


BMJ Open The UroLife study: protocol for a Dutch prospective cohort on lifestyle habits in relation to non-muscle-invasive bladder cancer prognosis and health-related quality of life

Liesbeth de Goeij ¹, Ellen Westhoff,¹ J Alfred Witjes,² Katja KH Aben,^{1,3} Ellen Kampman,⁴ Lambertus ALM Kiemeneij,^{1,2} Alina Vrieling ¹

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¹Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, The Netherlands

²Department of Urology, Radboud university medical center, Nijmegen, The Netherlands

³Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands

⁴Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

Correspondence to

Dr Alina Vrieling;
Alina.Vrieling@radboudumc.nl

ABSTRACT

Introduction Patients with non-muscle-invasive bladder cancer (NMIBC) have a good survival but are at high risk for tumour recurrence and disease progression. It is important to identify lifestyle habits that may reduce the risk of recurrence and progression and improve health-related quality of life (HRQOL). This paper describes the rationale and design of the UroLife study. The main aim of this study is to evaluate whether lifestyle habits are related to prognosis and HRQOL in patients with NMIBC.

Methods and analysis The UroLife study is a multicentre prospective cohort study among more than 1100 newly diagnosed patients with NMIBC recruited from 22 hospitals in the Netherlands. At 6 weeks and 3, 15 and 51 months after diagnosis, participants fill out a general questionnaire, and questionnaires about their lifestyle habits and HRQOL. At 3, 15 and 51 months after diagnosis, information about fluid intake and micturition is collected with a 4-day diary. At 3 and 15 months after diagnosis, patients donate blood samples for DNA extraction and (dietary) biomarker analysis. Tumour samples are collected from all patients with T1 disease to assess molecular subtypes. Information about disease characteristics and therapy for the primary tumour and subsequent recurrences is collected from the medical records by the Netherlands Cancer Registry. Statistical analyses will be adjusted for age, gender, tumour characteristics and other known confounders.

Ethics and dissemination The study protocol has been approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494). Patients who agree to participate in the study provide written informed consent. The findings from our study will be disseminated through peer-reviewed scientific journals and presentations at (inter)national scientific meetings. Patients will be informed about the progress and results of this study through biannual newsletters and through the website of the study and of the bladder cancer patient association.

INTRODUCTION

Urinary bladder cancer is the sixth most common cancer in the male population worldwide and tenth if considering both genders.¹ Approximately 75% of patients is

Strengths and limitations of this study

- Large multicentre prospective cohort study of non-muscle-invasive bladder cancer patients recruited shortly after diagnosis.
- Extensive dietary, lifestyle, medical and health-related quality of life data at multiple time points after diagnosis.
- Availability of blood samples at 3 and 15 months after diagnosis, and formalin-fixed, paraffin-embedded tumour tissue.
- Limited power for subgroup analyses.
- Loss to follow-up potentially influencing validity of results.

diagnosed with non-muscle-invasive bladder cancer (NMIBC, stages Ta, T1 and Tis) and 25% with muscle-invasive bladder cancer (stages T2, T3 and T4).² Patients with NMIBC have a good survival but are at high risk for tumour recurrence and disease progression.³ They are therefore subjected to frequent follow-up by cystoscopy and treatment. This makes bladder cancer the most expensive cancer in terms of healthcare expenditures per patient per year.⁴ The high recurrence rate may also impact health-related quality of life (HRQOL).⁵ Lifestyle factors have been linked to the prognosis and quality of life in patients with several cancer types^{6 7} but evidence in patients with NMIBC is scarce. If we can identify lifestyle habits that are related to the risk of recurrence and progression and HRQOL in patients with NMIBC, optimal interventions can be developed to improve their prognosis and HRQOL.

