#### GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE



# Attitude towards ovarian tissue and oocyte cryopreservation for non-medical reasons: a cross-sectional study

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#### Abstract

Purpose To assess the attitude towards ovarian tissue and oocyte cryopreservation for non-medical reasons.

**Methods** Cross-sectional electronic survey in 248 Swiss women aged 15–35 years, nationally representative for educational level

Results Most women did not worry about an age-related fertility decline. Two-thirds of women would consider using hormone therapy (HT) for menopausal symptom relief although concerns about side effects and risks were still high. Acceptance of cryopreservation of oocytes (19%) or ovarian tissue (13%) for postponing fertility or menopause was generally low, but increased (37%) if both goals could be achieved with one surgery. Cryopreservation of ovarian tissue for postponing menopause was acceptable for 22% of women. Not having a suitable partner until age 35 increased the likelihood of considering postponing fertility by cryopreservation (p < 0.001) and had a stronger impact on that decision than the factor "pursuing a career" (p < 0.001).

**Conclusion** More education on age-related fertility decline, menopause and HT (benefit–risk ratio) is needed. Furthermore, the political and socioeconomic discussion should focus on women's needs, especially on compatibility of career and family.

**Keywords** Cryopreservation · Ovarian tissue · Oocyte · Hormone therapy · Fertility

## Introduction

In Switzerland, in the past 45 years, birth rates in women aged 20–24 declined by almost 80% while they increased by more than 50% in women aged 35–39 [1]. In married women, age at first delivery has increased since the 1970s to a mean age of 30.8 years in 2016 [2]. In the meantime, the employment rate of women at reproductive age has continuously increased being one of the possible reasons for

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delaying motherhood [3]. As fertility in women significantly declines until age 40, fertility preservation techniques might be a solution. "Social freezing" is permitted by law in Switzerland [4] and allows women to postpone their fertility to a higher age by cryopreservation of oocytes and/or ovarian tissue at a younger age, respectively [5]. This technique has been proven to be effective by the network for cryopreservation of oocytes and ovarian tissue in women with malignancies, FertiPROTECT [6]. Furthermore, cryopreserved ovarian tissue (not oocytes) could serve as natural hormone therapy (HT) in menopausal women. According to a previous study, middle-aged women preferred the idea of bioidentical over synthetic HT [7]. Thus, we hypothesise that an even more natural HT with one's own ovarian tissue would be rated even higher. Yet, it is unclear if the autologous retransplantation of cryopreserved ovarian tissue would have significant advantages over pharmacologic HT from a medical perspective [8, 9]. The aim of this cross-sectional survey was to assess women's attitude towards ovarian tissue and oocyte cryopreservation for non-medical reasons such as postponing fertility and/or treatment of short- and longterm menopausal estrogen deficiency sequelae. Furthermore

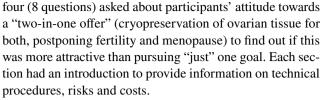


comparing to previous studies in this field [10–13] we wanted a cohort representative for Switzerland with (1) variety of educational and socio-economic background as well as (2) the complete age category of only biologically possible oocyte/ovarian tissue freezers (15–35 year old).

# **Methods**

# Study design

This was a cross-sectional online survey in Swiss women. The questionnaire was developed in three steps. First, we performed an item collection based on the only two available previous studies [10, 14], technical literature about test design [15] and personal expertise (PS, MvW). This initial questionnaire was applied to six female volunteers fulfilling the inclusion criteria described below in a face-to-face interview (NW) to test for applicability and comprehensibility and adapted accordingly. As no further new comments were made after four interviews the correction process was completed. In a second step, the adapted questionnaire was transformed into an electronic version (with Google Forms) and sent via e-mail link to another 36 female volunteers. The results were statistically evaluated and used to revise the online questionnaire for better statistical interpretability of answer possibilities. Finally, in a third step, the revised questionnaire was newly designed with Survey Monkey providing better possibilities for a more complex setup of the questionnaire and better evaluation methods. The link to the questionnaire was distributed by e-mail (social media, personal and job-related network of PS and NW) as broadly as possible using a snowball recruitment technique to recruit a wide range of women of different age groups (15–35 years) and different educational backgrounds (academics:nonacademics 1:1) [16]. Inclusion criteria were being female, having Swiss nationality, and being between 15 and 35 years of age, which was clearly indicated on the first page of the survey as well as in the invitation e-mail. About two-thirds of the responses were incomplete and therefore excluded right away before analysing the 248 complete surveys. The age limit was selected as oocyte cryopreservation is not recommended at an older age due to biological reasons [17, 18]. Incomplete family planning was another inclusion criterion for part 1 and 3 of the questionnaire. The questionnaire consisted of 50 questions covering five sections (supplementary file 1). The first section (10 questions) addressed participants' characteristics (e.g., age, religion, education, social status). The second section (21 questions) addressed participants' attitudes towards oocyte/ovarian tissue cryopreservation for postponing fertility. The third section (11 questions) addressed participants' attitudes towards ovarian tissue cryopreservation for postponing menopause. Section



