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Mental health in women 20-23 years after IVF treatment: A cross-sectional study

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24	ABSTRACT
25	Objective: To assess self-perceived mental health in women treated with in vitro fertilization
26	(IVF) 20-23 years previously, while comparing them to controls, and to determine any
27	differences in mental health between those who had given birth, those who had adopted a
28	child, those who had given birth and adopted a child and those who remained childless.
29	Design: Cross-sectional study.
30	Setting: A Center of Reproductive Medicine (RMC) at a Swedish University hospital
31	Participants: 520 women who had undergone at least one IVF cycle at the University
32	Hospital in Linköping between 1986 and 1989. 504 of the 520 women (97%) were eligible for
33	follow-up. While 34 women declined, 93 percent (n=470) agreed to participate. The reference
34	group consisted of 150 women from the Swedish population included in a study that was used
35	to validate the SCL-90.
36	Interventions: Follow-up was conducted in 2008-2009. The Symptom Check List – 90
37	(SCL-90) was used to measure the women's self-perceived mental health and a questionnaire
38	specific for this study was used to retain demographic information.
39	Outcome measures: The SCL-90 assesses 9 primary dimensions; somatization, obsessive
40	compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid
41	ideation, psychoticism. There is also a global index of distress.
42	Results: Women who had previously undergone IVF treatment were at increased risk of
43	symptoms of depression (p=.017), obsessive compulsion (p=.02) and somatization (p=<.001)
44	20 years later when compared to a control group. In addition, the women who have remained
45	childless are at increased risk of suffering symptoms of depression (p=.009) and phobic
46	anxiety (p=.017).
47	Conclusion: In general, the mental health in women who have undergone IVF treatment 20-
48	23 years previously appears to be good. However, women who remain childless and/or

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without partner after unsuccessful infertility treatment, constitute a vulnerable group even

later on in life. These women may be in need of follow-up.

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Stren	gths and limitations of the study
-	This is one of few studies on the long-term mental health of women who have been
	treated with IVF
-	The follow-up period is exceptionally long at 20-23 years
-	The participation rate was very high at ninety-three percent (n=470)
-	Unfortunately, possible confounding factors such as educational level and life events
	could not be controlled for

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61 INTRODUCTION

62	Infertility, its investigations and treatment can cause psychological distress[1], such as
63	symptoms of anxiety and depression[2-4]. The infertility treatment itself further adds to the
64	strain created by the infertility [5, 6]. Psychological wellbeing in women after in vitro
65	fertilization (IVF) treatment is dependent upon treatment results. Studies examining
66	psychological wellbeing up to ten years after IVF treatment have found that women who
67	remain childless are at increased risk of anxiety, [6, 7] depression, [,6,7, 8] and stress [8] and
68	have a lower sense of coherence, [7] self-esteem [8] and satisfaction with life [8,9] than those
69	who had given birth after treatment. Also, women who give birth after treatment are at
70	decreased risk of hospitalization due to psychiatric disorders [10, 11] and show a more
71	positive long-term emotional status. [4] Gameiro et al. (2014) showed that women who had
72	undergone infertility treatment 11-17 years previously suffered more mental health problems,
73	when compared to the general population, and that a sustained child-wish negatively affected
74	mental health.[12] Meanwhile, studies have shown that most women come to terms with their
75	parenthood goals.[12-14] This shows that reorientation and coping after unsuccessful IVF
76	treatment is important [4,15-17] and that couples may be in need of counselling after
77	unsuccessful IVF treatment to resolve the grieving process.[18] Twenty years after infertility
78	treatment the relationship quality in the couples who have previously undergone infertility
79	treatment is good [19] although a qualitative study on 14 women showed that they still
80	suffered negative effects of the infertility which were especially great when the women were
81	going through the grandparent phase.[20]
82	
83	Thus, there are only a few studies on the mental health of women who have been treated with
84	IVF from a long-term perspective. It is still unclear what effects infertility and its treatment
85	has on women in a long-term perspective.

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The aim of the present study was to assess self-perceived mental health in a group of won treated with IVF 20-23 years earlier. Secondly, we wanted to study possible differences in mental health between the four groups; those who had given birth, those who had adopted child, those who had given birth and adopted a child and those who remained childless. METHOD Subjects All women (n=520) who had received at least one IVF treatment cycle at the Center of Reproductive Medicine, University Hospital in Linkoping between 1986 and 1989 were, i 2008 to 2009, sent an introductory letter asking them to participate in the study. Six of the women were deceased and ten women never received the letter, thus 504 out of 520 (97% women were eligible for follow-up. Out of these, ten women returned the letter declining participation and 24 women did not answer. Thus, a total of 470 out of the 504 (93%) wor eligible for follow-up agreed to participate. Out of the ninety-three percent (n=470) of the women who agreed to participate 55.1% (n=259) had biological children, 19.4% (n=91) h adoptive children, 5.3% (n=25) had both biological and adoptive children and 20.2% (n=55) had remained childless. As a reference group we used score mean values for 150 women of the averaged to participate. This data was device defendence of the terms of the terms to the terms of terms of terms of the terms of terms of the terms of	nen 1
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the general Swedish population. This data was derived from a population based study, three	ough
which the SCL-90 was validated, of women older than 40 years of age.[21, 22]	
Treatment procedures 1986-1989	
The couples were given three or more publically funded IVF treatments during this time	
period. Some of the couples might have had at least one child before entering treatment	

