Meer); Maasziekenhuis Pantein, Boxmeer (E. van Boven);  
22  
23 300 Maxima Medisch Centrum, Veldhoven/Eindhoven (L.M.C.L. Fossion, K. de Laet); Meander  
24  
25 301 Medisch Centrum, Amersfoort (F.S. van Rey); Radboudumc, Nijmegen; Rijnstate,  
26  
27 302 Arnhem/Velp/Zevenaar (G.A.H.J Smits); Slingeland Ziekenhuis, Doetinchem (A.D.H.  
28  
29 303 Geboers); St. Jansdal Ziekenhuis, Harderwijk (W.J. Kniestedt); UMC Utrecht (R.P. Meijer);  
30  
31 304 Ziekenhuis Gelderse Vallei, Ede (M.D.H. Kortleve); Ziekenhuisgroep Twente,  
32  
33 305 Almelo/Hengelo (S. Stomps). In addition, we thank Ms. Ivy Beeren, Ms. Monique  
34  
35 306 Eijgenberger, Ms. Jolanda van Haren and Ms. Ursula Oldenhof for their assistance in data  
36  
37 307 collection. We also thank the data managers and research assistants of the Netherlands  
38  
39 308 Cancer Registry held by the Netherlands Comprehensive Cancer Organisation (IKNL) for  
40  
41 309 inviting patients and collecting the clinical data.  
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47 311 **Authors' contributions**

48  
49 312 AV, EK, JPM, JSFM, KKHA, and LALMK contributed to the conception and design of the  
50  
51 313 study. AV provides overall study management and coordinates the project. JSFM contributed  
52  
53 314 to data collection. AV and JSFM drafted the manuscript. All authors have critically read and  
54  
55 315 revised the manuscript. All authors approved the final version of the manuscript.  
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59  
60 317 **Funding**

1  
2  
3 318 This project is funded by the Dutch Cancer Society (KUN 2015-7948). Sponsors were not  
4  
5 319 involved in the study design nor will they be in the collection, analysis, and interpretation of  
6  
7 320 data, or in the publications that will result from this study.  
8

9 321

### 11 322 **Competing interests**

13 323 The authors declare that they have no competing interests.  
14  
15 324

### 17 325 **Ethics approval and consent to participate**

19 326 The study protocol has been approved on March 2, 2017 by the Committee for Human  
20  
21 327 Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in  
22  
23 328 the study provided a written informed consent.  
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25 329

### 28 330 **Consent for publication**

30 331 Not applicable.  
31  
32 332

### 34 333 **Availability of data and material**

36 334 Data and material are not yet available since data collection has not been completed yet.  
37  
38 335 After completion of data collection, data will be made available by the corresponding author  
39  
40 336 upon reasonable request.  
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3 469 **Figure 1.** Timeline and study design of the ReLife study  
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5 470 **Figure 2.** Flow chart of the ReLife study  
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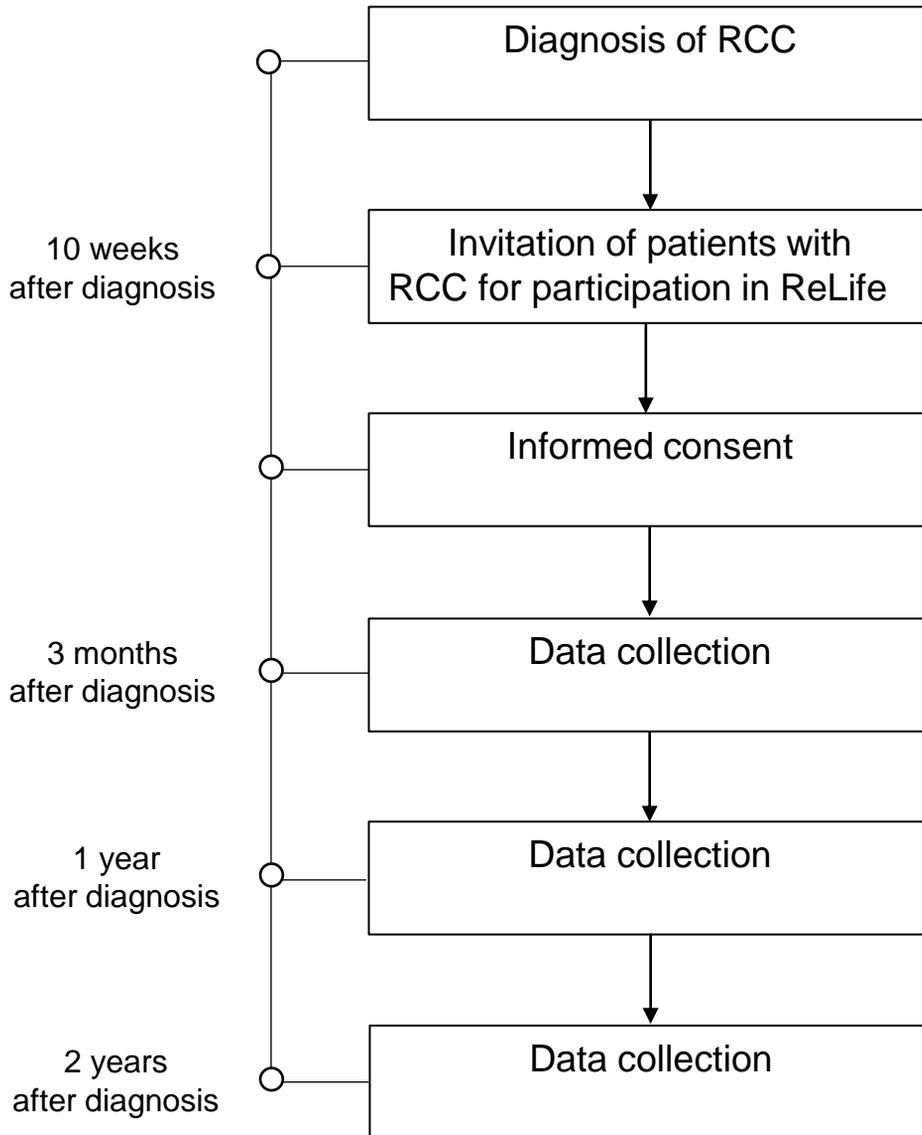
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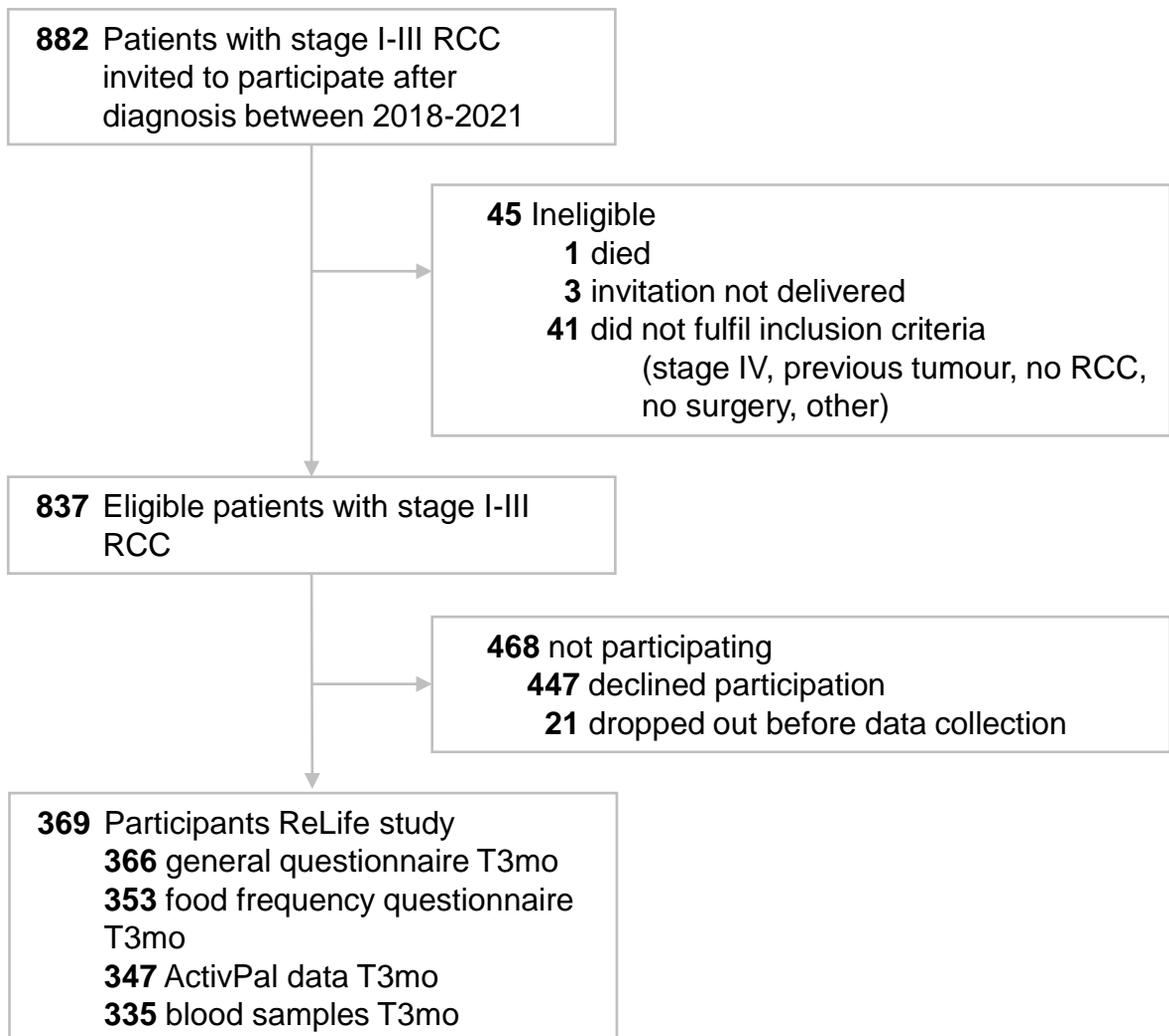
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## Overview ReLife study