The study design was sent to the local cantonal ethic committee. Since we did not collect personal data, approval by the ethic committee was not requested (Req-2016-00788).

# **Statistics**

Our goal was to receive at least 196 completed questionnaires to get a margin of error (range in % that population's answers may deviate from study population) of no more than 7% for representation of the Swiss female population in this age group. These numbers were calculated with Survey Monkey Sample Size Calculator and the data from Swiss Federal Statistical Office [19, 20]. The descriptive statistics were then mostly calculated directly by Survey Monkey while correlations and answer specificities among certain groups were analysed by our statistician (NB). For characterization of the primary outcomes (attitude towards Social Freezing), 95% confidence intervals were calculated. For items with ordinal scale, additionally, the 95% confidence intervals of their mean scores were evaluated. For the comparison of the response behaviour between subgroups the variance analysis according to Kruskal-Wallis was used since the responses were set up as scores and therefore no normal distributions were present. Correlations between items were investigated by the correlation analysis according to Spearman.

## Results

# Subjects' characteristics

Data collection was performed from March till May 2017. Overall, 248 women completed the survey of whom the majority (n=210; 85%) had not yet completed family planning. Table 1 presents subjects' characteristics on age, nationality, religion, education and monthly gross income. Mean age was  $25.1 \pm 4.9$  years, 120 (48.4%) were singles whereas 105 (42.3%) lived in a partnership with 7.7% being married. Among women living in a partnership, mean satisfaction with life was  $78.7 \pm 18.8$  and with their partnership  $90.4 \pm 13.8$  (scale 0-100; 100 corresponding to total satisfaction). In contrast, mean satisfaction with current compatibility of work and family was only  $62.0 \pm 24.4$ . However, most women (86.3%) believed that at some point in their life they would have to rely on a good compatibility of work and family. Age (r=0.15, p=0.02), education (r=0.17,



Table 1 Subjects' characteristics

	n = 248	% = 100
Women's age (years)		
16–20	37	14.9
21–25	109	44
26–30	62	25
31–35	40	16
Nationality		
Swiss	248	100
Double citizenship	20	8.1
Religion		
Roman-catholic	92	32.7
Evangelical reformed (protestant)	81	37.1
Without confession	75	30.2
Highest educational qualification		
Compulsory education (9 years)	17	6.9
Vocational diploma (apprenticeship)	36	14.5
Federal vocational baccalaureate	25	10.1
Baccalaureate	50	20.2
Bachelor's degree	76	30.6
Master's degree	35	14.1
Higher degree (PhD etc)	9	3.6
Monthly gross income		
< 1000 CHF/month	86	34.7
1000-4000 CHF/month	67	27
4000-7000 CHF/month	85	34.3
7000-10,000 CHF/month	10	4
> 10,000 CHF/month	0	0

p = 0.007) and income (r = 0.23, p = 0.001) had a significant impact on general satisfaction with life. Age, religion and financial resources did not have a significant impact on the attitude towards cryopreservation of oocytes or ovarian tissue, respectively. However, satisfaction with compatibility of work and family significantly changed women's attitude towards cryopreservation for non-medical reasons. The better the perceived compatibility the less attractive cryopreservation: r = -0.19, p = 0.006; ovarian tissue cryopreservation: r = -0.19, p = 0.009).