The primary risk factor for bladder cancer is smoking, which accounts for 43% of bladder cancer cases in men and 26% in women in Europe.⁸ Other important risk



factors for bladder cancer are occupational exposures to carcinogens like aromatic amines and polycyclic aromatic hydrocarbons, family history and specific low penetrance germline genetic variants.⁹ Recent meta-analyses suggest that excess body weight¹⁰ and physical inactivity¹¹ may also increase bladder cancer risk. The World Cancer Research Fund/American Institute for Cancer Research report found probable evidence that arsenic in drinking water increases the risk of bladder, and limited suggestive evidence that higher consumption of fruit and vegetables and of tea decreases the risk of bladder cancer.¹² For other dietary and lifestyle factors, this report concluded that data were of too low quality, inconsistent or the number of studies were insufficient to draw conclusions.¹²

Available evidence about the role of lifestyle habits on prognosis in patients with NMIBC is restricted to smoking^{13 14} and excess body weight.¹⁵ A systematic review¹³ and recent meta-analysis of 10 studies including a total of 6307 patients with NMIBC¹⁴ found that current and former smokers at diagnosis had an approximately 25% increased risk of recurrence compared with never smokers. Our recent meta-analysis¹⁵ of three studies^{16–18} showed that overweight and obesity compared with normal weight at diagnosis were associated with increased risk of recurrence but not progression in patients with NMIBC, although power for progression was limited.¹⁵ Smoking cessation and weight loss after diagnosis in relation to clinical outcomes have hardly been investigated. Evidence for other lifestyle habits, such as fluid intake and micturition, physical activity, and fruit and vegetable consumption, is very limited or not available.¹⁵ Also, most studies on lifestyle and NMIBC prognosis included a heterogeneous study population with different tumour stages and grades of bladder cancer. However, NMIBC prognosis is clearly different for these subgroups¹⁹ and may also differ by molecular subtype.^{20 21} Whether associations of lifestyle habits with NMIBC prognosis are mediated and/or modified by tumour stage and by molecular subtype has not yet been investigated.

Despite the high frequency of surveillance and repeated treatments, relatively little is known about the HRQOL of patients with NMIBC,²² and research with validated bladder cancer-specific instruments is needed.²³ A systematic review of five studies on lifestyle and HRQOL in bladder cancer patients found some evidence for a positive association between physical activity and HRQOL, but insufficient evidence to draw any conclusions for consumption of fruit and vegetables or smoking cessation.²⁴

The aim of our study is to evaluate the association of pre- and post-diagnosis lifestyle habits (and habit changes) with risk of recurrence and progression and HRQOL. Also, we want to explore whether this association is mediated and/or modified by tumour stage and molecular subtype.

METHODS AND ANALYSIS

The UroLife study (**U**rothelial cell cancer: **L**ifestyle, prognosis and quality of **L**ife) is a prospective cohort study including patients with newly diagnosed NMIBC. The study has been designed to evaluate the association of lifestyle habits with risk of recurrence and progression and HRQOL. Patients are recruited in 22 hospitals in the east, south and central parts of the Netherlands. Before the start of the study, permission was asked from all urologists of the participating hospitals to select and invite eligible patients from the Netherlands Cancer Registry (NCR), held by the Netherlands Comprehensive Cancer Organisation (IKNL). Once every 1 to 2 weeks, new patients are identified through IKNL using notification lists of the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA Foundation). Approximately 4 weeks after diagnosis, patients are invited on behalf of their urologist to participate in this study. Patients who agree to participate provide a written informed consent.

Patient population

Eligible participants are Dutch speaking patients between 18 and 80 years old who are newly diagnosed with a histologically confirmed primary stage Ta, T1 and Tis NMIBC tumour and underwent a transurethral resection (TUR). Patients with a previous diagnosis of cancer in the past 5 years and those with a lymph node metastasis or distant metastasis are not eligible.

Patient and public involvement

Patients were not involved in the design, recruitment and conduct of the study.

Data collection and management

Questionnaires

Participants are asked to complete self-administered web-based or paper-and-pencil-based questionnaires at 6 weeks (T6wk), 3 months (T3mo), 15 months (T15mo) and 51 months (T51mo) after diagnosis (figure 1, table 1). Web-based questionnaires are collected using the data collection tool of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry.²⁵ Follow-up telephone calls are made to non-responding participants and to respondents whose questionnaires have missing items.

