

1 **Psychological impact and health-related quality of life outcomes of Mayer-Rokitansky-**
2 **Küster-Hauser syndrome: a systematic review and narrative synthesis**

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14

15 **Abstract**

16 Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome causes absence or underdevelopment of
17 uterus and vagina, but women's subjective experience remains understudied. This systematic
18 review was conducted to examine the psychological and health-related quality of life outcomes
19 of MRKH syndrome. Twenty-two articles identified through electronic search matched the
20 inclusion criteria and were included in our review. MRKH syndrome may be associated with
21 psychological symptoms and impaired quality of life, but especially with poor sexual esteem and
22 genital image. Women may experience difficulties managing intimacy and disclosing to partners.
23 Mothers are often overprotective and overinvolved, with consequent negative emotions in
24 women with the disease.

25

26 **Keywords**

27 Health-related quality of life, Mayer-Rokitansky-Küster-Hauser syndrome, psychological health,
28 systematic review, vaginal agenesis

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Introduction

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34
35 Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, or Müllerian aplasia, is an important
36 cause of vaginal agenesis, a congenital condition that affects one in every 5000 female births
37 (Herlin et al., 2016) and is characterized by the underdevelopment or complete absence of uterus
38 and vagina, despite the presence of normal secondary sexual characteristics and external
39 genitalia, a 46,XX karyotype, and functioning ovaries and fallopian tubes (Dabaghi et al., 2019;
40 Fedele et al., 2010; Fliegner et al., 2014). The disease usually manifests itself during adolescence
41 with primary amenorrhea and is subsequently diagnosed by ultrasound and magnetic resonance
42 imaging in most cases (Bombard and Mousa, 2014).

43 Medical treatment of MRKH syndrome involves the creation of a neovagina using non-
44 surgical and surgical procedures. Non-surgical approaches entail vaginal enlargement with
45 dilators, using gradual simple pressure with increasingly larger devices (Frank method) (Dabaghi
46 et al., 2019). When non-surgical methods do not enable sexual intercourse, a variety of surgical
47 interventions with different techniques can be performed to create a neovagina (Watanabe et al.,
48 2017). All these procedures may have complications such as for example dyspareunia and
49 urinary tract obstruction (Dabaghi et al., 2019). Overall, women are more likely to prefer
50 surgical procedures because these interventions are experienced as faster and less frustrating than
51 non-surgical methods, which can be difficult to practice also due to cultural and social
52 limitations, with consequent feelings of embarrassment (Dabaghi et al., 2019).

53 In a 2009 literature review examining the psychological impact and quality of life (QoL)
54 outcomes of MRKH syndrome (the latest published review on this topic, at least to our
55 knowledge), Bean and colleagues (2009) reported that women may be able to physically engage
56 in penetrative sex after the creation of a neovagina, but having an anatomically intact vagina
57 does not necessarily lead to optimum sexual function, which also requires good psychological
58 conditions. The literature examined in the Bean et al. (2009) study provided evidence regarding

59 the disruptive impact of the disease on women’s sense of themselves, with poor self-esteem and
60 body disturbance. In this context, the inability to carry a pregnancy due to uterine absence or
61 abnormality (a condition referred to as absolute uterine factor infertility; Ejzenberg et al., 2019)
62 represents an important risk factor associated with feelings of inadequacy deriving from
63 comparisons with healthy women (Bean et al., 2009; Heller-Boersma et al., 2007).

64 Given this background, we reviewed the research evidence published in the last decade,
65 after the Bean et al. (2009) study, to describe the psychological impact of MRKH syndrome, as
66 well as the effects of the disease on women’s health-related QoL (HRQoL, a multidimensional
67 concept focused on the specific impact of health—including medical conditions and their
68 treatment—on people’s lives, in terms of physical, mental, and social functioning; Bourdel et al.,
69 2019).

70

71

Materials and methods

72

73 This review was designed to provide a comprehensive picture of the psychological and HRQoL
74 conditions of women with MRKH syndrome. Thus, we included quantitative and qualitative
75 studies reporting original research evidence on this topic. As far as possible for this review, we
76 followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA;
77 Moher et al., 2010).