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111	during this period. The upper age limit for the women was 38 years at the time of treatment.
112	The waiting time from acceptance to treatment was approximately three years.
113	
114	Outcome measures
115	The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived
116	mental health during the past week. The SCL-90 is an extensively used, multidimensional
117	psychological status symptom inventory consisting of 90 items.[13,14] It is an objective
118	method for symptom assessment requiring individuals to rate their psychopathological
119	problems and symptoms. These symptoms are then used to compute scores for depression and
120	anxiety. The scale is a five-point Likert scale ranging from "not at all" (0) to "extremely" (4).
121	The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive,
122	interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and
123	psychoticism. There is also a global index of distress that can be used as a summary
124	dimension. The cut off score on the SCL-90 of < 70 was used as an indicator of mental health.
125	[21]
126	
127	Demographics
128	Age, employment status, marital status, same/different partner since time of IVF treatment,
129	number of children (biological and adopted), number of miscarriages and number of IVF
130	treatments were assessed through a questionnaire specific for this study. Those with
131	same/different partner since time of IVF treatment thus constitute a subgroup to those who
132	were married/cohabiting.
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134	Statistics
135	Two sided Chi2-tests were used to analyze differences between the subgroups in regard to
136	background variables and self-perceived mental health. Student's t-test, also two sided, was
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used to compare mean scores between all women who had received IVF treatment and those
in the reference group. Effect sizes using Cohen's distance was calculated in order to evaluate
the magnitude of the differences of the mean scores between IVF treated women and women
in the reference group. P-values <.05 was considered significant. All statistical analyses were
performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).

143 **RESULTS**

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145 **Demographics**

147 the women were older than 45 years at the time of follow-up. Those who had remained 148 childless and those who had adopted children were significantly (p=<.001) more likely to be 149 aged over 45 years than were those with biological children. While 41.5% (n=39) of the 150 women without children were divorced or separated the corresponding number for the women 151 with biological children were 7.0% (n=18) (p=<.001). Among those with adopted children, all 152 women were married or cohabiting. Also, those with adopted children were the most likely to 153 still be living with the same partner as they were at the time of IVF treatment (98.9%; n=90). 154 Those without children (90%; n=54) who were cohabiting or married were more likely than 155 those with biological children (70.6%; n=175) to have remained with the same partner 156 (p=<.001) (Table I). 157 The women had on average been through 2.7 (range=1-10) IVF cycles and 189 of the women 158 had experienced 1-10 miscarriages (mean=1.9). 159

The distribution of demographics across the three groups is shown in Table I. The majority of

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160 Self-perceived mental health

- 161 The women's own perceived mental health is displayed in table II. Women who had
- 162 biological or adoptive children were less likely to experience symptoms of phobic anxiety

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163	than who had remained childless (p=.017) (Table II). Also, women who had biological
164	children were also significantly less likely than women who had remained childless to
165	experience symptoms of depression (p=.009). Women, who were separated, lived alone or
166	who were unemployed showed more signs of depression, anxiety and obsessive-compulsive
167	problems compared to women who were married and were gainfully employed. Women who
168	were over 45 years of age also had more symptoms of mental illness. Women who had
169	changed partner since the time of IVF had more obsessive-compulsive symptoms compared to
170	women who still had the same partner but there were no other differences between these two
171	groups (Table II).
172	In regard to "Global severity index" and "Positive symptom total" the women who had
173	experienced infertility within the couple and who had been through a number of IVF
174	treatments 20-23 years earlier showed the same pattern as the age-matched reference group
175	(Table III). Only on the "Positive symptom distress index" did the IVF group have a higher
176	score indicating that these women had reported experiencing more intense symptoms. In
177	regard to the specific symptoms, the women who had previously undergone IVF treatment
178	were at increased risk of depressive and obsessive-compulsive symptoms as well as having
179	increased scores for somatization (Table III).
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182	DISCUSSION
183 184	Principal findings
185	The majority of the women who had been treated with IVF 20-23 years previously reported
186	few mental health problems. However, women who had remained childless 20 years after
187	infertility treatment reported negative psychological consequences to a greater degree than
188	those who had since become mothers. Childless women were more prone to symptoms of

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depression than were those with biological children and to symptoms of phobic anxiety than were the women who had biological or adopted children. Women who had remained childless were more likely to be separated or divorced, a group which to a greater degree reported suffering from depressive, anxiety and obsessive-compulsive symptoms. When all women who had undergone IVF treatment were compared to an age-matched control group we found that the IVF women were more prone to depressive and obsessive-compulsive symptoms as well as having increased scores for somatization. Strengths and limitations The major limitation in this study is that we do not have data on mental health and life events at the start of IVF treatment or during the 20 years that have passed for the participating women. We can assume that most of the women have experienced their share of difficulties related to one or more of major life events such as illness, job loss, death in the family and even trauma. However, it is reasonable to assume that the control group would be equally affected by such factors. Unfortunately, we have no information on educational level of the participants which might have influenced the results. Unfortunately, no additional information, for example parental status or fertility problems, was available for the reference group. A great strength in this study is the high participation rate of 93%. The reason for this surprisingly high rate might be the that these women who were pioneers when IVF treatment was started in Sweden have a strong desire to be involved in studies concerning questions on

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210 health, IVF, and childlessness.