# **Attitude towards postponing fertility**

For this part of the questionnaire (section 2) only subjects with incomplete family planning were included (n = 210, 85%). Less than half of subjects (n = 88, 41.9%) worried about an age-related fertility decline. Most women (89.5%) thought that the optimal age for having a first child was between 26 and 35 years, while for 10.5% of women the optimal age ranged between 36 and 40 years. Half of women (56.2%) agreed to postponing family planning in favour of a professional career, but only 11.9% of women would sacrifice motherhood to their professional career.

Women's attitude towards cryopreservation of oocytes or ovarian tissue for postponing family planning, respectively, was assessed on likelihood scales ranging from 0 (= not imaginable at all) to 100 (= very well imaginable) (Table 2). The mean score was  $26.8 \pm 28.9$  for oocyte and  $18.7 \pm 25.4$ 

Table 2 Key answers representing best the attitude towards cryopreservation of ovarian tissue and oocyte for non-medical reasons

	Oocyte cryopreservation for fertility preservation	vation for fertility preserva-	Ovarian tissue cryopreserva- tion for natural HT during menopause	Ovarian tissue cryo- preservation for combined purpose
	n=210	n=210	n=248	n = 210
Total answers > 50% [=(rather) yes]	39 (19%)	28 (13%)	54 (22%)	78 (37.1%)
Acceptance of actual offer	55 (26.2%)	_	43 (17.3%)	34 (16.2%)
If no suitable partner—35*	63 (30%)	48 (23%)		
For career	33 (16%)	22 (10%)		
Mean (range 0–100) with SD	)			
Age-related answers				
16–20	$17.8 \pm 21$	$11 \pm 15.5$	$34.3 \pm 27.4$	$30.4 \pm 25.4$
21–25	$30.8 \pm 32.2$	$22.4 \pm 28.6$	$28.5 \pm 27.3$	$33.3 \pm 27.4$
26–30	$27.5 \pm 28.4$	$17.8 \pm 25.1$	$20.2 \pm 23.8$	$23.6 \pm 24.1$
31–35	$21.4 \pm 22.4$	$16.4 \pm 21.2$	$24.8 \pm 25.1$	$23.7 \pm 28.8$
Total	$26.8 \pm 28.9$	$18.7 \pm 25.4$	$26.7 \pm 26.4$	$29.2 \pm 26.6$
Anticipated concerns about menopausal symptoms*	-	-	$42.7 \pm 28.1$	-
If caesarean section*			$42.7 \pm 33.9$	

<sup>\*</sup>These factors all showed a significant correlation (p < 0.05) with a positive attitude towards oocyte/ovarian tissue freezing for either fertility preservation or natural HT during menopause, respectively. Additionally, the factor "no suitable partner" compared to "career" showed significantly (p < 0.001) greater impact on the attitude towards oocyte/ovarian tissue freezing for the purpose of fertility preservation



for ovarian tissue cryopreservation, respectively. 25% of women graded their attitude towards oocyte cryopreservation with at least 45 points (Q75=45) while the corresponding score for ovarian tissue cryopreservation was lower with 27 points (Q75=27). Overall, 19% of participants (n=39) scored above 50% on the scale assuming a positive attitude towards cryopreservation of oocyte. The respective number for cryopreservation of ovarian tissue was 13% (n=28). There was a significantly positive correlation between the attitudes towards oocyte and ovarian tissue cryopreservation, respectively (r=0.86, p<0.001).

Overall, there was no significant correlation between age and attitude towards oocyte or ovarian tissue cryopreservation. However, when differentiating between age groups, approval was significantly lower in women aged 16-20 compared to women aged 21-25 (oocyte cryopreservation:  $17.8 \pm 21.0$  vs.  $30.8 \pm 32.2$ , p=0.041 ovarian tissue cryopreservation:  $11.0 \pm 15.5$  vs.  $22.4 \pm 28.6$ , p=0.025).