78

Electronic search

80 From June to August 2019 we conducted a systematic electronic search of two databases
81 (PubMed and PsycINFO). The search process is displayed in Supplemental Figure 1. After
82 preliminary examination of title, abstract, and keywords of a sample of articles focused on the
83 topic of interest, we identified the following set of search terms that were combined using
84 appropriate Boolean operators (AND / OR): “Mayer-Rokitansky-Küster-Hauser syndrome”,

85 “vaginal agenesis”, Rokitansky, psychological, anxiety, depression, coping, personality, “lived
86 experience”, neuroticism, “quality of life”, distress, vaginoplasty, sigmoid, dilator, Vecchietti,
87 Davydov, McIndoe, Frank. The reference lists of the studies included in this review were also
88 examined to identify other eligible studies.

89

90 **Article selection**

91 We included articles written in English and reporting psychological and HRQoL outcomes of the
92 disease and/or its treatment. Given that Bean et al. (2009) considered studies published between
93 1955 and 2007, we included articles published from January 2008 to August 2019. We excluded
94 literature reviews, commentaries, case reports, doctoral theses, and opinion papers. Due to the
95 psychological focus of our research question, we did not include studies reporting exclusively
96 sexological outcomes (i.e., vaginal length, sexual function, sexual distress, and sexual
97 satisfaction) of MRKH treatments (a systematic review of this body of literature was recently
98 conducted by Dabaghi et al., 2019). However, we included studies that explored the association
99 between sexological outcomes and psychological factors, such as for instance women’s feelings
100 and emotions, self-esteem and body image. We excluded studies that reported psychological and
101 HRQoL outcomes of MRKH and other genital anomalies without discriminating between
102 malformation types. After duplicates elimination, articles were screened independently by the
103 first three authors, starting with titles and abstracts, and subsequently retrieving full texts.

104

105 **Data extraction and quality assessment**

106 Data extraction involved the creation of an Excel recording spreadsheet to summarize
107 information of interest (i.e., authors, date and country of publication, research aims, sample
108 description, study design and methods, main results). The first three authors independently
109 assessed and subsequently discussed the quality of all eligible studies following seven criteria
110 applicable to both quantitative and qualitative studies (Culley et al., 2013; Shepherd et al., 2006):

111 (1) presence of a comprehensive theoretical framework; (2) clear explanation of research aims;
112 (3) appropriate description of factors important for result interpretation; (4) precise sample
113 description; (5) detailed presentation of materials and methods; (6) data analysis performed by
114 more than one researcher; (7) rigorous (vs. speculative) interpretation of results based on the
115 original research evidence provided in the study. The included studies had to meet at least four
116 of these seven criteria (Canzi et al., 2019). All discrepancies among authors were discussed until
117 consensus was reached.

118

119 **Analysis and narrative synthesis**

120 The analytic process entailed a three-step thematic analysis (Dixon-Woods et al., 2005) that
121 involved (1) reading all articles to identify relevant issues, (2) categorizing these issues to define
122 the prominent themes, and (3) providing a narrative synthesis of the findings. A narrative
123 approach—rather than standard systematic review methodology—is particularly appropriate to
124 summarize findings from very different types of studies, such as those included in this review
125 (Culley et al., 2013).

126

127 **Results**

128

129 **Selection and characteristics of the studies**

130 A total of 185 articles were initially retrieved from electronic search (Supplemental Figure 1). At
131 the end of the selection process, 22 research articles were included in our review. No further
132 material was identified after reference lists examination. Characteristics and main findings of the
133 included articles are summarized in Table 1. Of these 22 studies, 16 (73%) were quantitative, 2
134 (9%) were qualitative, and 4 (18%) used a mixed-methods design. Six studies (27%) focused on
135 the outcomes of specific treatments, mainly surgical procedures (Carrard et al., 2012;
136 Cheikhelard et al., 2018; Gatti et al., 2010; Labus et al., 2011; Leithner et al., 2015; Sabatucci et

137 al., 2018). Most of these studies examined not only sexual function, but also women's body
138 image and genital perception, sense of femininity, self-esteem, as well as psychological
139 symptoms and QoL. The other 16 studies (73%) were primarily focused on women's subjective
140 reaction to the disease, including coping styles, psychological and sexual health, impact of
141 diagnosis, infertility and attitudes toward motherhood.

142 Almost all studies (86%) originated in Europe, especially in the UK, Germany, and
143 Poland. Two studies were conducted out of Europe, specifically in North America (Ernst et al.,
144 2014) and Australia (Kimberly et al., 2011), and one study involved both Italy and Bangladesh
145 (Gatti et al., 2010). Only one study reported longitudinal findings (Sabatucci et al., 2018). Two
146 articles (Ernst et al., 2014; Patterson et al., 2014) described findings from qualitative studies
147 providing an in-depth exploration of women's lived experience of MRKH syndrome, while the
148 remaining 19 articles (86%) reported cross-sectional results.