212 Interpretation

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213	These results are in line with those of previous studies which have found infertility treatment
214	to be an emotionally draining process that can result in negative psychological consequences
215	long term, especially for those whose treatment was unsuccessful, and for a long time remain
216	a major life theme.[7, 9,20] Meanwhile, studies have also shown that long term psychological
217	wellbeing is dependent on the ability to use coping skills [11,15-17] in order to overcome the
218	grief process [18] and also on whether or not the woman still sustains a wish for biological
219	children. [12] However, even if coping skills are successfully utilized, the grandparent phase,
220	which the women of our study were just about to enter, might revoke the negative feelings
221	that childlessness cause.[20] While some previous studies have shown that the difference in
222	psychological symptoms depend on whether there are any children in the family, biological or
223	adoptive,[9] others have shown only a positive influence of having biological children.[11]
224	We found that some symptoms were decreased in both groups with children while the risk of
225	depressive symptoms was only decreased in those with biological children.
226	Mental health is an important issue to study in the clinics where infertility investigations are
227	conducted. The mental health and the lifestyle of women and men can be an indicator of, and
228	explanation for, the fact that some women have trouble getting pregnant. For instance, anxiety
229	disorders and depression might interfere with the couple's relationship and sexuality in a
230	negative way thus decreasing quality of life. It is often believed that emotional stress before
231	trying to achieve pregnancy, naturally or through infertility treatment will have a negative
232	effect on pregnancy outcome. However, Boivin et al (2011) showed, in a meta-analysis on 14
233	prospective studies, that pretreatment emotional distress did not negatively influence
234	treatment outcome [23]
235	In the future, we need to further explore the women who have a history of mental disorders or
236	are vulnerable for mental ill health in the IVF setting in order to not jeopardize their future
237	mental health which could be negatively affected if the infertility treatment is unsuccessful.

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2 3	238	Also, for women who show signs of suffering from a mental disorder at the time of infertility
4 5 6	239	investigation, counseling and treatment are important and medically correct actions need to be
0 7 8	240	taken before starting infertility treatment. Moreover, women who remain childless after
9 10	241	infertility treatment might be in need of follow-up and counselling to cope with their situation
11 12	242	many years after infertility treatment.
13 14 15	243	
16 16 17	244	Conclusion
18 19	245	In conclusion, the majority of the women who have been treated with IVF 20-23 years
20 21 22	246	previously appear to be in good mental health. However, women who remain childless after
22 23 24	247	unsuccessful infertility treatment constitute a vulnerable group that needs to be observed in
25 26	248	healthcare settings in order to prevent the evolvement of anxiety and depression symptoms
27 28	249	and their side effects on somatic and psychological health.
29 30	250	
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39 40	256	Footnotes
41 42	257	Ethics. The study has been approved by the Human Research Ethics Committee in Linköping
43	258	University (nr 03-338 September 9 th 2003)
44 45	250	University (in 05-550, September 7–2005).
46	259	
47 48	260	Contributors: JV participated in analysis, manuscript drafting and critical discussion and final
49 50	261	preparation of the manuscript. AJ participated in analysis, manuscript drafting and critical
51 52	262	discussion. MB participated in study design, execution and analysis. GS was involved in the
53 54	263	research idea, design and execution, analysis, manuscript drafting and critical discussion. GS
55 56 57	264	is the guarantor for the study.
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268	
269	Declaration of competing interests: All authors have completed the ICMJE uniform disclosure
270	form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for
271	the submitted work; no financial relationships with any organisations that might have an
272	interest in the submitted work in the previous three years; no other relationships or activities
273	that could appear to have influenced the submitted work.
274	
275	Data sharing: Full dataset and statistical code available from the corresponding author at
276	josefin.vikstrom@liu.se. Consent was not obtained but the presented data are anonymised and
277	risk of identification is low.
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		To	otal	l chi	No ldren	Biole chil	ogical dren	Ad ch	Adoptive children		Adoptive children		Adoptive children		Adoptive children		logical and optive ildren	
		n	%	n	%	n	%	n	%	n	%	p-va						
Employment status	Employed	349	74.3	66	78.6	189	78.8	75	87.2	19	79.2	0.3						
	Missing	36	7.7	-	-	-	-	-	-	-	-							
Marital status	Married/ Cohabiting	411	87.4	55	58.5	240	93.0	91	100.0	25	100.0	<0.0						
	Separated/divorced/ Other Missing	57	12.1	39	41.5	18	7.0	0	0.0	0	0.0							
_	Missing	2	.4	-	-	-	-	-	-	-	-							
Same partner	Yes	343	73.0	54	90.0	175	70.6	90	98.9	24	96.0	<0.0						
	Missing	46	9.8															
Children	No Children	95	20.2	-	-	-	-	-	-	-	-							
	Biological children	259	55.1 10.4	-	-	-	-	-	-	-	-							
	Biological and adoptive children	25	5.3	-	-	-	-	-	-	-	-							
Age at follow-up	>=45 years old	289	61.5	75	78.9	136	52.5	63	69.2	15	60.0	<0.0						