The baseline questionnaire contains questions on demographics (age, sex, ethnicity, education, living situation, occupation, marital status) and (family) history of cancer. All questionnaires collect information about height, body weight, amount and frequency of alcohol consumption during week and weekend days, smoking habits, comorbidities and the use of medication. Information on smoking habits is collected in detail, including age or date of starting and stopping smoking, number of cigarettes smoked per day, duration of smoking and passive exposure to smoking. Information about habitual physical activity is collected by using the previously

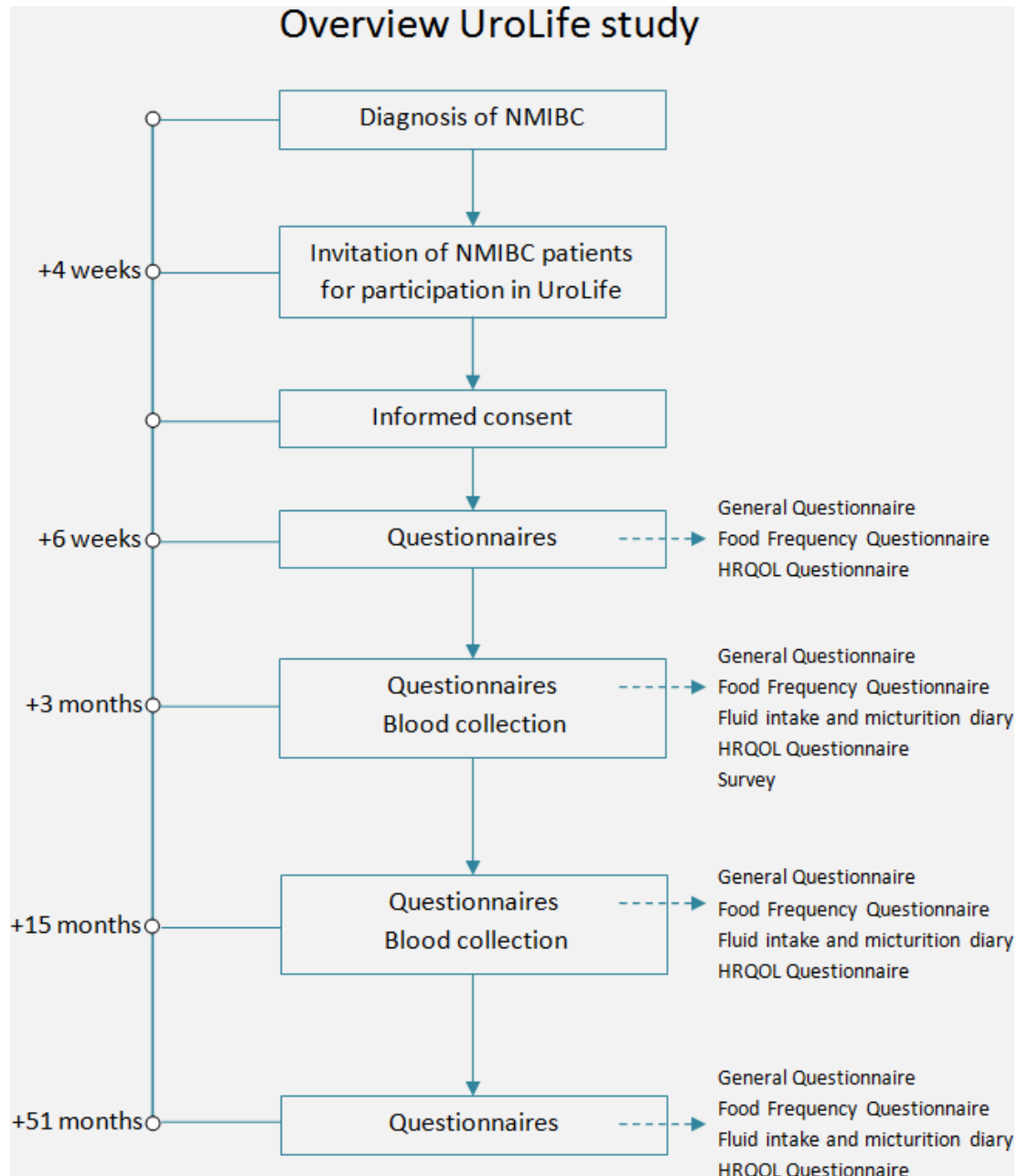


Figure 1 Timeline and study design of the UroLife study. HRQOL, health-related quality of life; NMIBC, non-muscle-invasive bladder cancer.