# RE LIFE



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066909.R1
Article Type:	Cohort profile
Date Submitted by the Author:	13-Feb-2023
Complete List of Authors:	Maurits, Jake; Radboudumc, Department for Health Evidence Sedelaar, Michiel; Radboudumc, Department of Urology Aben, Katja; Netherlands Cancer Registry; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University & Research, Division of Human Nutrition and Health; Radboudumc, Department for Health Evidence Kiemeneij, Lambertus; Radboudumc, Department for Health Evidence Vrieling, Alina; Radboudumc, Department for Health Evidence
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Oncology
Keywords:	NUTRITION & DIETETICS, Kidney tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PREVENTIVE MEDICINE

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3 1 **Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life)**  
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5 2 **study in the Netherlands**  
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9 4 Jake. S.F. Maurits<sup>a</sup>, J.P. Michiel Sedelaar<sup>b</sup>, Katja K.H. Aben<sup>a,c</sup>, Ellen Kampman<sup>a,d</sup>, Lambertus  
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11 5 A.L.M. Kiemeney<sup>a,b</sup>, Alina Vrieling<sup>a</sup>  
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40 17 Tel: +31 24 3616944, Fax: +31 24 3613505, e-mail: Alina.Vrieling@radboudumc.nl  
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44  
45 19 **Keywords:** renal cell cancer, diet, lifestyle, body composition, biomarkers, quality of life,  
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47 20 cohort profile  
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53 22 **Word count:** 2349  
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**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  $62.5 \pm 9.0$  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.

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3 **51 STRENGTHS AND LIMITATIONS**  
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5 52 - The ReLife study is the first population-based prospective cohort study on lifestyle-related  
6  
7 53 factors and clinical outcomes in patients with localized RCC worldwide.

8  
9 54 - Comprehensive data on lifestyle-related factors and quality of life are collected at 3 months,  
10  
11 55 1 year and 2 years after treatment.

12  
13 56 - Both self-reported and objective data on body composition and physical activity are collected.

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15 57 - A limitation is that power for survival analyses is likely to be insufficient and future pooling  
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17 58 with other studies may be required.  
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## 59 INTRODUCTION

60 Incidence rates of kidney cancer are increasing (1), which is partly explained by the increased  
61 use of diagnostic imaging but also by the increased prevalence of obesity (2). The worldwide  
62 number of new kidney cancer cases was estimated to be over 430,000 in 2020 (3). In the  
63 Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 (4). More than  
64 90% of kidney cancers are renal cell cancers (RCC) (5). Of all RCC patients, about 70-80%  
65 are diagnosed with localised disease (stage I-III) and about 20-30% with advanced or  
66 metastatic disease (stage IV) (2). Almost all RCC patients with localised disease are treated  
67 with partial or radical nephrectomy (6). Despite this treatment, 20-30% of patients with localised  
68 disease will have a relapse or develop metastatic RCC during follow-up (7). Five-year relative  
69 survival rates are approximately 90% (stage I and II), 65% (stage III), and 12% (stage IV) (2).

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

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

1  
2  
3 86 Body composition refers to the content of fat, lean tissue and bone in the human body.  
4  
5 87 The amount and distribution of these tissues may be independent of BMI; subjects with similar  
6  
7 88 BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose  
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9 89 tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional  
10  
11 90 areas and mean radiodensity of these tissues can be assessed by analysis of computed  
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13 91 tomography (CT) scans at the level of the third lumbar vertebra (L3), using established  
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15 92 Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and  
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17 93 SM areas at L3 are linearly related to body TAT and SM mass (15-17).

18  
19  
20 94 High VAT mass, low SM index (SMI (SM/height<sup>2</sup>)), and low SM radiodensity (SMD) have  
21  
22 95 been associated with adverse postoperative (18) and survival outcomes (19-21) in several  
23  
24 96 cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated  
25  
26 97 with increased overall mortality in patients with metastatic RCC (22). No meta-analysis could  
27  
28 98 be performed for localized RCC due to the limited number of studies and heterogeneity in body  
29  
30 99 composition parameters and outcomes (22). Studies also suggested an association of low vs.  
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32 100 high SMI with higher overall and cancer-specific mortality (23) and of lower SMD with higher  
33  
34 101 overall mortality (24). Other studies found that low vs. high VAT was associated with a higher  
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36 102 risk of recurrence (25), cancer-specific (26, 27), and overall mortality (24).

37  
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39 103 Body composition is known to differ by age, gender and race (28, 29). Studies on the  
40  
41 104 association of tumour characteristics with body composition features are inconsistent (30, 31)  
42  
43 105 and studies on the association of lifestyle habits and circulating biomarkers with body  
44  
45 106 composition parameters are not available in patients with RCC. Smoking has been associated  
46  
47 107 with increased RCC risk and RCC-specific mortality (32). Studies on dietary factors and  
48  
49 108 physical activity are inconsistent for RCC risk (33) and not available for clinical outcomes  
50  
51 109 including health-related quality of life (HRQoL). Some studies suggest that circulating  
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53 110 biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size (34), invasion,  
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55 111 progression or metastasis (34-36) and survival (37, 38) in patients with RCC but results are  
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57 112 inconsistent.  
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3 113 Thus, the association of patient and tumour characteristics, lifestyle habits and circulating  
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5 114 biomarkers with body composition features in patients with localized RCC needs to be clarified.  
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7 115 Further, there is a clear need to obtain more insight in body composition features and lifestyle  
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9 116 habits and their relation with clinical outcomes in patients with localized RCC. This information  
10  
11 117 is important to develop personalized evidence-based lifestyle advice for patients with localized  
12  
13 118 RCC to improve their clinical outcomes. Therefore, the objectives of this study are to evaluate  
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15 119 1) the association of patient and tumour characteristics, lifestyle habits, and circulating  
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17 120 biomarkers with body composition features, and 2) the association of body composition  
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19 121 features, lifestyle habits and circulating biomarkers with clinical outcomes, including  
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21 122 postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression,  
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23 123 survival, and HRQOL.  
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## 124 **COHORT DESCRIPTION**

### 125 **Setting**

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

139 **Figure 1** Timeline and study design of the ReLife study

### 141 **Patient and public involvement**

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

### 151 **Participants**

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3 152 Eligible participants were between 18 and 75 years old who were newly diagnosed with a  
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5 153 histologically confirmed primary stage I-III RCC tumour and who underwent a (partial)  
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7 154 nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since  
8  
9 155 all study materials and questionnaires were only available in Dutch. Patients with a previous  
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11 156 diagnosis of cancer in the five years before RCC diagnosis and those with a lymph node  
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13 157 metastasis or distant metastasis were not eligible.  
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## 17 159 **Data collection and management**

### 18 160 *Questionnaires*

19  
20 161 Participants are asked to complete self-administered web-based or paper-and-pencil-based  
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22 162 questionnaires at 3 months (3mo), 1 year (1y) and 2 years (2y) after treatment (**Figure 1, Table**  
23  
24 163 **1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone calls are  
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26 164 made to non-responding participants and to respondents whose questionnaires have missing  
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28 165 items.  
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31  
32 166 The general questionnaire at 3mo contains questions on demographics (age, sex, ethnicity,  
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34 167 education, living situation, occupation, marital status) and personal and family history of  
35  
36 168 cancer. All questionnaires collect information about height, body weight, amount and  
37  
38 169 frequency of alcohol consumption during week- and weekend days, smoking habits,  
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40 170 comorbidities and the use of dietary supplements and medication. Information on smoking  
41  
42 171 habits is collected in detail, including age or date of starting and stopping smoking, number of  
43  
44 172 cigarettes smoked per day, and duration of smoking. Information about habitual physical  
45  
46 173 activity is collected by using the validated short questionnaire to assess health-enhancing  
47  
48 174 physical activity (SQUASH) (39). The SQUASH questionnaire assesses the average time,  
49  
50 175 i.e. number of days per week and hours and minutes per day, spent in commuting  
51  
52 176 activities, leisure time activities, household activities, and activities at work in a normal week  
53  
54 177 in the past month. At all three time points, patients are also asked to measure and report  
55  
56 178 their waist and hip circumference.  
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179 **Table 1.** Overview of data collection in ReLife at the three time points after treatment