Somatization			Somatization %			Interpersonal Sensitivity%				Depression %				Anxiety %				Hostility %			
		No	Yes	p-v	value	No	Yes	p-value	N	0	Yes	p-value	No		Yes	p-value	No	Yes	p-value		
Employment	Employed	80.4	80.	0 0	.962	81.2	69.0	0.108	8	81.8	65.8	0.017	81	.8	59.3	0.004	80.5	78.6	0.860		
Marital status	Married/cohabiting Separated/divorced/ Other	88.4 11.6	76.2 23.2	2 0. 8	.095	88.4 11.6	80.0 20.0	0.176	8	88.8 11.2	76.9 23.1	0.030	88 11	.6 .4	75.9 24.1	0.042	88.1 11.9	80.0 20.0	0.347		
Age at follow-up	>=45 years old	60.7	77.	3 0.	.119	61.5	61.3	0.981	e	60.0	77.5	0.030	60	.7	73.3	0.168	61.7	56.3	0.661		
Same partner	Yes	81.1	. 75.	0 0.	.541	81.5	70.8	0.197	8	81.2	77.4	0.609	81	.3	73.9	0.381	81.3	66.7	0.203		
Children	No children Biological children	19.9 56.0) 27.1) 36.4	3 0. 4	.159	19.4 56.0	32.3 41.9	0.188	1	18.4 56.7	40.0 37.5	0.009	19 55	.5 .9	30.0 43.3	0.420	20.0 55.3	25.0 50.0	0.961		
	Adoptive children	19.2	22.	7		19.6	16.1		1	19.3	20.0		19	.1	23.3		19.4	18.8			
	Biological and adoptive children	4.9	13.0	6		5.0	9.7			5.6	2.5		5	.5	3.3		5.3	6.3			
Table II	continued															· ·					
			Phob	ic anxie	ety %	Pa	ranoid I	deation %]	Psychoti	cism %		Obses	sive-Con	npulsive %					
			No	Yes	p-value	No	Y	es p-v	alue	No	Ý	es p-va	lue	No	Yes	p-value					
Employmen	nt Employed		81.9	57.7	0.003	81	.3 6	5.2 0.	.059	80.4	80	.0 0.9	62	81.6	63.0	0.018					
Marital stat	us Married/cohabitin Separated/divorce	g d/	88.4 11.9	77.8 22.2	0.100	87 12	8 8 2 1	37.5 0. 2.5	.961	88.4 11.6	76 23	.2 0.0	95	88.6 11.4	75.9 24.1	0.042					
Age at follo	ow-up >=45 years old		60.2	82.1	0.021	61	.9 5	54.2 0.	.449	60.7	77	.3 0.1	19	60.7	77.3	0.119					
Same partn	er Yes		80.6	85.7	0.973	82	.1 5	57.1 0	.095	81.1	75	.0 0.5	41	82.3	56.5	0.002					
Children	No children Biological childre Adoptive children Biological and adoptive children	n	18.8 56.1 19.9 5.2	42.9 39.3 10.7 7.1	0.017	20 54 19 5	4 1 7 6 7 1 2	6.7 0. 52.5 2.5 8.3	.693	19.9 56.0 19.2 4.9	27 36 22 13	.3 0.1 .4 .7 .6	59	19.1 55.7 20.0 5.2	36.7 46.7 10.0 6.7	0.099					

Significance level <.05

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		IVF we	omen 470	Reference	e group age		
	Cronbach's Alpha	Mean	Std. Deviation	n=156 Mean	Std. Deviation	Effect size Cohen's Distance	p-value
Somatization	0.856	0.62	0.72	0.43	0.44	0.32*	< 0.001
Obsessive-Compulsive	0.864	0.57	0.68	0.49	0.52	0.13	0.020
Interpersonal Sensitivity	0.884	0.41	0.68	0.42	0.47	0.02	0.763
Depression	0.921	0.62	0.80	0.52	0.58	0.14	0.017
Anxiety	0.870	0.49	0.70	0.43	0.48	0.10	0.079
Hostility	0.778	0.32	0.57	0.29	0.41	0.06	0.285
Phobic Anxiety	0.746	0.13	0.41	0.11	0.26	0.06	0.303
Paranoid Ideation	0.746	0.30	0.57	0.27	0.39	0.06	0.278
Psychoticism	0.762	0.15	0.41	0.14	0.24	0.03	0.599
Global Severity Index	0.975	0.41	0.60	0.38	0.38	0.06	0.291
Positive Symptom Distress Index		3.84	6.15	1.40	0.43	0.56**	< 0.001
Positive Symptom Total		25.63	18.63	24.58	16.86	0.06	0.296

Table III. The study group of 470 women compared to the reference group of 156 age matched women

Significance level <.05

*** Effect size Cohen's Distance: ≥0.2small*, ≥0.5=medium**, ≥0.8=large***

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	7
		(d) If applicable, describe analytical methods taking account of sampling strategy	7
		(e) Describe any sensitivity analyses	7
Results			

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Darticipanta	12*	(a) Depart numbers of individuals at each store of study	L L
Participants	13.	(a) Report numbers of individuals at each stage of study—eg numbers potentially engible, examined for engibility,	5
		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	7-8
		(b) Indicate number of participants with missing data for each variable of interest	Tables
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	8
		interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and	9-10
		magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	10-11
		similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	12
		which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mental health in women 20-23 years after IVF treatment: A Swedish cross-sectional study

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Primary Subject Heading :	Obstetrics and gynaecology
Secondary Subject Heading:	Reproductive medicine
Keywords:	Infertility, childlessness, MENTAL HEALTH, IVF , depression

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25 ABSTRACT

26 **Objective:** To assess self-perceived mental health in women treated with in vitro fertilization 27 (IVF) 20-23 years previously, while comparing them to a reference group, and to determine 28 any differences in mental health between those who had given birth, those who had adopted a 29 child, those who had given birth and adopted a child and those who remained childless. 30 **Design:** A cross-sectional study. 31 Setting: A Center of Reproductive Medicine (RMC) at a Swedish University hospital. 32 **Participants:** 520 women who had undergone at least one IVF cycle at the University 33 Hospital in Linköping between 1986 and 1989. 504 of the 520 women (97%) were eligible for 34 follow-up. While 34 women declined, 93 percent (n=470) of the women agreed to participate. 35 The reference group consisted of 150 women of the Swedish population included in a study 36 that was used to validate the SCL-90. 37 Interventions: Follow-up was conducted in 2008-2009. The Symptom Check List – 90 38 (SCL-90) was used to measure the women's self-perceived mental health and a questionnaire 39 specific for this study was used to retain demographic information. 40 Outcome measures: The SCL-90 assesses 9 primary dimensions; somatization, obsessive 41 compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid 42 ideation, psychoticism. There is also a global index of distress. 43 **Results:** Women who had previously undergone IVF treatment were at increased risk of 44 symptoms of depression (p=.017), obsessive compulsion (p=.02) and somatization (p=<.001) 45 when compared to a reference group. In addition, the women who have remained childless are 46 at increased risk of symptoms of depression (p=.009) and phobic anxiety (p=.017). 47 Conclusion: The majority of the women who have been treated with IVF 20-23 years 48 previously appear to be in good mental health. However, women who remain childless and/or 49 without partner after unsuccessful infertility treatment, constitute a vulnerable group even 50 later on in life.