validated short questionnaire to assess health-enhancing physical activity (SQUASH),²⁶ which is fairly reliable and valid in an adult population.^{26–28} The SQUASH questionnaire assesses the average time, that is, number of days per week and hours and minutes per day, spent in commuting activities, leisure time activities, household activities and activities at work in a normal week in the past month. At T3mo, T15mo and T51mo, patients are also asked to measure and report their waist and hip circumference.

Habitual dietary intake is collected using a 163-item validated and reproducible self-administered food frequency questionnaire that was developed by Wageningen University.²⁹ The questionnaire contains questions about the frequency of consumption of food products

and the portion size during the previous year (T6wk) or the previous months (T3mo, T15mo, and T51mo). Frequency and portion size of consumed food products are multiplied to obtain their intake in grams per day. Nutrient intake is calculated using the Dutch Food Composition Database NEVO 2011.³⁰ Information about fluid intake and micturition is collected with a 4-day diary at T3mo, T15mo and T51mo.

HRQOL is assessed at all four time points with the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)³¹ and a 24-item module for patients with NMIBC, i.e. the EORTC QLQ-NMIBC24.³² The EORTC QLQ-C30 contains five function scales (physical,

**Table 1** Overview of data collection in UroLife at the four time points

	Included topics	T6wk	T3mo	T15mo	T51mo
Questionnaires					
Sociodemographic data	Date of birth, gender, living situation, marital status, country of birth of participant, father, mother, race, highest level of education, working history, occupational exposure	X			
Anthropometry	Height at diagnosis, weight 2 years before diagnosis, weight at age 18 years, average weight during adult life	X			
	Current body weight, waist and hip circumference	X	X	X	X
Lifestyle	Current and past smoking behaviour, environmental smoke exposure	X	X	X	X
	SQUASH ²⁶	X	X	X	X
	Frequency and amount of alcohol consumption during week and weekend days	X	X	X	X
	Changes in eating habits and reasons for/type of changes		X	X	X
Medical history	Previously diagnosed with cancer, family history of cancer	X			
	Comorbidities, medication use, dietary supplement use	X	X	X	X
Questions for females	Menstruation, menopause, use of contraceptives, use of hormone replacement therapy	X	X	X	X
	Pregnancy	X			
Diet	163-item Food Frequency Questionnaire	X	X	X	X
HRQOL	EORTC QLQ-C30 ³¹ and EORTC QLQ-NMIBC24 ³²	X	X	X	X
Awareness risk factors and lifestyle advice	Awareness of cancer risk factors, received lifestyle advice, attitudes towards lifestyle advice		X		
Four-day diary	Frequency micturition, amount and type of fluid intake		X	X	X
Blood	EDTA whole blood for DNA isolation		X		
	EDTA plasma, heparin plasma		X	X	
Tissue	Formalin-fixed paraffin-embedded tissue of the primary tumour	X			
Clinical data	Disease characteristics, therapy	X	X	X	X
	Recurrence and progression			X	X

EORTC QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; HRQOL, health-related quality of life; NMIBC, non-muscle-invasive bladder cancer; SQUASH, Short questionnaire to assess health-enhancing physical activity.

role, cognitive, emotional and social functioning), three symptom scales (fatigue, nausea, pain and vomiting) and six single items (dyspnea, insomnia, loss of appetite, constipation, diarrhoea, and financial impact), all scored from 1 (not at all) to 4 (very much) and a global health status scale with ranges from 1 (very poor) to 7 (excellent). The EORTC QLQ-NMIBC24 contains six scales (urinary symptoms, malaise, future worries, bloating and flatulence, sexual function and male sexual function) and five single items (intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems) scored from 1 (not at all) to 4 (very much). All scores will be linearly transformed to a 0–100 scale.