Education had a great impact on the attitude towards oocyte and ovarian tissue cryopreservation. For women with the lowest educational degree cryopreservation was almost not imaginable (oocyte cryopreservation  $8.7 \pm 12.9$ ; ovarian tissue cryopreservation  $4.9 \pm 7.3$ ), while women with moderate non-academic educational level had the highest degree of approval (oocyte cryopreservation  $35.1 \pm 36.2$ ; ovarian tissue cryopreservation  $29.6 \pm 34.8$ ). Comparisons of the two lowest to the three highest educational levels (= academics) showed that the attitude towards cryopreservation of oocytes/ovarian tissue for non-medical reasons was significantly more positive in academic groups (oocyte freezing: p = 0.008, ovarian tissue freezing: p = 0.048). Most women (94.6%) being interested in oocyte or ovarian tissue cryopreservation for postponing family planning would do so after the age of 25. Besides age and education, the factors "pursuing a career" and "presence of a suitable partner" were also taken into account regarding their influence on the attitude towards cryopreservation of ovarian tissue or oocytes for non-medical reasons. Interestingly, having a career did not strongly affect women's attitude towards oocyte  $(21.4 \pm 25.7)$  and ovarian tissue  $(17.1 \pm 23.4)$  cryopreservation. In contrast, not having a suitable partner to have children with up to age 35 significantly (p < 0.001) for oocyte/ovarian tissue cryopreservation) increased the likelihood of considering cryopreservation as an option for postponing fertility (oocyte cryopreservation  $33.1 \pm 30.8$ ; ovarian tissue cryopreservation  $26.1 \pm 29.2$ ) and also turned out to be significantly (p < 0.001) more influencing compared to the factor "pursuing a career". Assuming that in some certain situations women could imagine oocyte cryopreservation, subjects were asked how they would prefer their oocytes to be stored (all fertilized, all non-fertilized, half fertilized and half non-fertilized). The majority (69%) preferred to freeze non-fertilized oocytes (43.3% half fertilized and half non-fertilized, 36.7% fertilized oocytes). Most women (79%) thought that the woman herself should cover the cost for cryopreservation while only 15.7% would like health insurances to take over. Age  $45.8 \pm 5.5$  years was rated the mean upper socially acceptable age limit for motherhood. However, respondents considered themselves at age  $40.3 \pm 3.8$  years to be too old for having children. Yet, half of women (51.4%) agreed that oocyte cryopreservation should be offered to women of all age groups. When being asked if they would accept an offer for oocyte/ovarian tissue cryopreservation during the next upcoming year 26.2% agreed.

# Attitude towards postponing menopause

For this part of the questionnaire, (section 3) all women, regardless of their family planning, were included. In general, women were quite familiar with the climacteric syndrome, and 77.8% knew at least someone experiencing menopausal symptoms. Yet, they did not worry much about experiencing menopausal symptoms at some point in life [mean  $42.7 \pm 28.1$ ; scale ranging from 0 (= no worries) to 100 (= deep concern)]. Two in three women (62.1%) considered using HT for menopausal symptom relief with 41.1% (n=154) preferring natural HT and 19.8% (n=49) pharmacologic HT (n = 97 declining HT). This is a significant difference regarding that the confidence intervals (=CI) of these two answers (natural HRT: CI 34.9-47.6%, pharmacologic: CI 14.9%—25.3%) do not overlap (Table 3). If natural HT was less effective than pharmacologic HT, 61% would still prefer natural HT, while 39% would then prefer pharmacologic HT. The main concerns about pharmacologic HT were to experience psychological side effects (60.1%), cancer (36.7%), cardiovascular diseases (30.6%) and dementia (24.6%) (multiple answers possible). One-third (33.1%) was not afraid of HT while almost the same number of women (39.1%) completely rejected any kind of HT.

On average, women could not imagine to postpone menopause by cryopreservation of ovarian tissue (score  $26.0 \pm 26.2$ , scale ranging from 0 (= not imaginable at all) to 100 (= very well imaginable)). However, this technique became significantly more attractive if it was performed during a caesarean section (score  $42.7 \pm 33.9$ , p < 0.001). Overall, 22% of participants (n=54) scored above 50% on the scale assuming a positive attitude towards cryopreservation of ovarian tissue for postponing menopause. In this sub-cohort, women were significantly more likely to accept an actual offer for ovarian tissue cryopreservation (54.5% with score > 50 vs. 6.7% with score  $\leq$  50%, p < 0.001). In addition, age and the anticipated concerns about menopausal symptoms had a significant impact on the attitude towards postponing menopause by cryopreservation of ovarian tissue. The younger (r=0.131, p=0.039) and the bigger the anticipated concerns about menopausal symptoms