149 The number of MRKH patients included in the studies ranged from 5 to 131 (total N =
150 1017), and the median number was 46. Age at diagnosis ranged from 13 to 21 years and time
151 since diagnosis ranged from 1 to 39 years. In 7 studies (32%), women with MRKH were
152 exclusively compared with healthy controls (Bargiel-Matusiewicz et al., 2015; Beisert et al.,
153 2015; Gatti et al., 2010; Heller-Boersma et al., 2009; Leithner et al., 2015; Pastor et al., 2016;
154 Weijenborg et al., 2019). In 6 studies (27%), comparisons were made with women with complete
155 androgen insensitivity syndrome (CAIS) and/or polycystic ovarian syndrome (PCOS) (Brunner
156 et al., 2015; Dear et al., 2019; Fliegner et al., 2014, 2018; Krupp et al., 2012; Laggari et al.,
157 2009). In 4 studies (18%), MRKH patients were exclusively compared with general or
158 standardization population (Cheikhelard et al., 2018; Kimberly et al., 2011; Liao et al., 2011;
159 Sabatucci et al., 2018).

160 Various questionnaires (either standardized or non-standardized and researcher-made)
161 were used to measure MRKH psychological and HRQoL outcomes. The Beck Depression
162 Inventory (BDI) and the Brief Symptom Inventory (BSI) were the most used scales to assess

163 psychological symptoms (Fliegner et al., 2014, 2018; Gatti et al., 2010; Krupp et al., 2012;
164 Labus et al., 2011; Laggari et al., 2009), while HRQoL was mostly evaluated using the World
165 Health Organization Quality of Life - Brief version (WHOQoL-BREF) (Cheikhelard et al., 2018;
166 Kimberly et al., 2011; Leithner et al., 2015).

167

168 **Narrative synthesis**

169 The thematic analysis conducted led to the identification of 8 prominent themes: (1) reactions to
170 diagnosis and coping styles; (2) psychological symptoms; (3) body image; (4) self-esteem and
171 female identity; (5) infertility and attitudes toward motherhood; (6) sexuality and intimate
172 relationships; (7) family and social relationships; (8) HRQoL.

173

174 *Reactions to diagnosis and coping styles.* Four studies (18%) reported information regarding
175 women's reactions to diagnosis and coping styles (Bargiel-Matusiewicz et al., 2013, 2015;
176 Kimberly et al., 2011; Patterson et al., 2014). Women's reactions to diagnosis are commonly
177 characterized by negative emotions, or even suicidal thoughts in a minority of cases (Kimberly et
178 al., 2011). Being diagnosed with MRKH syndrome entails dealing with increased sense of
179 difference compared with peers (Patterson et al., 2014). Therefore, young women with the
180 disease may try to minimize or even avoid exposure to stressful situations that involve social
181 comparisons (e.g., being around pregnant women) (Patterson et al., 2014). In the study by
182 Patterson et al. (2014), women also tried to avoid thinking about MRKH by focusing for instance
183 on their careers and plans for the future. As demonstrated by Bargiel-Matusiewicz et al. (2013,
184 2015), women's emotional state may also be influenced by their personality, especially by
185 neuroticism, which enhances negative emotions such as uncertainty, disappointment, anger, and
186 depression. The authors also showed that women who had been aware of their condition for
187 more than 6 years reported higher levels of neuroticism and lower problem-focused strategies
188 compared with healthy controls (Bargiel-Matusiewicz et al., 2015). Women with MRKH seemed

189 more likely to use emotion-focused strategies that led them, combined with neuroticism, to be
190 excessively focused on negative emotions (Bargiel-Matusiewicz et al., 2013, 2015).