Furthermore, at T3mo patients are asked to report whether they are aware of possible risk factors for (bladder) cancer, received lifestyle advice from their physician and what their attitudes are towards physicians giving lifestyle advice.

Blood samples

Non-fasting blood samples are collected at T3mo and T15mo. At T3mo, 10 mL EDTA whole blood (for DNA isolation), 10 mL EDTA plasma and 10 mL heparin plasma are collected. At T15mo, 10 mL EDTA plasma and 10 mL heparin plasma are collected. Heparin plasma tubes are wrapped in aluminium foil to protect them from light. All blood samples are collected, processed and stored

at -80°C locally in the participating hospitals according to a standard protocol before transportation on dry ice to the Radboud Biobank. The blood samples are stored in the Radboud Biobank at -80°C for future analyses of genetic and other biomarkers. Analysis of heparin plasma levels of nine biomarkers of fruit and vegetable consumption is planned. Concentration of six carotenoids (ie, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, lycopene and zeaxanthin), alpha-tocopherol, beta- and gamma-tocopherol and retinol will be measured by High Performance Liquid Chromatography (Thermo Scientific Accela LC system; Thermo Fisher Scientific) and analysed by using ChromQuest 5.0, V.3.2.1 software (Thermo Fisher Scientific).

Tumour samples

From patients diagnosed with T1 NMIBC, tumour specimens will be collected in two batches in 2019 and 2021. Tumour blocks will be identified by using the PALGA Foundation and retrieved using the Dutch National Tissuebank Portal from the local pathology laboratories. Pathology review will be performed and tissue microarrays will be constructed. Molecular subtypes will be assessed by immunohistochemistry in 2021. As the development of a molecular classification system for NMIBC is still in progress and no consensus system is available yet,³³ we will use the most suitable evidence-based subtyping method that will then be available.

Clinical data

For all patients with NMIBC, information about disease characteristics and therapy for the initial tumour is collected from the medical records by data managers of the NCR. Information about tumour characteristics includes incidence date, clinical Tumour, Node, Metastasis (cTNM) and post-surgical Tumour, Node, Metastasis (pTNM) stage,² tumour grade, concomitant carcinoma in situ, multifocality, number of tumours and histology. With respect to therapy, information is collected on type of cystoscopy (white or blue light) and on TUR, that is, date of TUR, presence of detrusor in the surgical specimen and presence of lymphovascular invasion. Furthermore, data on local treatment (eg, intravesical chemotherapy, intravesical immunotherapy) with start and stop dates and, if applicable, on cystectomy (eg, date, type) are collected.

Data on clinical outcomes, that is, recurrence and progression, with dates of diagnosis, tumour characteristics and therapy is also collected from the medical records by data managers of the NCR. Information on vital status is collected by linkage with the Personal Records Database. All patients will be followed for at least 5 years.

Power considerations & Data analysis

Risk of recurrence (or progression) will be evaluated as time to first recurrence (or progression). The association of pre- and post-diagnostic lifestyle factors, as well as changes in lifestyle factors, with risk of recurrence and

progression will be evaluated by estimating hazard ratios and 95% CI using Cox proportional hazards regression analyses. All analyses will be adjusted for age, gender, tumour characteristics and other known confounders. Analytical techniques for longitudinal data and multiple outcomes will also be explored and applied. Our power calculation is based on 1100 patients who will be followed for 5 years. For comparing the highest ($n=275$) versus lowest quartile ($n=275$) of a lifestyle factor (or vice versa), this study will be sufficiently powered (two-sided $\alpha=0.05$, power 80%) to detect a HR of ≥ 1.5 or ≥ 1.3 (or ≤ 0.7 or ≤ 0.8) when assuming a 5-year recurrence risk of 31% or 78%,³⁴ respectively.^{35 36} With an assumed loss to follow-up of 25% after 5 years, detectable hazard ratios will increase to ≥ 1.6 or ≥ 1.4 (or ≤ 0.6 or ≤ 0.7), respectively. Lower hazard ratios can be detected when lifestyle factors are modelled continuously.