	Measures	3mo	1y	2y
<b>Questionnaires</b>				
<i>Sociodemographic data</i>	Date of birth, gender, country of birth of participant, father, mother, race, living situation, marital status, highest level of education, working history	X		
<i>Anthropometry</i>	Height at baseline, weight two years before diagnosis, weight loss 3-6 months before diagnosis, average weight during adult life	X		
<i>Lifestyle</i>	Current body weight, waist and hip circumference	X	X	X
	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
<i>Medical history</i>	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
	Previously diagnosed with cancer, family history of cancer	X		
<i>Diet</i>	Comorbidities, medication use, dietary supplement use	X	X	X
	163- item Food Frequency Questionnaire	X	X	X
<i>Health-related quality of life</i>	EORTC QLQ-C30 (44)	X	X	X
<b>Accelerometer</b>				
	Habitual physical (in)activity, sedentary behavior	X	X	X
<b>Blood</b>				
	EDTA whole blood for DNA isolation	X		
	EDTA plasma, serum	X	X	X
<b>Tissue</b>				
	Formalin-fixed paraffin-embedded tissue of the primary tumour	X <sup>a</sup>		
<b>CT scan</b>				
	Diagnostic CT scan	X		
	Follow-up CT scans		X <sup>b</sup>	X <sup>b</sup>
<b>Clinical data</b>				
	Disease characteristics, treatment	X	X	X
	Postoperative outcomes, recurrence and progression	X	X	X

180 <sup>a</sup> To date only permission, no actual collection.; <sup>b</sup> Dependent on availability.

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3 181 Habitual dietary intake is collected at all three time points using a 163-item validated and  
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5 182 reproducible self-administered food frequency questionnaire that was developed by  
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7 183 Wageningen University (40-42). The questionnaire contains questions about the frequency of  
8  
9 184 consumption of food products and the portion size during the previous month. Frequency and  
10  
11 185 portion size of consumed food products are multiplied to obtain their intake in grams per day.  
12  
13 186 Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) (43).

14  
15  
16 187  
17  
18 188 Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-  
19  
20 189 C30 (44). The EORTC QLQ-C30 contains five function scales (physical, role, cognitive,  
21  
22 190 emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting)  
23  
24 191 and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial  
25  
26 192 impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with  
27  
28 193 ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100  
29  
30 194 scale.

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#### 34 196 *Accelerometer*

35  
36 197 Habitual physical (in)activity is objectively measured at all three time points using the activPAL  
37  
38 198 physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to  
39  
40 199 be an accurate tool for measuring daily physical activity levels (45). Participants are asked to  
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42 200 wear the device continuously on the front right thigh for seven consecutive days. Data are  
43  
44 201 uploaded using the activPAL software.

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#### 48 203 *Blood samples*

49  
50 204 Non-fasting blood samples are collected at all three time points. At 3mo, 10 ml EDTA  
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52 205 whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At  
53  
54 206 the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood  
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56 207 samples are collected, processed and stored at -80°C locally in the participating hospitals  
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58 208 according to a standard protocol before transportation on dry ice to the Radboud Biobank.

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3 209 The blood samples are stored in the Radboud Biobank at -80°C for future analyses of  
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5 210 genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory  
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7 211 for Experimental Internal Medicine of Radboudumc using commercially available  
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9 212 enzyme-linked immunosorbent assays is planned.  
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11 213

#### 13 214 *Tumour samples*

15 215 From all patients, permission for collection of tumour specimens is requested for future  
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17 216 assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic alterations  
18  
19 217 (e.g. in the *BAP1* or *PBRM1* genes) (6). Formalin-fixed paraffin-embedded tumour blocks can  
20  
21 218 be identified by using the PALGA foundation and retrieved using the Dutch National  
22  
23 219 Tissuebank Portal (DNTP) from the local pathology laboratories.  
24

25 220

#### 27 221 *CT scans*

28  
29 222 CT scans are retrieved from medical records of all patients for the assessment of body  
30  
31 223 composition. Diagnostic CT scans are available from almost all RCC patients as they are used  
32  
33 224 for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well.  
34  
35 225 From these CT scans, cross-sectional areas (cm<sup>2</sup>) and mean radiodensity of SM, VAT, SAT  
36  
37 226 and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).  
38

39 227

#### 41 228 *Clinical data*

42  
43 229 Information about disease characteristics and treatment for the initial tumour and subsequent  
44  
45 230 recurrences is collected from the medical records by data managers of the Netherlands Cancer  
46  
47 231 Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and  
48  
49 232 post-surgical (pTNM) stage, Fuhrman grade and morphology. With respect to therapy,  
50  
51 233 information is collected on type of treatment (type of nephrectomy, type of ablation), operation  
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53 234 time, blood loss, complications (Clavien-Dindo classification) and length of hospital stay.  
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55 235 Furthermore, data on performance status (e.g. WHO performance status, ASA score) are  
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57 236 collected.  
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5 238 Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and  
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7 239 Fuhrman grade, and survival, are also collected. We will continue to collect further information  
8  
9 240 on these clinical outcomes in the future to evaluate their association with body composition  
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11 241 features, lifestyle habits and circulating biomarkers.

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#### 15 243 *Power calculation and data analyses*

16 244 The power calculation of this study is based on our initial research question, i.e. the cross-  
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18 245 sectional association of patient and tumour characteristics, lifestyle habits, and circulating  
19  
20 246 concentrations of biomarkers with body composition features. With 369 patients, we will have  
21  
22 247 sufficient power ( $\geq 80\%$ ) to detect a multiple correlation coefficient of 0.30 (Cohen's  $f^2=0.10$  for  
23  
24 248 patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations  
25  
26 249 of biomarkers with body composition features), corresponding to a small ( $f^2=0.02$ ) to medium  
27  
28 250 ( $f^2=0.15$ ) effect size (46). This power calculation is based on 276 stage I-III patients (assuming  
29  
30 251 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition  
31  
32 252 features as outcome variables (cross-sectional area and radiodensity of SM and cross-  
33  
34 253 sectional area of VAT). For the power calculation, we correct for multiplicity (3 body  
35  
36 254 composition features) by using the Bonferroni corrected alpha of 0.05/3.

37 255 Patient characteristics were described using means and standard deviations (SD), medians  
38  
39 256 and interquartile ranges (IQR), or total numbers and percentages where appropriate.  
40  
41 257 Differences in sociodemographic and clinical characteristics between participants and non-  
42  
43 258 participants were evaluated with chi-squared tests. Two-sided p-values  $< 0.05$  were considered  
44  
45 259 statistically significant. Multiple linear regression analyses will be used to estimate the cross-  
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47 260 sectional association of patient and tumor characteristics, lifestyle habits, and biomarkers with  
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49 261 body composition features. Longitudinal associations of body composition features, lifestyle  
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51 262 habits and biomarkers with HRQoL will be assessed using linear mixed models. Logistic  
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53 263 regression and Cox proportional hazard analyses will be used to estimate the association of  
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3 264 body composition features, lifestyle habits and biomarkers with other clinical outcomes. All  
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5 265 statistical analyses will be conducted in R.  
6

7 266

## 9 267 **FINDINGS TO DATE**

### 11 268 **Characteristics of study participants**

13 269 From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to  
14  
15 270 participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19  
16  
17 271 measures. In total, 836 patients were eligible and 368 patients agreed to participate and filled  
18  
19 272 out the first or second questionnaires (response rate 44%) (**Figure 2**). The median time  
20  
21 273 between time of treatment and time of the 3mo questionnaire completion was 13 weeks  
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23 274 (interquartile range 12-14 weeks). The number of questionnaires, ActivPal measurements and  
24  
25 275 blood samples available at 3mo are also shown in **Figure 2**.  
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### 30 277 **Figure 2** Flowchart of the ReLife study

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34 279 In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients  
35  
36 280 was  $62.4 \pm 9.0$  years and 70% was male. Most patients had stage I (65%) and Fuhrman grade  
37  
38 281 2 (50%) disease. The majority was treated with radical (57%) or partial nephrectomy (42%).  
39  
40 282 The majority of participants were overweight (44%) or obese (25%) and 50% were former  
41  
42 283 smokers. Participants were more likely to be female than non-participants but were  
43  
44 284 comparable with respect to age, tumour stage, tumour grade, morphology and type of  
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46 285 treatment (**Table 3**).  
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286 **Table 2.** Baseline characteristics of 368 patients with renal cell cancer included in the ReLife  
287 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 <sup>a</sup>	
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 <sup>2</sup> )	27.6 ± 4.7
BMI (kg/m <sup>2</sup> )	
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) <sup>b</sup>	101.2 ± 12.1
Hip circumference (cm) <sup>b</sup>	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 <sup>c</sup>	6 (2)
Comorbidities	
0	54 (15)
1	85 (23)
≥2	226 (61)
Missing	3 (1)

Values are mean ± SD or n (%).

