# **BMJ Open** Cross-sectional internet survey exploring women's knowledge, attitudes and practice regarding urinary tract infection-related symptoms in the Netherlands

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#### **ABSTRACT**

Objectives Urinary tract infections (UTIs) are the most prevalent cause for women to consult a general practitioner (GP) and are commonly treated with (broadspectrum) empirical antibiotics, even though 50% of UTIs are self-limiting. In this study, we aim to explore women's attitudes and experiences regarding UTIs, in order to determine patients' willingness to accept delayed antibiotic prescriptions.

**Design** An internet-based cross-sectional survey **Setting** We recruited participants during 2 weeks of March and April in 2020 through several social media platforms.

Participants We obtained 1476 responses, of which 975 were eligible for analysis.

**Results** We asked women about their knowledge, attitudes and practice regarding UTI-related symptoms. Participants ranked 'confirmation of diagnosis' (43.8%) as the most important reason to consult a GP with urinary symptoms, followed by 'pain relief' (32%), and 'antibiotic prescription' (14.3%). For treatment, 71% of participants reported that their GP prescribed immediate antibiotics, while only 3% received a delayed antibiotic prescription and 1% was advised pain medication. Furthermore, 50% of respondents were aware of the possible self-limiting course of UTIs and 70% would be willing to accept delayed antibiotic treatment, even if a certain diagnosis of UTI was established. Willingness to delay was lower in experienced patients compared to inexperienced patients.

Conclusions Women are quite receptive to delayed antibiotics as an alternative to immediate antibiotics for UTIs or urinary symptoms. GPs should consider discussing delayed antibiotic treatment more often with women presenting with urinary symptoms.

# INTRODUCTION

Urinary tract infections (UTIs) are the most prevalent cause for women to consult a general practitioner (GP). GPs in the Netherlands usually test the urine of women presenting with urinary symptoms using

# STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A large sample of women was surveyed about their knowledge, attitudes and practice regarding urinary tract infection (UTI)-related symptoms.
- ⇒ The survey was posted on several social media to obtain as many responses as possible.
- ⇒ Binary regression models were used to determine patient factors affecting women's knowledge on UTIs and willingness to delay antibiotic treatment.
- ⇒ Outcomes are based on patients' memory; therefore, there is a risk of recall bias

urinary dipsticks and subsequently prescribe empiric antibiotics as treatment. However, the predictive values of the urinary dipstick for the presence of an infection are inadequate for proper diagnosis.<sup>2</sup> Previous research has shown that a bacteriological confirmation of infection (as determined by urinary culture) is absent in 40% of women presenting with urinary symptoms that are prescribed antibiotics, which in part is caused by the lack of adequate point-of-care tests.<sup>3</sup> Furthermore, in recent years, the urinary culture, considered the golden standard for UTI diagnosis, has come under scrutiny, as it is not as sensitive for fastidious bacteria and is prone to contamination. 4-6 The inadequacy of the available tests has resulted in both overtreatment and undertreatment of UTI with antibiotics. To combat the excessive use of antibiotics for UTI, alternative treatment options have been suggested.

Different trials comparing placebo or non-steroidal anti-inflammatory (NSAIDs) to antibiotics showed that almost half of all UTIs are self-limiting in low-risk patients (non-pregnant adult women without



conditions affecting the urinary tract). Nhile antibiotics consistently outperformed the alternatives, researchers also saw a marked reduction of symptoms in the placebo and especially the NSAID arms of the trials, with a slight (2%–5%) increase in pyelonephritis cases. Place Therefore, symptomatic treatment combined with a delayed antibiotic prescription in case of worsening symptoms is a promising alternative to the immediate prescription of antibiotics. He

As a result, the Dutch College of General Practitioners altered the national UTI guidelines to incorporate a waitand-see approach for women presenting with urinary symptoms without a history of pyelonephritis. 15 Despite this amendment, immediate empirical antibiotics remain the most common treatment for UTIs in the Netherlands, not unlike in other countries with similar healthcare systems. 16-18 GPs seem hesitant to employ alternative strategies to combat UTI, likely caused by a discrepancy in what GPs think patients expect from a consultation and what patients' actual expectations are. 19 While delayed antibiotic prescriptions are not part of actual everyday practice at this moment, some studies have shown that patients would be willing to delay treatment with antibiotics.<sup>20–22</sup> However, studies looking into women's willingness to delay antibiotic treatment were of limited sample size thus far.