The association of lifestyle factors with HRQOL will be evaluated using longitudinal mixed-model analyses, taking into account the within-subject variation in lifestyle and HRQOL over time and the between-subject variation. All analyses will be adjusted for age, gender, tumour characteristics and other known confounders. Since we expect that the between-subject variation in lifestyle and HRQOL will be much larger than the within-subject variation, most information will come from the association observed between subjects and not from the association observed within subjects over time. Therefore, our power calculation is based on a cross-sectional correlation at one time point. With 825 patients (assuming a loss to follow-up of 25%) and using 10 predictor variables, we have 80% power to detect a small correlation (Cohen's f^2 of 0.02).^{37 38} Power will be higher when using repeated measurements over time, especially when there is within-subject variation of lifestyle factors and HRQOL over time.

Cohort status

Medical ethical approval was obtained on 17 January 2014. Patient recruitment started in May 2014. Between 8 May 2014 and 25 April 2017, 2133 patients with NMIBC initially diagnosed with Ta, T1 or Tis tumours have been identified and invited to participate in UroLife. Of these invited patients, 1193 patients agreed to participate and 77 dropped out before filling out the first questionnaires (response rate 52%). Since May 2017, recruitment of patients with T1 (but not Ta or Tis) tumours has continued and is still ongoing. We aim to recruit a total of at least 700 patients with T1 bladder cancer, and the projected date of recruitment completion is April 2021.

DISCUSSION

The UroLife study is one of the largest multicentre prospective cohort studies on lifestyle and NMIBC outcomes worldwide. UroLife will provide new and comprehensive insights into whether lifestyle habits (or habit changes) are related to NMIBC outcomes and

HRQOL, and whether these relations differ by tumour stage and molecular subtype. Unique features of UroLife are the recruitment of patients shortly after diagnosis, collection of extensive dietary, lifestyle, medical and HRQOL data at multiple time points after diagnosis, collection of blood (for DNA and biomarker analysis) and the availability of tumour tissue samples (for molecular classification).

As in many prospective cohort studies, non-participation may limit the generalisability of our findings. In addition, loss to follow-up may limit the validity of our findings. Information bias due to reliance on recall and self-report, or due to missing data, may be another potential limitation. Although our study is large, we intend to combine our data set in the future with other similar prospective studies in NMIBC to increase statistical power for subgroup analyses.

If the results of this study show that lifestyle factors are associated with clinical outcomes in NMIBC patients and these results are confirmed by other prospective studies or randomised trials, lifestyle recommendations and lifestyle interventions can be developed. Patients diagnosed with NMIBC could then be advised by their physician about their lifestyle and/or referred to a lifestyle intervention (eg, smoking cessation programme, exercise programme). Thus, our ultimate aim is to provide personalised evidence-based lifestyle advice to patients with NMIBC, also according to tumour stage and molecular subtype, to enable them to have an influence on their clinical outcome.

ETHICS AND DISSEMINATION

Patients who agree to participate in the study provide written informed consent. The findings from our cohort study will be disseminated through peer-reviewed scientific journals, and presentations at (inter)national scientific meetings. Patients will be informed about the progress and results of this study through biannual newsletters and through the website of the study (<https://www.radboudumc.nl/trials/urolife>) and of the bladder cancer patient association (<https://www.blaasofnierkanker.nl/>). Also, presentations will be given at contact days of the bladder cancer patient association.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol has been approved by the Committee for Human Research region Arnhem-Nijmegen (CMO 2013-494).

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ORCID iDs

Liesbeth de Goeij <http://orcid.org/0000-0001-6787-0404>

Alina Vrieling <http://orcid.org/0000-0002-8178-2125>

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