<sup>a</sup> Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university)

<sup>b</sup> Values for 8 participants were missing

<sup>c</sup> 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 <sup>a</sup>
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 <sup>b</sup>	35 (9)	42 (9)	
Treatment			
Radical nephrectomy	210 (57)	272 (58)	0.76
Partial nephrectomy	152 (41)	191 (41)	
Ablation <sup>c</sup>	6 (2)	5 (1)	

Values are n (%).

<sup>a</sup> From chi-squared test.

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2  
3 299 <sup>b</sup> Other morphology consists of adenocarcinoma with mixed subtypes (n=4 and n=5), eosinophilic solid and cystic  
4 300 renal cell carcinoma (n=1 and n=0), renal cell carcinoma not otherwise specified (n=28 and n=29), sarcomatoid  
5 301 renal cell carcinoma (n=2 and n=6), collecting duct carcinoma (n=0 and n=1), and clear cell papillary renal cell  
6 302 tumour (n=0 and n=1) for participants and non-participants, respectively.  
7 303 <sup>c</sup> Other treatment consists of cryoablation (n=2 and n=2), radiofrequency ablation (n=3 and n=2), and microwave  
8 304 ablation (n=1 and n=1) for participants and non-participants, respectively.  
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For peer review only

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3 306 **FUTURE PLANS**  
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5 307 We have already started and will first continue to work on the statistical analyses and writing  
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7 308 of manuscripts addressing our main study objectives, i.e. 1) the association of patient and  
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9 309 tumour characteristics, lifestyle habits, and circulating biomarkers with body composition  
10  
11 310 features, and 2) the association of body composition features, lifestyle habits and circulating  
12  
13 311 biomarkers with clinical outcomes, including postoperative outcomes (e.g. complications,  
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15 312 length of hospital stay), and HRQOL. Statistical analyses for recurrence, progression, and  
16  
17 313 survival will be conducted once follow-up is more mature or pooling with similar cohorts  
18  
19 314 becomes possible.  
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22 315

23  
24 316 **STRENGTHS AND LIMITATIONS**  
25

26 317 To our knowledge, the ReLife study is the first population-based prospective longitudinal  
27  
28 318 study on lifestyle-related factors and clinical outcomes in patients with localized RCC  
29  
30 319 worldwide. Comprehensive data on lifestyle-related factors and HRQOL are collected at 3  
31  
32 320 months, 1 year and 2 years after treatment. Besides questionnaire data on lifestyle-related  
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34 321 factors, also objective data on body composition and physical activity are collected. Data on  
35  
36 322 sociodemographic variables and comorbidity is available as well. Information on several  
37  
38 323 clinical outcomes is collected, including postoperative outcomes (e.g. complications, length  
39  
40 324 of hospital stay), recurrence, progression, survival, and HRQOL. Moreover, blood samples  
41  
42 325 are collected to measure lifestyle-related, disease-related and genetic biomarkers.  
43  
44

45 326 Permission is available from participants to use their tumour tissue blocks for assessment of  
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47 327 tumour characteristics and acquired genetic alterations.  
48

49 328 However, there are also some limitations to this study. As is the case for all longitudinal  
50  
51 329 studies, participants may drop out during the course of the study, potentially leading to  
52  
53 330 selection bias. Some variables have missing values which will be addressed using multiple  
54  
55 331 imputation when applicable. No information on lifestyle-related factors and HRQOL after the  
56  
57 332 two-years follow-up measurement is available. Power for survival analyses is likely to be  
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3 333 insufficient and future pooling with other studies may be necessary. Lastly, we did not use  
4  
5 334 RCC-specific measures of HRQOL in our study.  
6  
7 335 Results that can be obtained from this study are important to develop personalized evidence-  
8  
9 336 based lifestyle advice for patients with localized RCC to improve their clinical outcomes.  
10

11 337

## 12 338 **COLLABORATION**

13  
14  
15 339 The ReLife study group is open for collaborations with national and international colleagues.  
16  
17 340 Any person interested in collaborating on the ReLife study or in getting access to ReLife data  
18  
19 341 for data analyses can contact the corresponding author. Requests for data will be discussed  
20  
21 342 and decided by the ReLife study group and will require a Data Transfer Agreement.  
22  
23

24 343

## 25 344 **Abbreviations**

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28 345 BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal;  
29  
30 346 IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue;  
31  
32 347 NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National  
33  
34 348 Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT:  
35  
36 349 subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal  
37  
38 350 muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health;  
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40 351 TAT: total adipose tissue; 1y: 1 year after treatment; 2y: 2 years after treatment; 3mo: three  
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42 352 months after treatment; VAT: visceral adipose tissue.  
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3 353 **DECLARATIONS**

4  
5 354 **Acknowledgements**

6  
7 355 We are grateful to all the patients who participate in this study and we thank the following  
8  
9 356 hospitals for their involvement in recruitment for the ReLife study: Amphia Ziekenhuis,  
10  
11 357 Breda/Oosterhout (D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (A.Q.H.J. Niemer);  
12  
13 358 Canisius-Wilhelmina Ziekenhuis, Nijmegen (D.M. Somford); Catharina Ziekenhuis,  
14  
15 359 Eindhoven (W.A. Scheepens); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (P.J.M.  
16  
17 360 Kil, B.P. Wijsman); Elkerliek Ziekenhuis, Helmond (P.J. van Hest); Gelre Ziekenhuizen,  
18  
19 361 Apeldoorn/Zutphen (D.M. Bochove-Overgaauw); Jeroen Bosch Ziekenhuis, 's-  
20  
21 362 Hertogenbosch (S. van der Meer); Maasziekenhuis Pantein, Boxmeer (E. van Boven);  
22  
23 363 Maxima Medisch Centrum, Veldhoven/Eindhoven (L.M.C.L. Fossion, K. de Laet); Meander  
24  
25 364 Medisch Centrum, Amersfoort (F.S. van Rey); Radboudumc, Nijmegen; Rijnstate,  
26  
27 365 Arnhem/Velp/Zevenaar (G.A.H.J Smits); Slingeland Ziekenhuis, Doetinchem (A.D.H.  
28  
29 366 Geboers); St. Jansdal Ziekenhuis, Harderwijk (W.J. Kniestedt); UMC Utrecht (R.P. Meijer);  
30  
31 367 Ziekenhuis Gelderse Vallei, Ede (M.D.H. Kortleve); Ziekenhuisgroep Twente,  
32  
33 368 Almelo/Hengelo (S. Stomps). In addition, we thank Ms. Ivy Beeren, Ms. Monique  
34  
35 369 Eijgenberger, Ms. Jolanda van Haren and Ms. Ursula Oldenhof for their assistance in data  
36  
37 370 collection. We also thank the data managers of the Netherlands Cancer Registry held by the  
38  
39 371 Netherlands Comprehensive Cancer Organisation (IKNL) for inviting patients and collecting  
40  
41 372 the clinical data.  
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45 373

46  
47 374 **Authors' contributions**

48  
49 375 AV, EK, JPM, JSFM, KKHA, and LALMK contributed to the conception and design of the  
50  
51 376 study. AV provides overall study management and coordinates the project. JSFM contributed  
52  
53 377 to data collection. AV and JSFM drafted the manuscript. All authors have critically read and  
54  
55 378 revised the manuscript. All authors approved the final version of the manuscript.  
56  
57

58 379

59  
60 380 **Funding**

1  
2  
3 381 This project is funded by the Dutch Cancer Society (KUN 2015-7948). Sponsors were not  
4  
5 382 involved in the study design nor will they be in the collection, analysis, and interpretation of  
6  
7 383 data, or in the publications that will result from this study.  
8

9 384

### 11 385 **Competing interests**

13 386 The authors declare that they have no competing interests.

15 387

### 18 388 **Ethics approval and consent to participate**

20 389 The study protocol has been approved on March 2, 2017 by the Committee for Human  
21  
22 390 Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in  
23  
24 391 the study provided a written informed consent.

26 392

### 28 393 **Consent for publication**

30 394 Not applicable.

32 395

### 35 396 **Availability of data and material**

37 397 Data and material are not yet available since data collection has not been completed yet.

39 398 After completion of data collection, data will be made available by the corresponding author  
40  
41 399 upon reasonable request.