In this study, we aim to explore women's attitudes towards delayed antibiotic prescriptions for UTIs further. We conducted a cross-sectional internet survey, studying women's knowledge, attitudes, and practice regarding urinary symptoms and UTIs as well as their willingness to delay antibiotic treatment. Results of this study will establish factors that could aid in improving the treatment of UTIs and in turn reduce antibiotic prescriptions.

# METHODS Study design

We conducted a cross-sectional online survey in the Netherlands during the last week of April and first week of May in 2020. We used Qualtrics software (Qualtrics May 2020, Provo, Utah) to obtain responses. Distribution of invitations took place on different social media platforms, including WhatsApp (Facebook), Twitter, Facebook, Instagram (Facebook) and LinkedIn (Microsoft Corporation). We posted an announcement of the questionnaire on general pages as well as on pages whose visitors likely had an interest for the topic. These included a group page for medical students, a GP assistant's blog and a group page on UTIs. To ensure generalisability of responses, we considered a sample target of ≥384 to be adequate (~8 500 000 women in the Netherlands, 5% margin of error).

### **Setting and subjects**

Women of 18 years old and above who had suffered from a UTI at any point in time were eligible for participation. We excluded women who had suffered exclusively from UTI or urinary symptoms during pregnancy or bladder catheterisation. Participants did not receive any incentive to participate in the study. All participants provided written informed consent.

#### **Data collection**

The content of the questionnaire was derived from previous qualitative and quantitative research and expert opinion.<sup>21 23</sup> The survey included 25 questions with a varying number of subitems. The questions covered demographic characteristics as well as knowledge, attitudes, and practices regarding UTIs. Answer possibilities were agree/disagree, yes/no or Likert-type scale response elements, and some open-ended questions were included for respondents to explain their answers. A pilot sample of five women verified the face validity and readability of the questionnaire. To enhance data quality, the option to proceed to the next question only became available if the current question was completed. Additionally, respondents had to complete the survey within a week. A cookie placed on the browser of the respondent on submission prevented Ballot Box Stuffing. After the first week, a reminder was posted on all mentioned platforms.

#### **Data analysis**

Respondents' answers were automatically transferred into a data file and analysed using IBM SPSS Statistics V.26.0 (IBM 2019, Armonk, New York). Unanswered questions were scored as missing values. The answers to the openended questions were categorised for analysis.

Three statements that participants could either agree or disagree with tested their knowledge on UTIs. We presented the following statements: 'A UTI can resolve by increased fluid intake and taking pain medication', 'A urinary tract infection can resolve without using antibiotics', and 'not every UTI needs to be treated with antibiotics'. Respondents were deemed knowledgeable on UTIs if they answered all three statements correctly. Answers to the question: 'Knowing that UTIs can be self-limiting, would you be willing to delay antibiotic treatment, even if diagnosis is certain?' provided insight into respondents' willingness to delay antibiotic treatment. A similar question inquired about participants' willingness to delay in the context of uncertain diagnosis.

Analyses were based on frequencies and cross tabulations. Pearson's  $\chi^2$  tests were used to identify independent categorical variables associated with the dependent variables accurate knowledge on UTIs and willingness to delay antibiotic prescription for a UTI. Furthermore, univariate logistic regression models were used to calculate the associations between categorical independent variables and continuous independent variables with the previously described dependent variables. Analyses were adjusted for age (continuous), frequency of UTIs in the past (1 time/2 times/3 times/>3 times), waiting time before visiting a GP (<24 hours/24–48 hours/2–5 days/>5 days/never been to a GP), level of education (low (primary or secondary education)/intermediate (secondary vocational education)/high (university)), presence of underlying disease

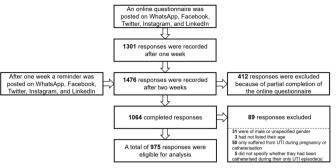


Figure 1 Flowchart of the included responses. We received 1476 responses after 2 weeks, of which 1064 were fully completed. Of the fully completed responses, 89 met one or more of the exclusion criteria. This left 975 responses eligible for analysis. UTI, urinary tract infection.