191
192 ***Psychological symptoms.*** Evidence regarding the presence of psychological symptoms (such as
193 for instance anxiety, depression, eating disorders, psychoticism) was provided by 11 studies
194 (50%), of which 7 reported information about the psychological health of MRKH patients
195 regardless of medical treatment (Fliegner et al., 2014, 2018; Heller-Boersma et al., 2009; Krupp
196 et al., 2012; Laggari et al., 2009; Liao et al., 2011; Weijenborg et al., 2019), whereas the other 4
197 focused on the outcomes of specific types of surgical interventions (Carrard et al., 2012; Gatti et
198 al., 2010; Labus et al., 2011; Leithner et al., 2015). The first subgroup of articles reported
199 conflicting findings. Three studies indicated that MRKH patients may display high rates of
200 depression (Fliegner et al., 2014, 2018; Laggari et al., 2009). In the study by Fliegner et al.
201 (2014), the rates of depression were three times higher than expected, and clinically significant
202 depression was reported by 29% of patients (Fliegner et al., 2018) and 40% of patients (Laggari
203 et al., 2009), respectively. There is also evidence that MRKH patients may be more likely to be
204 affected by anxiety, psychoticism, and eating disorder symptoms than healthy women (Heller-
205 Boersma et al., 2009; Laggari et al., 2009), with 54% of patients displaying high psychological
206 distress (Krupp et al., 2012). However, in a recent study (Weijenborg et al., 2019), the presence
207 of psychological symptoms in 54 MRKH patients and 79 healthy controls was assessed using the
208 Symptom Check-List-90 (SCL-90) and the Hospital Anxiety and Depression Scale (HADS),
209 with no significant differences between groups. The findings reported by the second subgroup of
210 studies focused on treatment outcomes indicated that overall women showed good psychological
211 health after surgery, with no remarkable difference compared to women who used dilators
212 (Carrard et al., 2012). In two of these studies, women who underwent surgical creation of a
213 neovagina did not report higher rates of psychological symptoms (including depression) than
214 healthy controls (Gatti et al., 2010; Leithner et al., 2015). Labus et al. (2011) observed that 78%

215 of patients who underwent rectosigmoid vaginoplasty did not have depressive symptoms. In the
216 Carrard et al. (2012) study, 28% of women reported signs of depression, despite increased sexual
217 function.

218
219 **Body image.** Evidence regarding body image, including subjective genital perception, was
220 reported in 5 studies (23%) (Carrard et al., 2012; Dear et al., 2019; Leithner et al., 2015; Pastor
221 et al., 2017; Weijenborg et al., 2019). The worst outcomes were found when body image was
222 assessed in terms of vaginal image and perceptions, for instance using the Female Genital Self-
223 Image Scale (FGSIS) (Pastor et al., 2017; Weijenborg et al., 2019). It was observed that MRKH
224 patients tend to negatively perceive their vagina (e.g., too small, or needing an increase in size)
225 before (Dear et al., 2019) and after treatment, with poor satisfaction (Pastor et al., 2017). In the
226 Leithner et al. (2015) study, body image was assessed from a broader perspective, i.e., not
227 specifically focused on female genitals, with no significant differences between the MRKH
228 group and healthy controls. In the Carrard et al. (2012) study, body image was generally assessed
229 in terms of “body image perception” (positive, neither positive nor negative, negative) by means
230 of a questionnaire developed by the researchers, and changes in body image since treatment were
231 evaluated. In both studies, MRKH women reported positive outcomes, without differences
232 related to treatment (sigmoid vaginoplasty vs. Frank method) (Carrard et al., 2012) and
233 compared with healthy controls (Leithner et al., 2015).

234
235 **Self-esteem and female identity.** In 4 studies (18%) (Fliegner et al., 2014; Gatti et al., 2010;
236 Heller-Boersma et al. 2009; Weijenborg et al 2019), self-esteem was assessed using the
237 Rosenberg Self-Eteem Scale (RSES). In 3 of these studies (Fliegner et al., 2014; Gatti et al.,
238 2010; Weijenborg et al 2019), women with the disease did not report impaired self-esteem.
239 However, Heller-Boersma et al. (2009) found poorer self-esteem in the MRKH group compared
240 with healthy controls. Four studies (Brunner et al., 2015; Carrard et al., 2012; Labus et al. 2011;

241 Patterson et al. 2014) provided information regarding female identity and sense of femininity.
242 Gender self-perception was investigated by Brunner et al. (2015), who observed that the majority
243 of MRKH participants reported having a female gender with heterosexual orientation. Two
244 studies (Carrard et al., 2012; Labus et al., 2011) reported satisfactory femininity in women who
245 underwent rectosigmoid vaginoplasty (Labus et al., 2011) and sigmoid vaginoplasty or dilation
246 (Carrard et al., 2012). On the other hand, in a qualitative study by Patterson et al. (2014) women
247 described MRKH as a threat to their femininity, describing feelings of inadequacy, an overall
248 loss of self confidence after diagnosis, and worries about the fact that others may detect their
249 condition without being told.