1		
2 3	51	
4 5 6	52	Strengths and limitations of the study
7 8	53	- This is one of few studies on the long-term mental health of women who have been
9 10	54	treated with IVF
11 12	55	- The follow-up period is exceptionally long at 20-23 years
13 14 15	56	- The participation rate was very high at ninety-three percent (n=470)
16 17	57	- Unfortunately, possible confounding factors such as educational level and life events
18 19	58	could not be controlled for
20 21	59	
22 23	60	
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INTRODUCTION Infertility, its investigations and treatment can cause psychological distress[1], such as symptoms of anxiety and depression [2-4]. The infertility treatment itself further adds to the strain created by the infertility [5, 6]. In addition, childbirth is a known trigger for first time episodes of psychiatric illness [7-8]. However, Ross et al. (2011) found in their review that there were no significant differences in the risk of experiencing symptoms of depression between those who had conceived spontaneously and those who had been treated with IVF [9].

Studies using self-reported symptoms as outcome when examining psychological wellbeing up to ten years after IVF treatment have found that women who remain childless are at increased risk of anxiety, [6, 10] depression, [6, 10, 11] and stress [11] and have a lower sense of coherence, [10] self-esteem [11] and satisfaction with life [11,12] than those who had given birth after treatment. Women who give birth as a result of treatment show a more positive long-term emotional status. [4]

Register-based studies using psychiatric diagnoses as outcome when examining risk of psychiatric illness after IVF treatment have varied in their results. Agerbo et al (2013) found no differences between those who had given birth or remained childless after treatment in regard to risk of psychiatric illness but that the risk was lower among those who had adopted children [13]. Another Danish register-based study by Baldur-Felskov et al. (2013) found that women who go through unsuccessful IVF treatment were at increased risk of hospitalization due to most psychiatric disorders but that the risk of affective disorders were lower than for those who had given birth as a result of treatment [14]. Meanwhile, Yli-Kuha et al. (2010)

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85	showed that the risk of depression was increased in those who had gone through an
86	unsuccessful treatment [15].
87	In regard to long-term effects of infertility and its treatment, Gameiro et al. (2014) showed
88	that women who had undergone infertility treatment 11-17 years previously suffered more
89	mental health problems, when compared to the general population, and that a sustained child-
90	wish negatively affected mental health.[16] Meanwhile, studies have shown that most women
91	come to terms with their parenthood goals.[16-18] This shows that reorientation and coping
92	after unsuccessful IVF treatment is important [4,19-21] and that couples may be in need of
93	counselling after unsuccessful IVF treatment to resolve the grieving process.[22] Twenty
94	years after infertility treatment the relationship quality in the couples who have previously
95	undergone infertility treatment is good [23] although a qualitative study on 14 women showed
96	that they still suffered negative effects of the infertility which were especially great when the
97	women were going through the grandparent phase.[24] Most studies have shown that
98	childlessness does not influence psychological well-being in elderly individuals.[25-27]
99	
100	Thus, there are only a few studies on the mental health of women who have been treated with
101	IVF from a long-term perspective. It is still unclear what effects infertility and its treatment
102	has on women in a long-term perspective.
103	
104	The aim of the present study was to assess self-perceived mental health in a group of women
105	treated with IVF 20-23 years earlier. Secondly, we wanted to study possible differences in
106	mental health between the four groups; those who had given birth, those who had adopted a
107	child, those who had given birth and adopted a child and those who remained childless.
108	
109	METHOD
110	

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111 Subjects

112	All women (n=520) who had received at least one IVF treatment cycle at the Center of
113	Reproductive Medicine, University Hospital in Linkoping between 1986 and 1989 were, in
114	2008 to 2009, sent an introductory letter asking them to participate in the study. Six of the
115	women were deceased and ten women never received the letter, thus 504 out of 520 (97%)
116	women were eligible for follow-up. Out of these, ten women returned the letter declining
117	participation and 24 women did not answer. Thus, a total of 470 out of the 504 (93%) women
118	eligible for follow-up agreed to participate. Out of the ninety-three percent (n=470) of the
119	women who agreed to participate 55.1% (n=259) had biological children, 19.4% (n=91) had
120	adoptive children, 5.3% (n=25) had both biological and adoptive children and 20.2% (n=95)
121	had remained childless. As a reference group we used score mean values for 150 women of
122	the general Swedish population. This data was derived from a population based study, through
123	which the SCL-90 was validated, of women older than 40 years of age.[28, 29]
124	
125	Treatment procedures 1986-1989
126	The couples were given three or more publically funded IVF treatments during this time
127	period. Some of the couples might have had at least one child before entering treatment
128	during this period. The upper age limit for the women was 38 years at the time of treatment.
129	The waiting time from acceptance to treatment was approximately three years.
130	
131	Outcome measures
132	The Symptom Check List – 90 (SCL-90) was used to measure the women's self-perceived
133	mental health during the past week. The SCL-90 is an extensively used, multidimensional
134	psychological status symptom inventory consisting of 90 items.[28,29] It is an objective
135	method for symptom assessment requiring individuals to rate their psychopathological
136	problems and symptoms. These symptoms are then used to compute scores for depression and