(yes/no), UTI in the previous year (yes/no) and hospitalised due to UTI (yes/no) in a multivariable logistic model to check for independence of associations when applicable.

# Patients and public involvement

We involved the public during the design phase of the survey, where they helped determining which topics would be subject to questioning. Moreover, the public was involved in verification of the readability and face validity of the survey.

# **RESULTS**

# **Characteristics of study population**

The survey received 1476 responses after 2weeks. After exclusion of partial responses (n=412) and responses with exclusion criteria (n=89), 975 responses remained eligible for analysis (figure 1).

Table 1 summarises the characteristics of the participating women. Participants ranged in age from 18 to 87, with a mean age of 39.6 (SD=14.7). The majority of participants reported to have suffered from three or more UTIs in the past. Additionally, 533 respondents reported to have had a UTI within the past year.

## Patients' experiences and attitudes

The survey inquired how long participants had waited before visiting a GP for urinary symptoms. Around a fifth of the participants reported to have waited for less than 24 hours, while most participants had waited for 24–48 hours (table 1).

Furthermore, the survey required participants to rank four possible outcomes of a visit to the GP due to UTI symptoms in order of importance (table 2). Most participants (n=412, 43.8%) ranked confirmation of diagnosis as the most important outcome instead of obtaining an antibiotic prescription (n=134, 14.3%).

Additionally, participants could indicate which treatment they had received at their most recent visit. The majority of participants (n=687, 70.5%) reported to have received an immediate antibiotic prescription, while 196

	Total, n (%)		
Mean age, years (SD)	39.6 (14.7)		
18-65 years	920 (94.4)		
≥65 years	55 (5.6)		
Education level	970 (99.5)		
Low	75 (7.7)		
Middle	335 (34.5)		
High	560 (57.7)		
Last UTI episode	975 (100.0)		
<1 week ago	52 (5.3)		
1 week-1 month ago	89 (9.1)		
1-6 month(s) ago	221 (22.7)		
6 months-1 year ago	171 (17.5)		
>1 year ago	442 (45.3)		
Frequency of UTIs in the past	973 (99.8)		
1 time	61 (6.3)		
2 times	83 (8.5)		
3 times	108 (11.1)		
>3 times	721 (74.1)		
Waiting time before visiting GP	974 (99.9)		
<24 hours	212 (21.8)		
24-48 hours	332 (34.1)		
2–5 days	317 (32.5)		
>5 days	73 (7.5)		
Never been to GP for UTI	40 (4.1)		
Underlying (chronic) illness	140/973 (14.4		
Hospitalised for UTI in the past	110/974 (11.3		
Diagnosed with diabetes mellitus	35/974 (3.6)		

participants (20.1%) received an antibiotic prescription after a positive culture and 27 participants (2.8%) received a delayed antibiotic description. Only 11 participants (1.1%) obtained a prescription for (or advice on the use of) pain medication.

### **Knowledge on UTIs**

The questionnaire included three questions that tested whether participants were aware of the possible selflimiting course of UTIs. If participants had answered all three questions correctly, they were deemed knowledgeable about UTIs. Slightly less than half of participants (49.6%) answered all questions correctly.

Univariate binary regression analyses identified age, frequency of UTIs in the past, waiting time before visiting a GP, and education level as predictors for knowledge on UTIs (table 3). Younger participants were more likely to be knowledgeable on UTIs compared to older participants. Additionally, participants who had suffered from two or three UTI episodes were more knowledgeable compared

Table 2 Ranking of importance of GP consultation

outcomes					
Importance	Outcome of consultation	Prioritised as most important (%)			
	Confirmation of UTI diagnosis	43.8			
	Pain relief	32.0			
	Obtaining an antibiotic prescription	14.3			
	Obtaining advice on when to contact a general practitioner	9.9			
GP, general practitioner; UTI, urinary tract infection.					

to participants who did so only once. Participants' waiting time before visiting a GP also influenced their knowledge on UTIs and so did participants' education level. Multivariate analysis including the aforementioned variables revealed similar results.

# Willingness to delay antibiotic treatment

The questionnaire also inquired about the willingness of patients to delay antibiotic treatment when diagnosis of UTI was either certain or uncertain. In the case of uncertainty of the diagnosis, 742 participants (77.0%) would be willing to delay antibiotic treatment. However, in the context of a certain UTI diagnosis, 672 participants (69.7%) would be willing to delay antibiotic treatment ( $\Delta$ =7.3%, 95% CI 3.4%-11.2%). A minority of 142 participants (14.7%) would not be willing to delay antibiotic treatment in either case.