250
251 ***Infertility and attitudes towards motherhood.*** Four studies (Brunner et al., 2015; Fliegner et al.,
252 2018; Kimberly et al., 2011; Patterson et al., 2014) examined the role of infertility in women
253 with MRKH. In the Kimberly et al. (2011) study, 79% of participants reported that the reason for
254 their distress was infertility. Fliegner et al. (2018) observed that MRKH patients showed greater
255 distress regarding infertility, as well as thoughts and feelings of sadness compared with CAIS
256 participants. In another study by Brunner et al. (2015), infertility seemed to play an ambiguous
257 role: for some women, it represented the major source of distress, whereas other women
258 contradicted this. Attitudes toward motherhood were systematically explored by Fliegner et al.
259 (2018), who reported that the more positively women saw children, the greater their depression.
260 As regards reproductive options, the percentage of women who were interested in surrogacy
261 ranged from 36% (Pastor et al., 2017) to 82% (Carrard et al., 2018). In the Pastor et al. (2017)
262 study, 91% of women would consider uterus transplantation.

263
264 ***Sexuality and intimate relationships.*** The percentage of MRKH participants who had a partner
265 ranged from 37% (Bargiel et al., 2015) to 76% (Brunner et al., 2015). These percentages are
266 consistent with findings from other studies included in this review, indicating that women tend to

267 have sex before any treatment, although mostly non-penetrative sex (Dear et al., 2019). As
268 reported by Beisert et al. (2015), although the age of initiation of autoerotic activity can be
269 similar in women with MRKH compared with healthy women, attempted vaginal intercourse is
270 less frequent and dyadic sexual activity tends to start later among women with the disease. In a
271 study by Fliegner et al. (2014), the MRKH group reported pronounced feelings of inadequacy in
272 sexual situations compared with controls, which were strongly associated with impaired sexual
273 function. Moreover, women who were not sexually active had higher feelings of inadequacy in
274 social and sexual situations, and poorer self-esteem. Poor sexual esteem was also observed by
275 Liao et al. (2011) and Weijenborg et al. (2019), although in the latter and most recent study this
276 psychological factor was strongly associated with sexual dysfunction and sexual distress, while
277 Liao et al. (2011) did not find significant correlations between these factors. In the Weijenborg et
278 al. study (2019), impaired sexual function was also associated with anxiety and global self-
279 esteem. Managing intimacy represented an important difficulty for the women interviewed by
280 Patterson et al. (2014). Indeed, disclosure was an important issue, as also underlined by Ernst et
281 al. (2014). Trust and closeness were described as an important motivation for disclosing the
282 diagnosis, but at the same time women may prefer to wait for being more invested in the
283 relationship before discussing their condition (Ernst et al., 2014; Patterson et al., 2014). Fear of
284 rejection (especially due to inability to conceive) was identified as an important deterrent to
285 disclosure in both qualitative studies. The fact that the partner may find out their condition
286 represents a source of stress for women (Patterson et al., 2014). However, Pastor et al. (2017),
287 who examined partners' perspective using structured interviews, reported that 97% of men at
288 first did not recognize the artificial vagina and 83% of male partners stated that they did not
289 consider infertility as a reason for relationship breakup.

290

291 ***Family and social relationships.*** Information regarding women's relationship with their mother
292 was reported in two articles (Leithner et al., 2015; Patterson et al., 2014). In both studies,

293 mothers were described as particularly caring or even overinvolved. As reported in the
294 qualitative study by Patterson et al. (2014), women experience their diagnosis as personal and
295 hindering independence may be an issue when mothers are too intrusive (for instance, they take
296 the lead in consultations with professionals) or overprotective. In another study by Labus et al.
297 (2011), family was described as the main source of support by women who underwent
298 rectosigmoid vaginoplasty. Disclosure to friends occurs when women feel comfortable in a
299 relationship based on trust and sharing secrets, and negative feelings and outcomes related to
300 disclosing the diagnosis are less frequent with friends than with partners (Ernst et al., 2014). In a
301 study by Krupp et al. (2012), 90% of MRKH participants who had contacts with other affected
302 persons considered it beneficial, and 53% of those who did not report any contact wished for
303 such an experience. MRKH participants who did not want any contact were afraid of
304 experiencing distress due to an excessive focus on negative topics during the discussion.