43 400

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530 **Figure 1.** Timeline and study design of the ReLife study

531 **Figure 2.** Flow chart of the ReLife study

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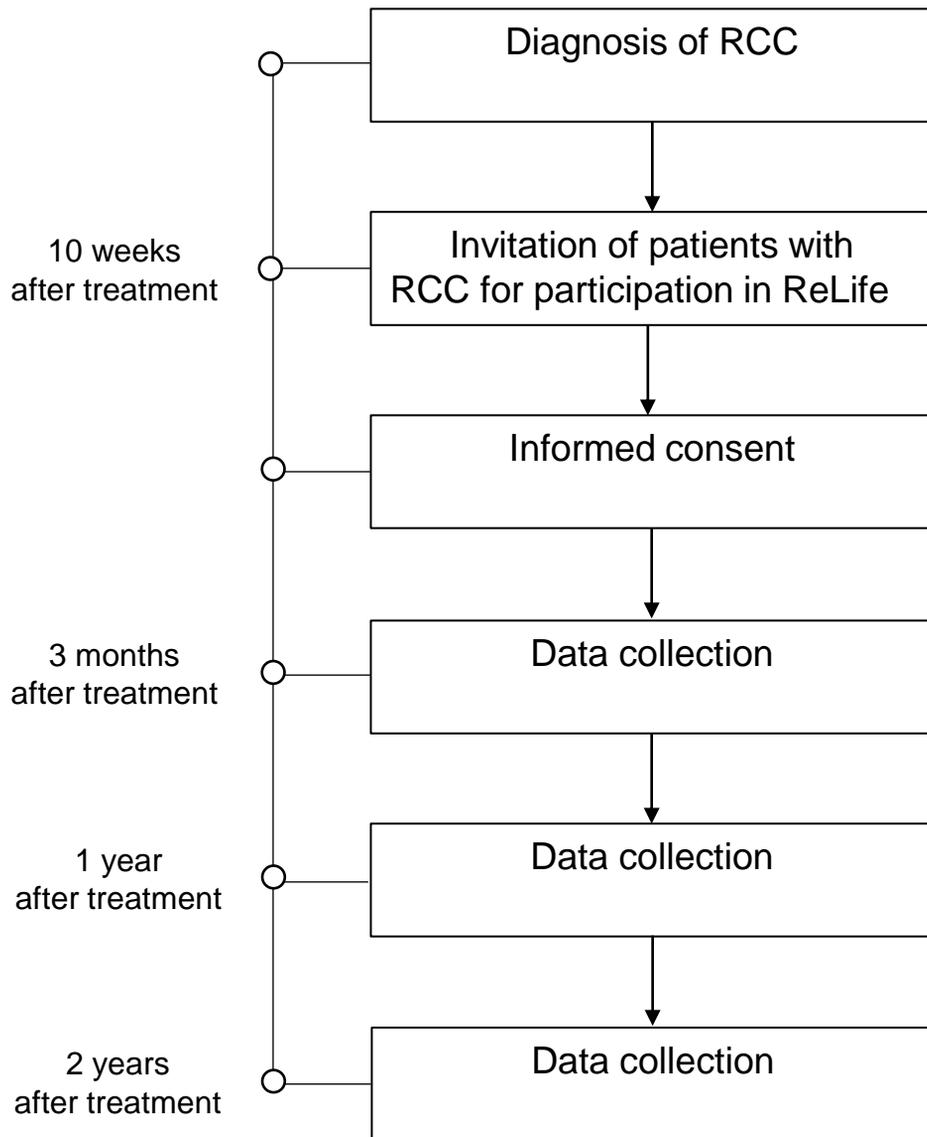
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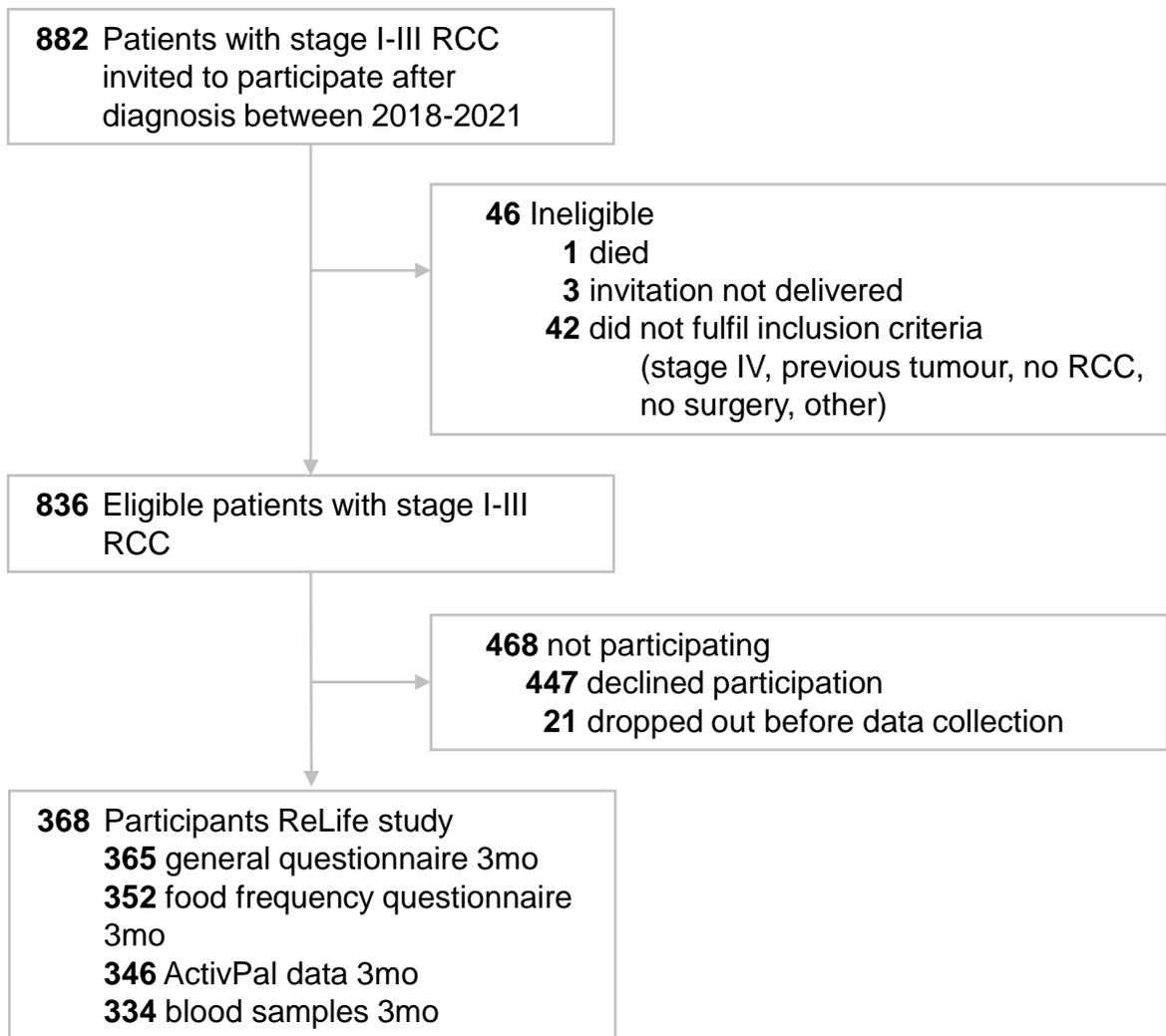
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## Overview ReLife study



# RE LIFE



# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-066909.R2
Article Type:	Cohort profile
Date Submitted by the Author:	09-Mar-2023
Complete List of Authors:	Maurits, Jake; Radboudumc, Department for Health Evidence Sedelaar, Michiel; Radboudumc, Department of Urology Aben, Katja; Netherlands Cancer Registry; Radboudumc, Department for Health Evidence Kampman, Ellen; Wageningen University & Research, Division of Human Nutrition and Health; Radboudumc, Department for Health Evidence Kiemeneij, Lambertus; Radboudumc, Department for Health Evidence Vrieling, Alina; Radboudumc, Department for Health Evidence
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Oncology
Keywords:	NUTRITION & DIETETICS, Kidney tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PREVENTIVE MEDICINE

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3 1 **Cohort profile: The ReLife (Renal cell cancer: Lifestyle, prognosis, and quality of life)**  
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5 2 **study in the Netherlands**  
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9 4 Jake. S.F. Maurits<sup>a</sup>, J.P. Michiel Sedelaar<sup>b</sup>, Katja K.H. Aben<sup>a,c</sup>, Ellen Kampman<sup>a,d</sup>, Lambertus  
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43 18  
44  
45 19 **Keywords:** renal cell cancer, diet, lifestyle, body composition, biomarkers, quality of life,  
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47 20 cohort profile  
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51 21  
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53 22 **Word count:** 2349  
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**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  $62.5 \pm 9.0$  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.

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3 **51 STRENGTHS AND LIMITATIONS**  
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5 52 - The ReLife study is the first population-based prospective cohort study on lifestyle-related  
6  
7 53 factors and clinical outcomes in patients with localized RCC worldwide.

8  
9 54 - Comprehensive data on lifestyle-related factors and quality of life are collected at 3 months,  
10  
11 55 1 year and 2 years after treatment.

12  
13 56 - Both self-reported and objective data on body composition and physical activity are collected.

14  
15 57 - A limitation is that power for survival analyses is likely to be insufficient and future pooling  
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17 58 with other studies may be required.  
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## 59 INTRODUCTION

60 Incidence rates of kidney cancer are increasing [1], which is partly explained by the increased  
61 use of diagnostic imaging but also by the increased prevalence of obesity [2]. The worldwide  
62 number of new kidney cancer cases was estimated to be over 430,000 in 2020 [3]. In the  
63 Netherlands, over 2,700 new cases with kidney cancer were diagnosed in 2019 [4]. More than  
64 90% of kidney cancers are renal cell cancers (RCC) [5]. Of all RCC patients, about 70-80%  
65 are diagnosed with localised disease (stage I-III) and about 20-30% with advanced or  
66 metastatic disease (stage IV) [2]. Almost all RCC patients with localised disease are treated  
67 with partial or radical nephrectomy [6]. Despite this treatment, 20-30% of patients with localised  
68 disease will have a relapse or develop metastatic RCC during follow-up [7]. Five-year relative  
69 survival rates are approximately 90% (stage I and II), 65% (stage III), and 12% (stage IV) [2].