Univariate binary regression analyses showed that in case of a certain diagnosis, the frequency of UTIs suffered by participants in the past affected their willingness to delay antibiotics (table 4). Furthermore, participants who waited longer before visiting a GP after developing UTI symptoms were more willing to delay antibiotic treatment, an effect that increased with waiting time until 2–5 days. Older participants were less willing to delay antibiotic treatment. Furthermore, participants who had previously been hospitalised due to UTI were less willing to delay antibiotics as well as participants who had had a UTI within the previous year. Participants knowledgeable on UTIs were more likely to be willing to delay

	Respondents (n)	Respondents with correct answers* (n (%))	OR† (95% CI)	OR‡ (95% CI)
Age	970	481 (49.6)	0.96 (0.96 to 0.97)	0.97 (0.96 to 0.98)
Frequency of UTIs in the past	968			
1 time	61	27 (44.3)	*	*
2 times	83	56 (67.5)	2.61 (1.32 to 5.17)	3.30 (1.53 to 7.08)
3 times	108	70 (64.8)	2.32 (1.22 to 4.41)	2.90 (1.42 to 5.92)
>3 times	716	327 (45.7)	1.06 (0.63 to 1.79)	1.81 (0.98 to 3.35)
Waiting time before visiting a GP	969			
<24 hours	212	63 (29.7)	*	*
24-48 hours	328	135 (41.1)	1.65 (1.15 to 2.39)	1.55 (1.08 to 2.33)
2-5 days	316	198 (62.7)	3.97 (2.74 to 5.76)	3.50 (2.43 to 5.31)
>5 days	73	50 (68.5)	5.14 (2.89 to 9.14)	5.18 (2.81 to 9.55)
Never been to GP for UTI	40	34 (85.0)	13.40 (5.36 to 33.51)	11.12 (4.16 to 29.73)
Education level	965			
Low	75	18 (24.0)	*	*
Middle	332	159 (47.9)	2.91 (1.64 to 5.16)	2.38 (1.23 to 4.61)
High	558	304 (54.5)	3.79 (2.18 to 6.61)	2.52 (1.30 to 4.88)
Chronic disease or diabetes	161/967	57 (35.4)	0.50 (0.35 to 0.71)	0.72 (0.48 to 1.07)

Cursive ORs have a p value<0.05.

<sup>\*</sup>Correct answers on the questions for knowledge, i.e. knowing that increased fluid intake and taking pain medication can resolve a UTI, knowing that a UTI can resolve without antibiotics, and knowing that not every UTI needs to be treated with antibiotics.

<sup>†</sup>Univariate logistic regression model.

<sup>‡</sup>Multivariate logistic regression model adjusted for age, frequency of UTIs, waiting time, education level, and presence of chronic disease or diabetes, hospitalisation due to UTI, and UTI in the last year.

GP, general practitioner; UTI, urinary tract infection.



Table 4 Factors influencing participants' willingness to delay antibiotics if UTI diagnosis is

	Respondents (n(%))	Respondents willing to delay if certain (n (%))	OR* (95% CI)	OR† (95% CI)
Age	971	675 (69.5)	0.99 (0.98 to 1.00)	1.01 (1.00 to 1.02)
Frequency of UTIs	969			
≤3 times	252 (26.0)	215 (85.3)		
>3 times	717 (74.0)	459 (64.0)	0.31 (0.21 to 0.45)	0.40 (0.26 to 0.61)
Waiting time before visiting a GP	970			
<24 hours	211 (21.7)	85 (40.3)		
24-48 hours	330 (34.0)	218 (66.1)	2.89 (2.02 to 4.12)	2.74 (1.88 to 4.01)
2-5 days	316 (32.6)	271 (85.8)	8.93 (5.87 to 13.57)	7.36 (4.73 to 11.45)
>5 days	73 (7.5)	64 (87.7)	10.54 (4.98 to 22.32)	9.38 (4.31 to 20.42)
Never been to GP for UTI	40 (4.1)	36 (90.0)	13.34 (4.58 to 38.86)	6.28 (2.04 to 19.27)
Hospitalised due to UTI	110/970 (11.3)	56 (50.9)	0.41 (0.27 to 0.61)	0.46 (0.29 to 0.73)
UTI within the previous year	530/971 (54.6)	101 (66.2)	0.71 (0.54 to 0.94)	0.94 (0.68 to 1.30)
Knowledgeable on UTIs	481/966 (49.8)	388 (80.7)	3.00 (2.25 to 4.01)	2.00 (1.43 to 2.79)

Cursive ORs have a p value<0.05.