305
306 **HRQoL.** HRQoL was systematically evaluated in 5 studies (23%) using well-known
307 standardized measures, and specifically the WHRQoL-BREF (Cheikhelard et al., 2018;
308 Kimberly et al., 2011; Leithner et al., 2015), the Short Form-12 Health Survey (SF-12) (Liao et
309 al., 2011) and the Psychological General Well Being Index (PGWBI) (Sabatucci et al., 2018).
310 Except for the Liao et al. (2011) study, the other articles mostly reported treatment outcomes.
311 Overall, women showed improved HRQoL after treatment as compared with their pre-treatment
312 situation (Sabatucci et al., 2018), healthy controls (Leithner et al., 2015), and the general
313 population (Kimberly et al., 2011). In the Cheikhelard et al. (2018) study, there were no
314 significant differences in HRQoL between the surgery group and the dilation only group,
315 although women reported poorer psychosocial functioning compared with the general
316 population. In another study (Liao et al., 2011), women showed good physical QoL, but lower
317 scores on the mental component of the SF-12 compared with a standardization population.

318

319 **Discussion**

320 This systematic review aimed at providing a comprehensive description of the psychological
321 impact and HRQoL outcomes of MRKH syndrome by summarizing the research evidence
322 published in the last decade. Through systematic electronic search, we identified 22 articles that
323 matched our inclusion criteria and were included in this review. Thematic analysis was
324 conducted and a narrative synthesis of the findings was provided.

325 The studies included in our review confirmed that MRKH diagnosis represents a stressful
326 event, with negative emotional reactions characterized by increased sensitivity to difference and
327 impaired sense of femininity, especially due to infertility (Kimberly et al., 2011; Patterson et al.,
328 2014). The psychological burden of the disease was highlighted in several studies (e.g., Heller-
329 Boersma et al., 2009), with women affected by MRKH displaying anxiety and depression,
330 psychoticism, and even eating disorder symptoms, and poor self-esteem, but more recent articles
331 reported contradicting findings (Weijenborg et al., 2019) and showed overall good QoL,
332 especially after treatment (Sabatucci et al., 2018). Such discrepancies may be partly explained by
333 the fact that women’s psychological reactions to the disease may be shaped by individual
334 characteristics such as personality traits (Bargiel-Matusiewicz et al. 2013, 2015), as well as by
335 psychological adjustment before the diagnosis (Bean et al., 2009).

336 Besides confirming the findings of previous studies (Bean et al., 2009), our review adds
337 to the extant literature by identifying other sources of psychological vulnerability in women with
338 MRKH syndrome. First, women’s genital image (rather than general body image) is often
339 negative, indicating that women are not satisfied with their vagina, to the point of feeling
340 embarrassed and uncomfortable during sexual contacts, with concerns about their genital
341 function (Pastor et al., 2017). These beliefs may have a negative impact on women’s sexual
342 esteem, which tends to be poor in women with MRKH and thus leads to sexual dysfunction
343 (Weijenborg et al., 2019), as well as to feelings of inadequacy and fear of being rejected or
344 considered “a freak” (Patterson et al., 2014). Second, women are worried that their partner may

345 detect their condition without being told, but this belief is not supported by research evidence,
346 which suggests that most men are not able to distinguish the neo-created from the natural vagina
347 (Pastor et al., 2017). Third, the quality of mother-daughter relationship also deserves attention,
348 because mothers may be perceived as excessively involved and intrusive, for instance during
349 treatment (Patterson et al., 2014).

350

351 **Limitations**

352 Due to the broad nature of our research question, as well as to the paucity of psychological
353 articles in the context of MRKH syndrome, we included studies with different objectives and
354 methodologies. The methodological variability across studies, in terms of research designs,
355 measures (i.e., standardized scales and researcher-made questionnaires), and assessment times
356 (time since diagnosis ranged from 1 to 39 years), may account for some of the discrepancies in
357 the findings, especially as regards psychological symptoms. Because systematic comparisons
358 between studies were not possible, we could not describe women's psychological health
359 trajectories during the years following diagnosis and treatment (e.g., short- vs. long-term
360 effects).

361

362 **Suggestions for future research and clinical practice**

363 Future studies should investigate women's pathways through MRKH syndrome in a more
364 systematic fashion, for instance by exploring the association between time since diagnosis and
365 onset of psychological symptoms. This would allow timely implementation and personalization
366 of multidisciplinary treatment. Longitudinal research is encouraged, considering that only one of
367 the included studies had an actual longitudinal design (Sabatucci et al., 2018).