70 Classical prognostic factors for localised RCC include anatomical (e.g., TNM  
71 classification), histological (e.g., tumour grade, histological subtype), clinical (e.g.,  
72 performance status, certain blood values), and molecular features (e.g., *BAP1* and *PBRM1*  
73 mutations), but the combination of these features does not have sufficient predictive accuracy  
74 [8]. In order to provide tailored treatment and follow-up care, the identification of additional  
75 prognostic factors that predict the expected clinical course in each individual patient is subject  
76 of active scientific research.

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

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3 86 Body composition refers to the content of fat, lean tissue and bone in the human body.  
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5 87 The amount and distribution of these tissues may be independent of BMI; subjects with similar  
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7 88 BMI may have different amounts of visceral adipose tissue (VAT), subcutaneous adipose  
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9 89 tissue (SAT), skeletal muscle (SM), and intermuscular adipose tissue (IMAT). Cross-sectional  
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11 90 areas and mean radiodensity of these tissues can be assessed by analysis of computed  
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13 91 tomography (CT) scans at the level of the third lumbar vertebra (L3), using established  
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15 92 Hounsfield Unit (HU) thresholds for each tissue. Cross-sectional total adipose tissue (TAT) and  
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17 93 SM areas at L3 are linearly related to body TAT and SM mass [15-17].

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19  
20 94 High VAT mass, low SM index (SMI (SM/height<sup>2</sup>)), and low SM radiodensity (SMD) have  
21  
22 95 been associated with adverse postoperative [18] and survival outcomes [19-21] in several  
23  
24 96 cancer types. In our meta-analysis, we showed that low SMI and low SMD are also associated  
25  
26 97 with increased overall mortality in patients with metastatic RCC [22]. No meta-analysis could  
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28 98 be performed for localized RCC due to the limited number of studies and heterogeneity in body  
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30 99 composition parameters and outcomes [22]. Studies also suggested an association of low vs.  
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32 100 high SMI with higher overall and cancer-specific mortality [23] and of lower SMD with higher  
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34 101 overall mortality [24]. Other studies found that low vs. high VAT was associated with a higher  
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36 102 risk of recurrence [25], cancer-specific [26, 27], and overall mortality [24].

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38  
39 103 Body composition is known to differ by age, gender and race [28, 29]. Studies on the  
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41 104 association of tumour characteristics with body composition features are inconsistent [30, 31]  
42  
43 105 and studies on the association of lifestyle habits and circulating biomarkers with body  
44  
45 106 composition parameters are not available in patients with RCC. Smoking has been associated  
46  
47 107 with increased RCC risk and RCC-specific mortality [32]. Studies on dietary factors and  
48  
49 108 physical activity are inconsistent for RCC risk [33] and not available for clinical outcomes  
50  
51 109 including health-related quality of life (HRQoL). Some studies suggest that circulating  
52  
53 110 biomarkers (e.g. adiponectin, leptin and CRP) are associated with tumour size [34], invasion,  
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55 111 progression or metastasis [34-36] and survival [37, 38] in patients with RCC but results are  
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57 112 inconsistent.  
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3 113 Thus, the association of patient and tumour characteristics, lifestyle habits and circulating  
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5 114 biomarkers with body composition features in patients with localized RCC needs to be clarified.  
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7 115 Further, there is a clear need to obtain more insight in body composition features and lifestyle  
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9 116 habits and their relation with clinical outcomes in patients with localized RCC. This information  
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11 117 is important to develop personalized evidence-based lifestyle advice for patients with localized  
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13 118 RCC to improve their clinical outcomes. Therefore, the objectives of this study are to evaluate  
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15 119 1) the association of patient and tumour characteristics, lifestyle habits, and circulating  
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17 120 biomarkers with body composition features, and 2) the association of body composition  
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19 121 features, lifestyle habits and circulating biomarkers with clinical outcomes, including  
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21 122 postoperative outcomes (e.g. complications, length of hospital stay), recurrence, progression,  
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23 123 survival, and HRQoL.  
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## 124 **COHORT DESCRIPTION**

### 125 **Setting**

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

139 **Figure 1** Timeline and study design of the ReLife study

### 141 **Patient and public involvement**

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

### 151 **Participants**

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3 152 Eligible participants were between 18 and 75 years old who were newly diagnosed with a  
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5 153 histologically confirmed primary stage I-III RCC tumour and who underwent a (partial)  
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7 154 nephrectomy or ablation. Patients had to have sufficient command of the Dutch language since  
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9 155 all study materials and questionnaires were only available in Dutch. Patients with a previous  
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11 156 diagnosis of cancer in the five years before RCC diagnosis and those with a lymph node  
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13 157 metastasis or distant metastasis were not eligible.  
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## 17 159 **Data collection and management**

### 18 160 *Questionnaires*

19  
20 161 Participants are asked to complete self-administered web-based or paper-and-pencil-based  
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22 162 questionnaires at 3 months (3mo), 1 year (1y) and 2 years (2y) after treatment (**Figure 1, Table**  
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24 163 **1**). Web-based questionnaires are collected using Castor EDC. Follow-up telephone calls are  
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26 164 made to non-responding participants and to respondents whose questionnaires have missing  
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28 165 items.  
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32 166 The general questionnaire at 3mo contains questions on demographics (age, sex, ethnicity,  
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34 167 education, living situation, occupation, marital status) and personal and family history of  
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36 168 cancer. All questionnaires collect information about height, body weight, amount and  
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38 169 frequency of alcohol consumption during week- and weekend days, smoking habits,  
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40 170 comorbidities and the use of dietary supplements and medication. Information on smoking  
41  
42 171 habits is collected in detail, including age or date of starting and stopping smoking, number of  
43  
44 172 cigarettes smoked per day, and duration of smoking. Information about habitual physical  
45  
46 173 activity is collected by using the validated short questionnaire to assess health-enhancing  
47  
48 174 physical activity (SQUASH) [39]. The SQUASH questionnaire assesses the average time,  
49  
50 175 i.e. number of days per week and hours and minutes per day, spent in commuting  
51  
52 176 activities, leisure time activities, household activities, and activities at work in a normal week  
53  
54 177 in the past month. At all three time points, patients are also asked to measure and report  
55  
56 178 their waist and hip circumference.  
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179 **Table 1.** Overview of data collection in ReLife at the three time points after treatment

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

180 <sup>a</sup> To date only permission, no actual collection.; <sup>b</sup> Dependent on availability.

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3 181 Habitual dietary intake is collected at all three time points using a 163-item validated and  
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5 182 reproducible self-administered food frequency questionnaire that was developed by  
6  
7 183 Wageningen University [41-43]. The questionnaire contains questions about the frequency of  
8  
9 184 consumption of food products and the portion size during the previous month. Frequency and  
10  
11 185 portion size of consumed food products are multiplied to obtain their intake in grams per day.  
12  
13 186 Nutrient intake is calculated using the Dutch Food Composition Table (NEVO 2010) [44].  
14

15  
16 187  
17  
18 188 Health-related quality of life is assessed at all three time points with the validated EORTC QLQ-  
19  
20 189 C30 [45]. The EORTC QLQ-C30 contains five function scales (physical, role, cognitive,  
21  
22 190 emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting)  
23  
24 191 and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial  
25  
26 192 impact), all scored from 1 (not at all) to 4 (very much)) and a global health status scale with  
27  
28 193 ranges from 1 (very poor) to 7 (excellent). All scores will be linearly transformed to a 0 to 100  
29  
30 194 scale.  
31

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33 195

#### 34 196 *Accelerometer*

35  
36 197 Habitual physical (in)activity is objectively measured at all three time points using the activPAL  
37  
38 198 physical activity monitor (PAL Technologies, Glasgow, UK). This accelerometer has shown to  
39  
40 199 be an accurate tool for measuring daily physical activity levels [46]. Participants are asked to  
41  
42 200 wear the device continuously on the front right thigh for seven consecutive days. Data are  
43  
44 201 uploaded using the activPAL software.  
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#### 48 203 *Blood samples*

49  
50 204 Non-fasting blood samples are collected at all three time points. At 3mo, 10 ml EDTA  
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52 205 whole blood (for DNA isolation), 10 ml EDTA plasma and 8.5 ml serum is collected. At  
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54 206 the other two time points, 10 ml EDTA plasma and 8.5 ml serum is collected. All blood  
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56 207 samples are collected, processed and stored at -80°C locally in the participating hospitals  
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58 208 according to a standard protocol before transportation on dry ice to the Radboud Biobank.  
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3 209 The blood samples are stored in the Radboud Biobank at -80°C for future analyses of  
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5 210 genetic and other biomarkers. Analysis of adiponectin, leptin, and CRP by the Laboratory  
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7 211 for Experimental Internal Medicine of Radboudumc using commercially available  
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9 212 enzyme-linked immunosorbent assays is planned.