Table 3 Key answers representing best the preferences regarding natural hormone replacement

		n		%
Q.28–30: Would you free answers were possible)	ze fertilized, unfer	tilized or half fertilize	ed/half unfertilized oocytes? (mul	tiple
Fertilized	77			36.7
Unfertilized		145		
Half-half		91		43.3
		n = 248		% = 100
relief during menopause Yes		154	al OR pharmacologic) for sympto	62.1
No		94		37.9
	n = 248	% = 100	Confidence interval indicate significant difference in an	_
Q.35: Would you prefer a macologic hormone rep		replacement (= your o	own replanted ovarian tissue) to a	phar-
Yes, natural	102	41.1	34.9–47.6	
No, pharmacologic	49	19.8	14.9–25.3	
No, no difference	97	39.1	_	

(r=0.40, p<0.001) the more attractive this therapeutic option became. There was a significant positive correlation between the attitudes towards postponing fertility and menopause (oocyte cryopreservation: r=0.42, p<0.001 and ovarian tissue cryopreservation: r=0.46, p<0.001). The preferred age for cryopreservation of ovarian tissue was between 31 and 35 years (69.2%). Most thought that each woman herself should cover the costs (75.8%). However, if offered the option of cryopreservation for ovarian tissue during the upcoming year the majority declined (82.7%).

# Attitude towards postponing both, fertility and menopause

When informed that cryopreservation of ovarian tissue (not oocytes) could be used for both, postponing fertility and menopause, most stated that this would not (28.1%) or probably not (34.8%) change their prior decision. The mean attitude score was  $29.2 \pm 26.6$  [scale ranging from 0 (= not imaginable at all) to 100 (= very well imaginable)]. Yet, 3.3% would accept, and 33.8% would probably accept an offer for cryopreservation of ovarian tissue for the combined target, respectively. Accordingly, 25% of women graded their attitude towards oocyte cryopreservation with at least 52 points (Q75 = 52). Overall, 37% of participants (n = 78)scored above 50% on the scale assuming a positive attitude towards cryopreservation of ovarian tissue for both, postponing fertility and menopause. There was a significant positive correlation between the attitude towards postponing menopause alone and both, fertility and menopause (r=0.75,p < 0.001). Again, the preferred age for cryopreservation of ovarian tissue was between 31 and 35 years (58.0%). However, if offered the option for cryopreservation of ovarian tissue during the upcoming year the majority declined (83.8%). One reason for declining the offer could be being afraid of the surgical procedure. Indeed, the degree of fear varied [mean score  $53.8 \pm 32.5$ , Q25=23, Q75=79; scale ranging from 0 (= not afraid at all) to 100 (= deep concern)]. Accordingly, the mean perceived benefit–risk ratio was scored  $46.7 \pm 26.3$  reflecting more perceived risks than benefits.

#### Discussion

To our knowledge, this is the first study to assess premeno-pausal women's attitude towards cryopreservation of oocytes and ovarian tissue for non-medical reasons, e.g., postponing fertility and/or menopause, respectively. We found that (1) most women did not worry about an age-related fertility decline, (2) two-thirds of women would consider using HT for menopausal symptom relief although concerns about side effects and risks were still high, (3) acceptance of cryopreservation of oocytes or ovarian tissue for postponing fertility or menopause was generally low, but increased if (4) both goals could be achieved with one surgery, and (5) education and having no suitable partner had a significant impact on women's attitude towards cryopreservation of oocytes and ovarian tissue for non-medical reasons.

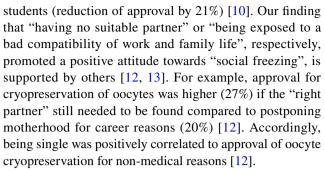
Despite the generally high educational level in women in Western countries, knowledge about their biology and reproductive competence is surprisingly low [21, 22].



Cryopreservation of oocytes and ovarian tissue may offer an opportunity to overcome the female biological limits. However, it is not a guarantee for successful motherhood as success rates of IVF/ICSI are about 30% only [17]. Furthermore, delaying pregnancy to an older age may increase the risk of complicated pregnancy and does not improve the socioeconomic stress women face due to disadvantageous work–family compatibility [23, 24].

In our cohort, acceptance of HT for menopausal symptom relief was higher than the current prevalence of HT in menopausal women [25]. This might be due to the younger age and simply other generation of our cohort that had not been confronted with the Women's Health Initiative (WHI) drama [26] in person. Still, anxiety of side effects and risks associated with HT was high supporting previous findings. However, education and the intensity of menopausal symptoms were found to counterbalance the fear [27, 28].