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137	anxiety. The scale is a five-point Likert scale ranging from "not at all" (0) to "extremely" (4).
138	The SCL-90 assesses 9 primary dimensions; somatization, obsessive compulsive,
139	interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and
140	psychoticism. The cut-off score for each primary dimension was set at the 95 th percentile of
141	self-reported symptoms in the study population in order to indicate a severe level of
142	symptoms.[30,31] Hence > 95 th percentile indicated "Yes" meaning the occurrence of
143	clinically relevant symptoms and $\leq 95^{\text{th}}$ percentile indicated "No". There is also a global index
144	of distress that can be used as a summary dimension. The cut off score on the SCL-90 of < 70
145	was used as an indicator of mental health. [28]
146	
147	Demographics
148	Age, employment status, marital status, same/different partner since time of IVF treatment,
149	number of children (biological and adopted), number of miscarriages and number of IVF
150	treatments were assessed through a questionnaire specific for this study. Those with
151	same/different partner since time of IVF treatment thus constitute a subgroup to those who
152	were married/cohabiting.
153	
154	Statistics
155	Two sided Chi2-tests were used to analyze differences between the subgroups in regard to
156	background variables and self-perceived mental health. Student's t-test, also two sided, was
157	used to compare mean scores between all women who had received IVF treatment and those
158	in the reference group. Effect sizes, using Cohen's distance was calculated in order to
159	evaluate the magnitude of the differences of the mean scores between IVF treated women and
160	women in the reference group. P-values <.05 was considered significant. All statistical
161	analyses were performed using IBM SPSS version 19 (IBM Corporation, Armonk, NY).
162	

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163	RESULTS
164	
165	Demographics
166	The distribution of demographics across the three groups is shown in Table I. The majority of
167	the women were older than 45 years at the time of follow-up. Those who had remained
168	childless and those who had adopted children were significantly (p=<.001) more likely to be
169	aged over 45 years than were those with biological children. While 41.5% (n=39) of the
170	women without children were divorced or separated the corresponding number for the women
171	with biological children were 7.0% (n=18) (p=<.001). Among those with adopted children, all
172	women were married or cohabiting. Also, those with adopted children were the most likely to
173	still be living with the same partner as they were at the time of IVF treatment (98.9%; n=90).
174	Those without children (90%; n=54) who were cohabiting or married were more likely than
175	those with biological children (70.6%; $n=175$) to have remained with the same partner
176	(p=<.001) (Table I).
177	The women had on average been through 2.7 (range=1-10) IVF cycles and 189 of the women
178	had experienced 1-10 miscarriages (mean=1.9).
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180	Table I. Demographic data for the women treated with IVF > 20 years ago (n=470)
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		T	otal	chi	No ldren	Biol chi	ogical ldren	Ad ch	loptive ildren	Bic ad ch	ological and optive iildren
		n	%	n	%	n	%	n	%	n	%
Employment status	Employed	349	74.3	66	78.6	189	78.8	75	87.2	19	79.2
	Missing	36	7.7	-	-	-	-	-	-	-	-
Marital status	Married/ Cohabiting	411	87.4	55	58.5	240	93.0	91	100.0	25	100.0
	Separated/divorced/ Other	57	12.1	39	41.5	18	7.0	0	0.0	0	0.0
	Missing	2	.4	-	-	-	-	-	-	-	-
Same partner	Yes	343	73.0	54	90.0	175	70.6	90	98.9	24	96.0
	Missing	46	9.8								
Children	No Children Biological children	95 259 91	20.2 55.1	-	-	-	-	-	-	-	-
	Biological and adoptive children	25	5.3	-	-	-	-	-	-	-	-
Age at follow-up	>=45 years old	289	61.5	75	78.9	136	52.5	63	69.2	15	60.0
Significance leve	el <.05										
Self-perceive	d mental health										
The women's	own perceived mental	health	is displa	yed in	n table]	II. Woi	men wh	io had	l		
biological or a	adoptive children were	less lik	ely to ex	xperie	nce syr	nptoms	s of pho	bic a	nxiety		
than who had	remained childless (p=	.017) (Table II)). Also	o, wom	en who	had bi	ologi	cal		
children were also significantly less likely than women who had remained childless to $\frac{\exists}{a}$											

problems compared to women who were married and were gainfully employed. Women who

were over 45 years of age also had more symptoms of mental illness. Women who had

changed partner since the time of IVF had more obsessive-compulsive symptoms compared to on May 15, 2025 at Department GEZ-LTA

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198 Table II. The study-group women's self-perceived mental health assessed by the SCL-90