11 213

#### 13 214 *Tumour samples*

15 215 From all patients, permission for collection of tumour specimens is requested for future  
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17 216 assessment of tumour characteristics (e.g. tumour necrosis) and acquired genetic alterations  
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19 217 (e.g. in the *BAP1* or *PBRM1* genes) [6]. Formalin-fixed paraffin-embedded tumour blocks can  
20  
21 218 be identified by using the PALGA foundation and retrieved using the Dutch National  
22  
23 219 Tissuebank Portal (DNTP) from the local pathology laboratories.

26 220

#### 28 221 *CT scans*

30 222 CT scans are retrieved from medical records of all patients for the assessment of body  
31  
32 223 composition. Diagnostic CT scans are available from almost all RCC patients as they are used  
33  
34 224 for diagnosis and staging of the disease. If available, follow-up CT scans are collected as well.  
35  
36 225 From these CT scans, cross-sectional areas (cm<sup>2</sup>) and mean radiodensity of SM, VAT, SAT  
37  
38 226 and IMAT are quantified at the landmark level of the third lumbar vertebra (L3).

41 227

#### 43 228 *Clinical data*

45 229 Information about disease characteristics and treatment for the initial tumour and subsequent  
46  
47 230 recurrences is collected from the medical records by data managers of the Netherlands Cancer  
48  
49 231 Registry. Information about tumour characteristics includes incidence date, clinical (cTNM) and  
50  
51 232 post-surgical (pTNM) stage, Fuhrman grade and morphology. With respect to therapy,  
52  
53 233 information is collected on type of treatment (type of nephrectomy, type of ablation), operation  
54  
55 234 time, blood loss, complications (Clavien-Dindo classification) and length of hospital stay.  
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57 235 Furthermore, data on performance status (e.g. WHO performance status, ASA score) are  
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59 236 collected.

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5 238 Data on clinical outcomes, i.e. recurrence and progression with dates of diagnosis, stage and  
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7 239 Fuhrman grade, and survival, are also collected. We will continue to collect further information  
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9 240 on these clinical outcomes in the future to evaluate their association with body composition  
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11 241 features, lifestyle habits and circulating biomarkers.

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15 243 *Power calculation and data analyses*

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17 244 The power calculation of this study is based on our initial research question, i.e. the cross-  
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19 245 sectional association of patient and tumour characteristics, lifestyle habits, and circulating  
20  
21 246 concentrations of biomarkers with body composition features. With 369 patients, we will have  
22  
23 247 sufficient power ( $\geq 80\%$ ) to detect a multiple correlation coefficient of 0.30 (Cohen's  $f^2=0.10$  for  
24  
25 248 patient and tumour characteristics, dietary and lifestyle habits, and circulating concentrations  
26  
27 249 of biomarkers with body composition features), corresponding to a small ( $f^2=0.02$ ) to medium  
28  
29 250 ( $f^2=0.15$ ) effect size [47]. This power calculation is based on 276 stage I-III patients (assuming  
30  
31 251 75% available and analyzable CT scans), 19 predictor variables, and 3 body composition  
32  
33 252 features as outcome variables (cross-sectional area and radiodensity of SM and cross-  
34  
35 253 sectional area of VAT). For the power calculation, we correct for multiplicity (3 body  
36  
37 254 composition features) by using the Bonferroni corrected alpha of 0.05/3.

38  
39 255 Patient characteristics were described using means and standard deviations (SD), medians  
40  
41 256 and interquartile ranges (IQR), or total numbers and percentages where appropriate.  
42  
43 257 Differences in sociodemographic and clinical characteristics between participants and non-  
44  
45 258 participants were evaluated with chi-squared tests. Two-sided p-values  $< 0.05$  were considered  
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47 259 statistically significant. Multiple linear regression analyses will be used to estimate the cross-  
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49 260 sectional association of patient and tumor characteristics, lifestyle habits, and biomarkers with  
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51 261 body composition features. Longitudinal associations of body composition features, lifestyle  
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53 262 habits and biomarkers with HRQoL will be assessed using linear mixed models. Logistic  
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55 263 regression and Cox proportional hazard analyses will be used to estimate the association of  
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3 264 body composition features, lifestyle habits and biomarkers with other clinical outcomes. All  
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5 265 statistical analyses will be conducted in R.  
6

7 266

## 9 267 **FINDINGS TO DATE**

### 11 268 **Characteristics of study participants**

13 269 From January 2018 to June 2021, 882 patients diagnosed with stage I-III RCC were invited to  
14  
15 270 participate. Recruitment was paused between 16 March and 18 May 2020 due to Covid-19  
16  
17 271 measures. In total, 836 patients were eligible and 368 patients agreed to participate and filled  
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19 272 out the first or second questionnaires (response rate 44%) (**Figure 2**). The median time  
20  
21 273 between time of treatment and time of the 3mo questionnaire completion was 13 weeks  
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23 274 (interquartile range 12-14 weeks). The number of questionnaires, ActivPal measurements and  
24  
25 275 blood samples available at 3mo are also shown in **Figure 2**.  
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### 30 277 **Figure 2** Flowchart of the ReLife study

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34 279 In **Table 2**, the baseline characteristics of the cohort are presented. The mean age of patients  
35  
36 280 was  $62.4 \pm 9.0$  years and 70% was male. Most patients had stage I (65%) and Fuhrman grade  
37  
38 281 2 (50%) disease. The majority was treated with radical (57%) or partial nephrectomy (42%).  
39  
40 282 The majority of participants were overweight (44%) or obese (25%) and 50% were former  
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42 283 smokers. Compared to non-participants, participants were less likely to be male but were  
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44 284 comparable with respect to age, tumour stage, tumour grade, morphology and type of  
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46 285 treatment (**Table 3**).  
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286 **Table 2.** Baseline characteristics of 368 patients with renal cell cancer included in the ReLife  
287 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 <sup>a</sup>	
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 <sup>2</sup> )	27.6 ± 4.7
BMI (kg/m <sup>2</sup> )	
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) <sup>b</sup>	101.2 ± 12.1
Hip circumference (cm) <sup>b</sup>	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 <sup>c</sup>	6 (2)
Comorbidities	
0	54 (15)
1	85 (23)
≥2	226 (61)
Missing	3 (1)

Values are mean ± SD or n (%).

<sup>a</sup> Low (primary, secondary, vocational education), medium (intermediate vocational education, higher general secondary education, pre-university education), high (university of vocational education, university)

<sup>b</sup> Values for 8 participants were missing

<sup>c</sup> 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 <sup>a</sup>
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 <sup>b</sup>	35 (9)	42 (9)	
Treatment			
Radical nephrectomy	210 (57)	272 (58)	0.76
Partial nephrectomy	152 (41)	191 (41)	
Ablation <sup>c</sup>	6 (2)	5 (1)	

Values are n (%).

<sup>a</sup> From chi-squared test.

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299 <sup>b</sup> Other morphology consists of adenocarcinoma with mixed subtypes (n=4 and n=5), eosinophilic solid and cystic  
300 renal cell carcinoma (n=1 and n=0), renal cell carcinoma not otherwise specified (n=28 and n=29), sarcomatoid  
301 renal cell carcinoma (n=2 and n=6), collecting duct carcinoma (n=0 and n=1), and clear cell papillary renal cell  
302 tumour (n=0 and n=1) for participants and non-participants, respectively.  
303 <sup>c</sup> Other treatment consists of cryoablation (n=2 and n=2), radiofrequency ablation (n=3 and n=2), and microwave  
304 ablation (n=1 and n=1) for participants and non-participants, respectively.  
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## 306 **FUTURE PLANS**

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

315

## 316 **STRENGTHS AND LIMITATIONS**

317 To our knowledge, the ReLife study is the first population-based prospective longitudinal  
318 study on lifestyle-related factors and clinical outcomes in patients with localized RCC  
319 worldwide. Comprehensive data on lifestyle-related factors and HRQoL are collected at 3  
320 months, 1 year and 2 years after treatment. Besides questionnaire data on lifestyle-related  
321 factors, also objective data on body composition and physical activity are collected. Data on  
322 sociodemographic variables and comorbidity is available as well. Information on several  
323 clinical outcomes is collected, including postoperative outcomes (e.g. complications, length  
324 of hospital stay), recurrence, progression, survival, and HRQoL. Moreover, blood samples  
325 are collected to measure lifestyle-related, disease-related and genetic biomarkers.

326 Permission is available from participants to use their tumour tissue blocks for assessment of  
327 tumour characteristics and acquired genetic alterations.

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

1  
2  
3 333 insufficient and future pooling with other studies may be necessary. Lastly, we did not use  
4  
5 334 RCC-specific measures of HRQoL in our study.

6  
7 335 Results that can be obtained from this study are important to develop personalized evidence-  
8  
9 336 based lifestyle advice for patients with localized RCC to improve their clinical outcomes.

10  
11 337

## 12 13 338 **COLLABORATION**

14  
15 339 The ReLife study group is open for collaborations with national and international colleagues.