368 Patients' subjective experience of dilators requires further exploration and qualitative
369 research may be particularly useful to explore sociocultural and psychological implications of
370 this type of treatment, as well as the role of family. In this regard, MRKH patients are often

371 adolescents and come to the visits with their parents, who also experience emotional distress.
372 Psychological counseling may help parents and especially mothers, who are sometimes
373 perceived by patients as intrusive and overinvolved (Patterson et al., 2014), improve the quality
374 of the support provided to their daughter.

375 MRKH syndrome is complex and a biopsychosocial perspective should always guide
376 research and multidisciplinary treatment. The creation of a neovagina, either with or without
377 surgery, may contribute to decrease women's concerns about their vagina and thus reduce
378 feelings of difference, especially when properly managed by a multidisciplinary team (Leithner
379 et al., 2015). However, the creation of the neovagina itself, although not associated with negative
380 psychological and HRQoL outcomes, is not able to provide a definitive relief to women with
381 MRKH syndrome, who experience multiple sources of distress. Therefore, psychological
382 counseling should be routinely offered to these patients, with assessment of women's beliefs
383 regarding their genitals and partner's perceptions. The issue of disclosure, especially to intimate
384 partners, should also be addressed and discussed. Reproductive options should be clearly
385 explained to patients, as well as the specific type of infertility related to MRKH syndrome. In
386 fact, these women are not able to carry a pregnancy due to uterine absence or abnormality, but
387 they may have normally functioning ovaries.

388 The language used by professionals is fundamental in the context of MRKH syndrome
389 (Bean et al., 2009), as well as good doctor-patient communication, especially when working with
390 young adolescents who are building their identity. Psychologists may help physicians manage
391 the complexity of the disease and improve the quality of their relationship with patients and their
392 families.

393

394 **Declaration of conflicting interests**

395 There are no conflicts of interest and there has been no financial support for this work.

396

397 **Funding**

398 No research funding was received for this study.

399

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Table 1. Characteristics of the studies included in the systematic review

Authors, year of publication, country of analysis	Study aim/research question	MRKH (n)	Non-MRKH (n)	Evaluation of psychological and HRQoL outcomes	MRKH Treatment	Relevant findings
Bargiel-Matusiewicz et al, 2013 (Poland)	To examine the associations between neuroticism, coping styles, and positive/negative emotions, and the underlying mechanisms, in women with MRKH syndrome	46	—	Quantitative. NEO-FFI; CISS; Emotional State Survey	—	Emotional coping style mediated the relation between neuroticism and affects. Time of awareness of MRKH moderated the association between neuroticism and negative affects
Bargiel-Matusiewicz et al, 2015 (Poland)	To compare personality traits and coping styles in women with MRKH vs. healthy controls	46	44 healthy	Quantitative. NEO-FFI; CISS	—	Higher neuroticism, greater emotion-focused coping and lower problem-focused coping in the MRKH group
Beisert et al, 2015 (Poland)	To examine sexual activity in MRKH patients vs. healthy controls	31	31 healthy	Quantitative. Psychosexual biography	Surgery (n=21)	No significant differences regarding age at initiation of autoerotic and anal activity, and level of sexual arousal. In MRKH participants, less frequent vaginal and oral intercourse, later initiation of dyadic sexual activity, less frequent orgasm during intercourse
Brunner et al, 2015 (Germany)	To examine gender self-perception in women with CAIS vs. subfertile or infertile women with MRKH and PCOS	49	11 with CAIS; 55 with PCOS	Mixed-methods. Multidimensional questionnaire	—	The majority of MRKH participants did not report decreased female identity or doubts about female role

Carrard et al, 2012 (France)	To evaluate functional and psychosexual outcomes of sigmoid vaginoplasty	59	—	Quantitative. Questions assessing depression, body image, desire of motherhood	Sigmoid vaginoplasty (n=48); Frank's method (n=11)	Overall, 28% of women reported signs of depression, despite increased sexual function after treatment. No significant group differences in psychological outcomes
Cheikhelard et al, 2018 (France)	To compare dilation and surgery as regards QoL outcomes, anatomical results, and complications	131	—	Quantitative. WHOQoL-BREF	Dilation only (n=26); Surgery (Sigmoid vaginoplasty, Davydov, Dupuytren, Vecchietti, McIndoe) (n=84)	No significant differences in global quality of life across the two groups. Overall, lower psychosocial health and social relationship scores compared with the general population
Dear et al, 2019 (UK)	To examine pretreatment sexual experience in women with vaginal agenesis	115	22 with CAIS	Quantitative. Sexual Experiences Questionnaire; MSQ; Vaginal Self-Perceptions	—	The majority of women with MRKH syndrome reported sexual activity before treatment (mostly non-penetrative sex). Most women perceived their vagina as too small. No significant group differences
Ernst et al, 2014 (USA)	To investigate the process and the emotional impact of disclosing MRKH diagnosis to peers during adolescence and young adulthood	9	—	Qualitative. Semistructured telephone interviews	—	Motivations for disclosing were trust and closeness, honesty and responsibility towards partner. Deterrents were fear of rejection, or being misunderstood or considered a “freak”, lack of trust and comfort, and infertility.