GP, general practitioner; UTI, urinary tract infection.

antibiotics. Education level and underlying disease did not affect willingness to delay antibiotics. Multivariate analysis including the aforementioned variables revealed similar results; however, age and having had a UTI within the previous year no longer significantly predicted willingness to delay.

#### **DISCUSSION**

Women visiting their GP with urinary symptoms value confirmation of the UTI diagnosis as most important. Furthermore, only half of the participants knew that UTIs can be self-limiting and do not necessarily need antibiotic treatment. Only one out of a hundred participants received or got the advice to take pain medication and 7 out of 10 participants would be willing to accept delayed antibiotic treatment even if the diagnosis of UTI is certain.

The main strength of this study is its sample size. No study of this size investigating women's attitudes towards and experiences with UTIs in the Netherlands had been performed before. Results provide a unique insight into the factors influencing women's willingness to delay antibiotic treatment as well as a look into women's priorities when consulting a GP with urinary symptoms. One of the main limitations of this study is that it is based on participants' memory, resulting in a substantial risk of recall bias, for both the frequency and diagnosis of UTIs per participant as well as the treatment that they received. It is also difficult to differentiate between urinary symptoms and actual UTIs in our data, since respondents might not have completely understood the difference between the

two. Furthermore, this study recruited participants by using specific online networks. This seems appropriate, as most citizens of the Netherlands (97%) have access to the internet. However, social media use is substantially lower in people older than 65 and due to visual impairments or cognitive issues, the elderly may also face difficulty completing an online questionnaire. 24 25 This might explain the low number of elderly in this study (5.7%). Besides the selection bias for elderly, selection bias is intrinsic to internet-based surveys due to the nonrepresentative nature of the internet population and by the self-selection of participants, as non-participation in questionnaire-based studies is rarely random.<sup>26</sup> Responders to an online questionnaire are more likely to have a higher level of education, which is consistent with the high education levels found within our study.<sup>27</sup> Furthermore, the proportion of women who experienced more than three UTIs was larger in our study than can be expected to be present in the general population. A household survey performed in the UK found that 57% of women had experienced more than three UTIs, which is lower than the 74% found in our study. 28 Similarly, the proportion of women that had experienced a UTI in the year leading up to the start of the study was higher than the proportion of women in the general population (55% and 11%, respectively). This is perhaps unsurprising, since we relied on self-selection of women to respond to the survey. It stands to reason that women who often experience UTI and/or had a recent UTI are more likely to respond to an online survey about UTIs than women for

<sup>\*</sup>Univariate logistic regression model.

<sup>†</sup>Multivariate logistic regression model adjusted for age, frequency of UTIs, waiting time, education level and presence of chronic disease or diabetes, hospitalisation due to UTI, UTI in the last year, and knowledge on UTIs.

whom UTIs are not an issue. Furthermore, the invitations to the study were posted on pages for people with special interest in UTIs, which might also have contributed to the higher inclusion rate among experienced women. As we show in our results, experienced women are less acceptive of delayed antibiotic prescribing and are more likely to think that antibiotics are necessary to combat UTI than women with fewer UTIs. This might be caused by the prescription of immediate antibiotics during a previous UTI episode, which could have convinced the patient that antibiotics are a necessity to cure UTI. Therefore, caution is needed when translating the results of this study to the general population. However, the inclusion of more experienced women can also be viewed as a strength, as this study provides a clear insight into the needs and behaviour of the population that will probably most frequently consult a GP for UTIs. Moreover, if women most frequently affected by UTIs are willing to delay antibiotic treatment, then women presenting with their first UTI might be even more willing to do so.