1 2 3	196	women who s	till had	the same	e part	tner but	there v	were n	o oth	er differe	ences	between	thes	e two				BMJ Opei
4 5 6	197	groups (Table	II).															n: first
7 8	198	Table II. The	study-	group v	vome	n's self-	perce	ived n	nenta	l health	asse	ssed by t	he S	CL-90				publis
9 10	Sociodemog	graphic factors in % ³	*	Sc	matiza	tion		nterpers	onal Se	ensitivity		Depr	ression			A	Anxiety	hed
11	Employment	Employed		80.4	80.0	0.962		81.2	69.0	0.108		81.8 6	1	81.8	5 8 .3	<u>s</u> (
12 13 14	Marital status	Married/cohabiti Separated/divorc Other	ng ed/	88.4 11.6	76.2 23.8	0.095		88.4 11.6	80.0 20.0	0.176		88.8 7 11.2 2	76.9 23.1	0.030		88.6 11.4	7 6 ,9 2 6 ,1	ں 10.1136/
15	Age at follow-up	>=45 years old		60.7	77.3	0.119		61.5	61.3	0.981		60.0	7.5	0.030		60.7	7 5 .3	bmj (
16	Same partner	Yes		81.1	75.0	0.541		81.5	70.8	0.197		81.2	7.4	0.609		81.3	7 9 .9	iope (
17 18 10	Children	No children Biological childr	en	19.9 56.0	27.3 36.4	0.159		19.4 56.0	32.3 41.9	0.188		18.4 4 56.7 3	40.0 37.5	0.009		19.5 55.9	3 8 :0 4 3 3)n-201
20 21		Adoptive childre Biological and ac children	n loptive	19.2 4.9	22.7 13.6			19.6 5.0	16.1 9.7			19.3 2 5.6	20.0 2.5			19.1 5.5	2 5 .3 Etaidi	5-0094;
22	199	Table II conti	nued														ng f	26 0
23		Sociodemog	rapic facto	ors in %*		Pho	bic anxi	ety		Parano	id Idea	tion		Psyc	hoticis	m	Î	<u>ă</u> ses
25		Employment	Employ	ved		No 81.9	Yes 57.7	p-valu 0.00	e	No 81.3	Yes 65.2	<u>p-value</u> 0.059	N 8	o 0.4	Yes 80.0	<u>p-value</u> 0.962	8 8 8 8	186 186
26 27 28		Marital status	Married Separat	d/cohabitin ed/divorce	g d/	88.4 11.9	77.8 22.2	0.10)	87.8 12.2	87.5 12.5	0.961	8 1	8.4 1.6	76.2 23.8	0.095	Erās relatec	tober 2
29		Age at follow-up	Other >=45 y	ears old		60.2	82.1	0.02	1	61.9	54.2	0.449	6	60.7 [°]	77.3	0.119		୍ଚ୍ଚ ଜ
30 21		Same partner	Yes			80.6	85.7	0.97	3	82.1	57.1	0.095	8	31.1 ⁷	75.0	0.541	ti hag	23
32 33 34 35		Children	No chil Biologi Adopti Biologi	dren cal childre ve children cal and	n	18.8 56.1 19.9 5.2	42.9 39.3 10.7 7.1	0.01	7	20.4 54.7 19.7 5.2	16.7 62.5 12.5 8.3	0.693	1 5 1	9.9 6.0 9.2 4.9	27.3 36.4 22.7 13.6	0.159	je <u>s</u> chool . and data m	waloaged f
36 37 38 39 40	200 201 202 203 204	*Percentage of in P-values derived Cut-off for each	ndividual from Pea primary o	s exhibitin arson chi a dimension	ng the square a: Yes	demograp statistic v > 95 th per	bhic fac vith sig centile	tor for e nificanc (severe	ach ca e leve level o	ategory (Y 1 <.05. of symptor	es/ No ns). N	o). Io ≤95 th per	rcentil	le.			ining, Al trainin	rom http://bmjol
41 42 43	205	In regard to "	Global s	severity	index	and "I	Positiv	e symj	otom	total" th	e wo	men who	had				g, and :	pen.bm
44 45	206	experienced in	nfertility	y within	the c	ouple ar	nd who	o had b	een t	hrough a	. num	ber of IV	/F				similar	j.com/
40 47 48	207	treatments 20-23 years earlier showed the same pattern as the reference group (Table III).																
49 50	208	Only on the "Positive symptom distress index" did the IVF group have a higher score																
51 52 53	209	indicating that	t these v	women ł	nad re	eported e	experie	encing	more	e intense	symj	ptoms. In	rega	rd to			•)25 at I
54 55	210	the specific sy	mptom	s, the wo	omen	who ha	d prev	10usly	unde	ergone IV	/F tre	eatment v	vere a	at				Departi
56 57	211	increased risk	of depr	ressive a	nd ot	osessive-	comp	ulsive	symp	otoms as	well	as having	g inci	reased				ment (
58 59 60	212	scores for son	iatizatio	on (Tabl	e III).		10											jez-l'i
50							10											⊳

		IVF wo n=463-	omen 470	Reference matched	e group age sample		
	Cronbach's Alpha	Mean	Std. Deviation	Mean	Std. Deviation	Effect size Cohen's Distance	p-value
Somatization	0.856	0.62	0.72	0.43	0.44	0.32*	< 0.001
Obsessive-Compulsive	0.864	0.57	0.68	0.49	0.52	0.13	0.020
Interpersonal Sensitivity	0.884	0.41	0.68	0.42	0.47	0.02	0.763
Depression	0.921	0.62	0.80	0.52	0.58	0.14	0.017
Anxiety	0.870	0.49	0.70	0.43	0.48	0.10	0.079
Hostility	0.778	0.32	0.57	0.29	0.41	0.06	0.285
Phobic Anxiety	0.746	0.13	0.41	0.11	0.26	0.06	0.303
Paranoid Ideation	0.746	0.30	0.57	0.27	0.39	0.06	0.278
Psychoticism	0.762	0.15	0.41	0.14	0.24	0.03	0.599
Global Severity Index	0.975	0.41	0.60	0.38	0.38	0.06	0.291
Positive Symptom Distress Index		3.84	6.15	1.40	0.43	0.56**	<0.001
Positive Symptom Total		25.63	18.63	24.58	16.86	0.06	0.296

213 Table III. The study group of 470 women compared to the reference group of 156 age matched women

215 Significance level <.05

216 Effect size Cohen's Distance: ≥0.2small*, ≥0.5=medium**, ≥0.8=large***

218 DISCUSSION

Principal findings

221 The majority of the women who had been treated with IVF 20-23 years previously reported

few mental health problems. However, women who had remained childless 20 years after

- 223 infertility treatment reported negative psychological consequences to a greater degree than
- those who had since become mothers. Childless women reported more symptoms of
- 225 depression than were those with biological children and symptoms of phobic anxiety than
- 226 were the women who had biological or adopted children. Women who had remained childless
- 227 were to a greater degree separated or divorced, a group which to a greater degree reported

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suffering from depressive, anxiety and obsessive-compulsive symptoms. When all women

229 who had undergone IVF treatment were compared to a reference group we found that the IVF

230 women reported more depressive, obsessive-compulsive and somatization symptoms.