16  
17 340 Any person interested in collaborating on the ReLife study or in getting access to ReLife data

18  
19 341 for data analyses can contact the corresponding author. Requests for data will be discussed

20  
21 342 and decided by the ReLife study group and will require a Data Transfer Agreement.

22  
23 343

## 24 25 344 **Abbreviations**

26  
27 345 BMI, body mass index; cTNM: clinical TNM stage; DNTP: Dutch National Tissuebank Portal;

28  
29 346 IKNL: Netherlands Comprehensive Cancer Organisation; IMAT: intramuscular adipose tissue;

30  
31 347 NCR: Netherlands Cancer Registry; PALGA foundation: Pathological Anatomical National

32  
33 348 Automate Archive; pTNM: post-surgical TNM stage; RCC: renal cell cancer; SAT:

34  
35 349 subcutaneous adipose tissue; SD: standard deviation; SM: skeletal muscle; SMD: skeletal

36  
37 350 muscle density; SMI: skeletal muscle index; SQUASH: Short Questionnaire to Assess Health;

38  
39 351 TAT: total adipose tissue; 1y: 1 year after treatment; 2y: 2 years after treatment; 3mo: three

40  
41 352 months after treatment; VAT: visceral adipose tissue.

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2  
3 353 **DECLARATIONS**

4  
5 354 **Acknowledgements**

6  
7 355 We are grateful to all the patients who participate in this study and we thank the following  
8  
9 356 hospitals for their involvement in recruitment for the ReLife study: Amphia Ziekenhuis,  
10  
11 357 Breda/Oosterhout (D.K.E. van der Schoot); Ziekenhuis Bernhoven, Uden (A.Q.H.J. Niemer);  
12  
13 358 Canisius-Wilhelmina Ziekenhuis, Nijmegen (D.M. Somford); Catharina Ziekenhuis,  
14  
15 359 Eindhoven (W.A. Scheepens); Elisabeth-TweeSteden Ziekenhuis, Tilburg/Waalwijk (P.J.M.  
16  
17 360 Kil, B.P. Wijsman); Elkerliek Ziekenhuis, Helmond (P.J. van Hest); Gelre Ziekenhuizen,  
18  
19 361 Apeldoorn/Zutphen (D.M. Bochove-Overgaauw); Jeroen Bosch Ziekenhuis, 's-  
20  
21 362 Hertogenbosch (S. van der Meer); Maasziekenhuis Pantein, Boxmeer (E. van Boven);  
22  
23 363 Maxima Medisch Centrum, Veldhoven/Eindhoven (L.M.C.L. Fossion, K. de Laet); Meander  
24  
25 364 Medisch Centrum, Amersfoort (F.S. van Rey); Radboudumc, Nijmegen; Rijnstate,  
26  
27 365 Arnhem/Velp/Zevenaar (G.A.H.J Smits); Slingeland Ziekenhuis, Doetinchem (A.D.H.  
28  
29 366 Geboers); St. Jansdal Ziekenhuis, Harderwijk (W.J. Kniestedt); UMC Utrecht (R.P. Meijer);  
30  
31 367 Ziekenhuis Gelderse Vallei, Ede (M.D.H. Kortleve); Ziekenhuisgroep Twente,  
32  
33 368 Almelo/Hengelo (S. Stomps). In addition, we thank Ms. Ivy Beeren, Ms. Monique  
34  
35 369 Eijgenberger, Ms. Jolanda van Haren and Ms. Ursula Oldenhof for their assistance in data  
36  
37 370 collection. We also thank the data managers of the Netherlands Cancer Registry held by the  
38  
39 371 Netherlands Comprehensive Cancer Organisation (IKNL) for inviting patients and collecting  
40  
41 372 the clinical data.  
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45 373

46  
47 374 **Authors' contributions**

48  
49 375 AV, EK, JPMS, JSFM, KKHA, and LALMK contributed to the conception and design of the  
50  
51 376 study. AV provides overall study management and coordinates the project. JSFM contributed  
52  
53 377 to data collection. AV and JSFM drafted the manuscript. All authors have critically read and  
54  
55 378 revised the manuscript. All authors approved the final version of the manuscript.  
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58 379

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60 380 JSFM - Jake. S.F. Maurits

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3 381 JPMS - J.P. Michiel Sedelaar  
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5 382 KKHA - Katja K.H. Aben  
6

7 383 EK - Ellen Kampman  
8

9 384 LALAMK - Lambertus A.L.M. Kiemeneij  
10

11 385 AV - Alina Vrieling  
12

13  
14 386

15  
16 387 **Funding**

17  
18 388 This project is funded by the Dutch Cancer Society (KUN 2015-7948). Sponsors were not  
19  
20 389 involved in the study design nor will they be in the collection, analysis, and interpretation of  
21  
22 390 data, or in the publications that will result from this study.  
23

24 391

25  
26 392 **Competing interests**

27  
28 393 The authors declare that they have no competing interests.  
29

30 394

31  
32 395 **Ethics approval and consent to participate**

33  
34 396 The study protocol has been approved on March 2, 2017 by the Committee for Human  
35  
36 397 Research region Arnhem-Nijmegen (CMO 2016-3078). Patients who agreed to participate in  
37  
38 398 the study provided a written informed consent.  
39

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42  
43 400 **Consent for publication**

44  
45 401 Not applicable.  
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48  
49 403 **Availability of data and material**

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51 404 Data and material are not yet available since data collection has not been completed yet.

52  
53 405 After completion of data collection, data will be made available by the corresponding author  
54  
55 406 upon reasonable request.  
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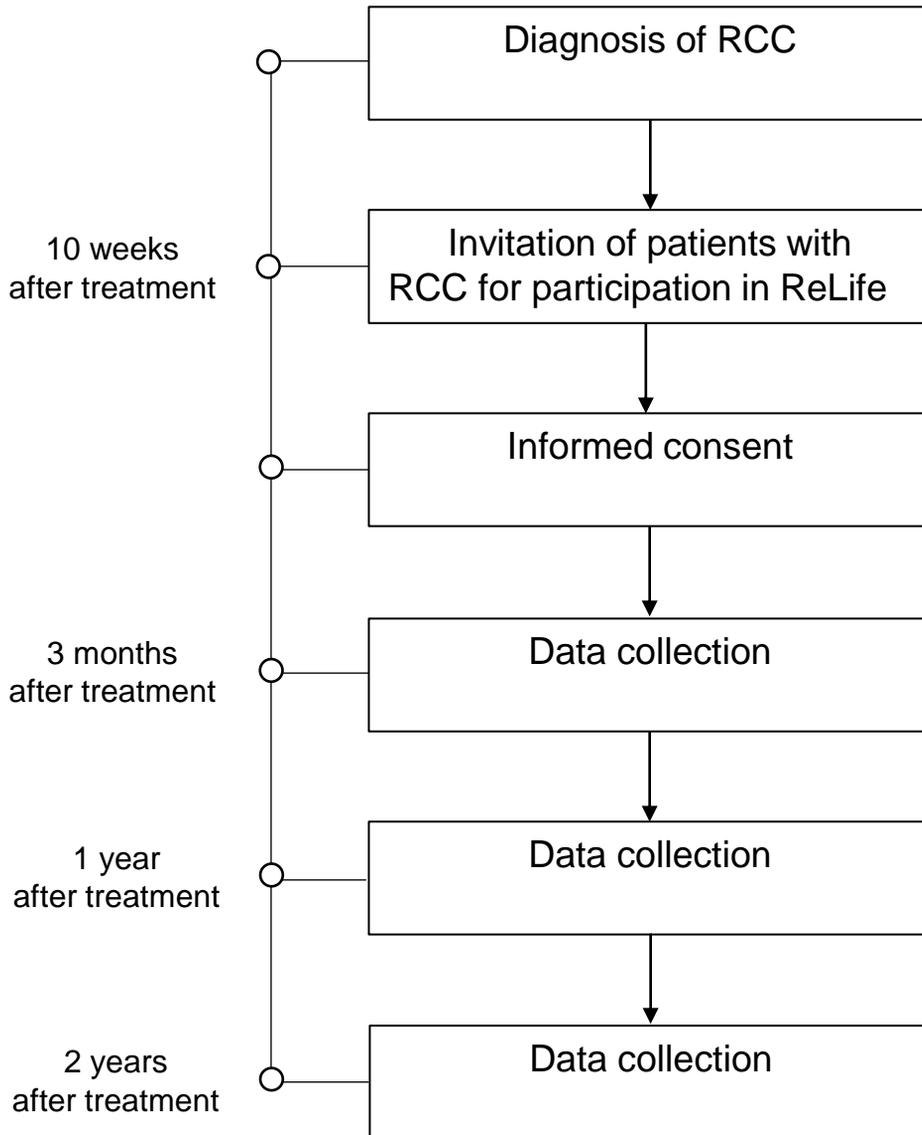
541 **Figure 1.** Timeline and study design of the ReLife study

542 **Figure 2.** Flow chart of the ReLife study

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## Overview ReLife study



# RE LIFE