Waiting time before consulting a GP influenced both women's willingness to delay antibiotic treatment and women's knowledge on UTIs. Moreover, the effects increased with waiting time until 2-5 days. The effects of waiting time on knowledge on UTIs seemed to increase even further after this, but the limited sample sizes in these groups meant that no significant further increase was seen. This finding is perhaps unsurprising, as patients who are more aware of the self-limiting course of UTIs are probably more prepared to wait before consulting a GP and, therefore, more willing to delay antibiotic treatment. However, this seemingly conflicts with the results of the study performed by Duane et al. 19 In their study, patients indicated that if they had waited for a considerable amount of time before consulting a GP, they would not want to be told to wait and see any longer and that they would prefer immediate treatment. While this highlights patients who would likely not accept delayed antibiotic treatment, they probably already waited the 3 days before visiting their GP that normally is asked from patients receiving a delayed prescription that visit their GP at the onset of symptoms. Therefore, GPs should consider the symptom duration and self-medication of presenting patients when discussing delayed antibiotic prescriptions.

The finding that women consider confirmation of diagnosis as the primary reason to visit a GP, together with the apparent willingness of women to delay antibiotic treatment, confirms that women's attitude towards UTIs is likely different than their attitude as perceived by GPs. This perception among GPs likely has contributed to the high prescription rate of antibiotics for UTIs in the Netherlands, especially in out-of-hours primary care. None-theless, our results showed that there is substantial support among women in the general population for delayed antibiotic treatment, even higher than previously reported. The finding that women's knowledge on UTIs influences their willingness to delay antibiotic treatment means that GPs might be able to convince women to delay antibiotic

treatment when providing proper information about the possible self-limiting course of UTIs during consultation.

Interestingly, while women who reported to have had two or three UTIs in the past were more knowledgeable than women with one UTI on the possible self-limiting course of UTIs, women with more than three UTIs were as knowledgeable as women with one UTI. This might be at least partly explained due to the presence of underlying disease in this group, making UTIs more prevalent and causing atypical course of disease. 30 31 However, the majority of participants (74%) reported to have had more than three UTI episodes, and only 161 participants (16.6%) suffered from a chronic disease. The frequency of UTIs itself might also explain the lower score in knowledge. The more UTIs women experience, the more likely they will experience a UTI that is not self-limiting. This could influence their answers to the questions that aimed to test their knowledge about UTIs, as these more severe episodes could have left a bigger impression on these women. This might also have contributed to the lower willingness to delay antibiotic treatment found in women who experienced more than three UTIs. To get better insight into these phenomena, a qualitative approach may be prudent. Qualitative research is an excellent method to elucidate patients' motivations behind their choices and can reveal more aspects of care provided for UTIs that could be improved. Furthermore, to investigate whether delayed antibiotic prescriptions for UTI are feasible in the Netherlands, an RCT could be performed where GPs in the intervention group would be encouraged to propose delayed antibiotic prescriptions to female patients presenting with symptoms of uncomplicated UTI. By subsequently monitoring the number of accepted delayed prescriptions and filled prescriptions, it would be possible to determine the level of acceptability for delayed prescriptions in the target population as well as the effect of delayed prescriptions on the amount of antibiotics consumed. A similar RCT was performed for respiratory tract infections and Vervloet et al found that only 11%-55% of delayed prescriptions were filled, which shows that it is an effective method of reducing antibiotic consumption.<sup>32</sup> Still, delayed prescriptions only constituted up to 3% of total antibiotic prescriptions even in the intervention group. If delayed prescriptions would become more widely used in the Netherlands, women might be more receptive to try it for UTI. Therefore, both GPs and patients need to be made aware of the possibility of delayed prescriptions to make them a successful UTI treatment option in the Netherlands.

#### **CONCLUSIONS**

Seven out of ten women are willing to accept delayed antibiotic treatment in the management of UTIs, even when the diagnosis is certain. The frequency of UTIs in the past and their knowledge on the self-limiting course of UTIs mainly affect women's willingness to delay antibiotic treatment. Most women value confirmation of diagnosis



over receiving antibiotic treatment. Symptomatic treatment of UTIs is still limited in the Netherlands; however, this study shows there is ample support in the population at risk for delayed antibiotic prescription. Therefore, GPs should consider discussing delayed antibiotic prescriptions for UTIs with patients more often

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Patient consent for publication Not applicable.

Ethics approval This study was approved by the Medical Ethics Committee of the Maastricht University Medical Centre, reference number 2019-1294. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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