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232 Strengths and limitations

233 The major limitation in this study is that we do not have data on mental health and life events 234 at the start of IVF treatment or during the 20 years that have passed for the participating 235 women. We can assume that most of the women have experienced their share of difficulties 236 related to one or more of major life events such as illness, job loss, death in the family and 237 even trauma but these are unfortunately not factors we could control for. However, it is 238 reasonable to assume that the reference group would be equally affected by such factors. 239 Unfortunately, we have no information on educational level of the participants which might 240 have influenced the results. Also no additional information, for example parental status or 241 fertility problems, was available for the reference group. 242 A great strength in this study is the high participation rate of 93%. The reason for this 243 surprisingly high rate might be the that these women who were pioneers when IVF treatment 244 was started in Sweden have a strong desire to be involved in studies concerning questions on 245 health, IVF, and childlessness. Another strength is the long period of observation. 246 247 Interpretation 248 In accordance with previous studies the results of this study indicate that infertility treatment, 249 especially when unsuccessful, might increase the risk of a negative psychological

250 symptomatology.[10, 12,24] Meanwhile, studies have shown that long-term psychological

251 wellbeing is dependent on the ability to use coping skills [14,19-21] in order to overcome the

252 grief process [22] and also on whether or not the woman still sustains a wish for biological

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253	children. [16] However, even if coping skills are successfully utilized, the grandparent phase,
254	which the women of our study were just about to enter, might revoke the negative feelings
255	that childlessness cause.[24] While some previous studies have shown that the difference in
256	psychological symptoms depend on whether there are any children in the family, biological or
257	adoptive,[12] others have shown only a positive influence of having biological children.[14]
258	Also, Munk-Olsen et al. found that adoptive parents were at reduced risk of psychiatric
259	illness.[13] We found that some symptoms were decreased in both groups with children while
260	the risk of depressive symptoms was only decreased in those with biological children.
261	Mental health is an important issue to study in the clinics where infertility investigations are
262	conducted. The mental health and the lifestyle of women and men can be an indicator of, and
263	explanation for, the fact that some women have trouble getting pregnant. For instance, anxiety
264	disorders and depression might interfere with the couple's relationship and sexuality in a
265	negative way thus decreasing quality of life. It is often believed that emotional stress before
266	trying to achieve pregnancy, naturally or through infertility treatment will have a negative
267	effect on pregnancy outcome. However, Boivin et al (2011) showed, in a meta-analysis on 14
268	prospective studies, that pretreatment emotional distress did not negatively influence
269	treatment outcome [32]
270	Due to the limitations presented above, no firm conclusions regarding the long term
271	consequences of infertility treatment on mental well-being can be drawn. However, our
272	results indicate that women who remain childless after IVF treatment might be at risk of
273	experiencing negative psychological symptoms 20 years after treatment. In the future, we
274	need to further explore the women who have a history of mental disorders or are vulnerable
275	for mental ill health in the IVF setting in order to not jeopardize their future mental health
276	which could be negatively affected if the infertility treatment is unsuccessful. Also, for
277	women who show signs of suffering from a mental disorder at the time of infertility

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278 investigation, counseling and treatment are important and medically correct actions need to be

279 taken before starting infertility treatment. Moreover, women who remain childless after

280 infertility treatment might be in need of follow-up and counselling to cope with their situation

281 many years after infertility treatment.

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283 Conclusion

284 In conclusion, the majority of the women who have been treated with IVF 20-23 years

285 previously report few negative psychological symptoms. However, women who remain

286 childless after unsuccessful infertility treatment constitute a vulnerable group that would

287 likely benefit from being observed in healthcare settings in order to prevent the evolvement of

288 anxiety and depression symptoms and their side effects on somatic and psychological health.

289

294

295 **Footnotes**

296 Ethics: The study has been approved by the Human Research Ethics Committee, in Linköping University (nr 03-338, September 9th 2003). 297

298

299 Contributors: JV participated in analysis, manuscript drafting and critical discussion and final

300 preparation of the manuscript. AJ participated in analysis, manuscript drafting and critical

301 discussion. MB participated in study design, execution and analysis. GS was involved in the

302 research idea, design and execution, analysis, manuscript drafting and critical discussion. GS

303 is the guarantor for the study.

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306	east of Sweden.
307	
308	Declaration of competing interests: All authors have completed the ICMJE uniform disclosure
309	form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for
310	the submitted work; no financial relationships with any organisations that might have an
311	interest in the submitted work in the previous three years; no other relationships or activities
312	that could appear to have influenced the submitted work.
313	
314	Data sharing: Full dataset and statistical code available from the corresponding author at
315	josefin.vikstrom@liu.se. Consent was not obtained but the presented data are anonymised and
316	risk of identification is low.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	ltem #	Recommendation	Reported on page #			
Title and abstract1(a) Indicate the study's design with a commonly used term in the title or the abstract		1				
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3			
Introduction						
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5			
Objectives	3	State specific objectives, including any prespecified hypotheses	5			
Methods						
Study design	4	Present key elements of study design early in the paper	5			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5			
Participants	Participants 6 (a) Give the eligibility criteria, and the sources and methods of selection of participants		5-6			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6			
Data sources/ measurement	Data sources/ 8* For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		5-6			
Bias	9	Describe any efforts to address potential sources of bias	7			
Study size	10	Explain how the study size was arrived at	5			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7			
		(b) Describe any methods used to examine subgroups and interactions	7			
		(c) Explain how missing data were addressed	7			
		(d) If applicable, describe analytical methods taking account of sampling strategy	7			
		(e) Describe any sensitivity analyses	7			
Results						

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	5
		confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	Tables
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	8
		interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and	9-10
		magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	10-11
		similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	12
		which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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