In contrast to previous studies [10, 29–32], our study found a low acceptance of cryopreservation for postponing fertility, e.g., 19% for cryopreservation of oocytes and 13% for cryopreservation of ovarian tissue, respectively. The differing results may be due to several reasons. First, we on purpose included women with a broad range of educational background to be able to assess the impact of education on the attitude towards cryopreservation of oocytes and ovarian tissue for non-medical reasons while others included for, e.g., medical students only [10]. Comparable to our results, a previous study from Germany showed a positive correlation between education and approval of "social freezing" [33]. Second, we on purpose excluded women above age 35 to avoid a mixture of prospective ("I will/would do so") and retrospective ("If I were still younger I would have done so") decisions. In addition, we wanted to reduce a possible risk of bias by accidently including women currently seeking medical help for infertility and being treated by in vitro fertilization (IVF). In Europe including Switzerland, the mean age of women being treated with IVF is above age 35 [34–36]. Third, we aimed to include women that were as objective as possible and not biased by, e.g., having had experienced infertility treatment before. This is in contrast to a Danish study that reported a more positive attitude towards cryopreservation of oocytes in 45% women above age 35 that were currently treated at an infertility centre [29]. These women were probably more aware of medical reproductive issues than our healthy and younger cohort. Finally, the amount of information provided in the questionnaire might also have mattered. In our questionnaire, we described the procedures necessary to obtain oocytes or ovarian tissue for cryopreservation and the estimated success rates for postponing fertility and menopause, respectively, in detail. When this information is not given, approval rates may be much higher (85.4%) [37] and may decline significantly when an information leaflet is provided as was shown even in medical



The prevalence of pharmacologic HT use has dropped significantly since the first publication of the WHI in 2002 [26]. Since then, menopausal women and treating physicians are afraid of over-emphasized possible risks associated with HT. As a consequence, many menopausal women prefer either no treatment of menopausal symptoms or a HT as bioidentical as possible. This may explain why one in five women of our cohort considered cryopreservation of ovarian tissue for postponing menopause. Interestingly, the percentage of women approving cryopreservation of ovarian tissue for postponing menopause increased to 46% if ovarian tissue could be removed simultaneously with a caesarean section. Similarly, approval rates were also higher if two goals (postponing both, fertility and menopause) could be achieved by one procedure (cryopreservation of ovarian tissue). Yet, this technique (re-transplantation of ovarian tissue for postponing menopause) is still experimental and cannot be offered to women at the moment.

Our study also has its limitations. We did not differentiate between rural and urban environments, which could have changed our results as a more positive attitude towards cryopreservation of ovarian tissue or oocytes for non-medical reasons was reported in urban cohorts [38]. We only included German speaking women that represent 63% of Switzerland's population [39]. From for, e.g., political decisions, it is known that across Switzerland, attitudes and decisions may differ depending on language background [40]. Finally, the sample size (n = 248) representing the population of all Swiss women aged 15–35, still leaves a margin of error (range in % that population's answers may deviate from study population) that accounts for 6–7% if calculated with Survey Monkey Sample Size Calculator [19].

# **Conclusion**

Approval of cryopreservation of ovarian tissue or oocytes for non-medical reasons such as postponing fertility and/or menopause, respectively was quite low. Alarmingly, knowledge about their reproductive biology also seemed to be low in women. Acceptance of HT for menopausal symptom relief was generally high. Thus, acceptance of cryopreservation of ovarian tissue to achieve both goals, postponing fertility and



menopause, was higher compared to when achievement of only one goal was promised. Not having a suitable partner until age 35 was a strong factor for approval of cryopreservation of ovarian tissue or oocytes for postponing fertility. More education on age-related fertility decline, menopause and HT (benefit-risk-ratio) is needed. Furthermore, the political and socioeconomic discussion should focus on women's needs, especially on compatibility of career and family.

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Author contributions NW: questionnaire set up, participants' recruitment, writing the manuscript. MvW: discussion of results, advise on manuscript. NB: statistics. PS: principle investigator, responsible for study idea, design, finances, supervision of doctoral student, finalizing the manuscript.

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# Compliance with ethical standards

**Conflict of interest** The author(s) declare that they have no competing interests in respect to the presented study.

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