Fliegner et al, 2014 (Germany)	To examine psychological and sexual wellbeing in women with CAIS vs. MRKH and the association between psychological factors and sexual function	49	11 with CAIS	Mixed-methods. FUSS; RSES; BSI (only depression subscale); open question	Dilation only (n=2); surgery (n=42)	In MRKH patients, feelings of inadequacy in sexual situations affected sexual function. High rates of depression (as for CAIS). Overall satisfaction with sexual life. Sexual problems related to issues regarding vaginal functioning. Worse psychological outcomes in non-sexually active patients
Fliegner et al, 2018 (Germany)	To explore the role of infertility and attitudes towards motherhood in women with CAIS and MRKH syndrome	49	12 with CAIS	Quantitative. Self-developed questionnaire; FEMu; BSI	—	In MRKH women, moderate wish for a child, with greater distress, thoughts, and sadness regarding infertility; 29% showed clinically significant depression; positive attitudes towards motherhood associated with depression
Gatti et al, 2010 (Italy and Bangladesh)	To investigate the psychological and psychosexual experience of MRKH patients who underwent total sigmoid vaginal replacement	43	30 healthy	Quantitative. RSES; BDI; CTLMA	Total sigmoid vaginal replacement	No significant differences in psychological function between MRKH patients and controls
Heller-Boersma et al, 2009 (UK)	To compare the psychological conditions of women with MRKH vs. healthy women; to examine whether the psychological impact of MRKH decreases over time	66	31 healthy	Quantitative. SCL-90-R; RSES; IIP-32; EDI	—	In MRKH patients, higher phobic anxiety and psychoticism; lower self-esteem; greater eating disorders symptoms. No significant correlations with time from diagnosis

Kimberly et al, 2011 (Australia)	To evaluate long-term quality of life and sexual function outcomes in women treated for vaginal agenesis	28	—	Quantitative. WHOQoL-BREF; Questionnaire assessing reactions to diagnosis	Sheare's or McIndoe procedure (n=4); dilators (n=16)	No significant differences in overall quality of life relative to Australian general population; negative feelings after diagnosis, mostly related to infertility
Krupp et al, 2012 (Germany)	To investigate how women with CAIS, MRKH, or PCOS experience contact with other affected individuals	49	11 with CAIS; 55 with PCOS	Mixed-methods. Questionnaire developed to examine different aspects of the contact experience; BSI	—	Among MRKH patients, 62% had contacts with other affected women; of these, 90% considered contact beneficial; 53% wished to have such contact. High levels of distress in 54% of MRKH women
Labus et al, 2011 (Serbia)	To evaluate sexual and psychosocial adjustment after rectosigmoid vaginoplasty	36	—	Quantitative. BDI; Questionnaire assessing postoperative satisfaction, social and sexual adjustment	Rectosigmoid vaginoplasty	79% of patients did not report depression. Most participants were satisfied with surgery, considered as the best treatment option; 94% reported satisfactory femininity with heterosexual orientation. Family was the main source of support
Laggari et al, 2009 (Greece)	To investigate anxiety and depression in women with MRKH and PCOS	5	22 with PCOS; 22 healthy	Quantitative. BDI; STAI; Stressful Life Events Schedule	—	40% of MRKH patients reported clinical depression and were more likely to report anxiety and depression than healthy women

Leithner et al, 2015 (Austria)	To examine sexual and psychosocial functioning in women with MRKH after surgical creation of a neovagina	10	20 healthy	Quantitative. PHQ; BSI; WHOQoL-BREF; FBeK; PBI	Wharton-Sheares.George technique	No significant group differences in depressive symptomatology, psychosocial burden, QoL and body image. Less psychological impairment in MRKH patients. Closer mother-daughter relationship
Liao et al, 2011 (UK)	To explore QoL, psychological health, and sexuality in MRKH patients	56	—	Quantitative. SF-12; HADS; MSQ	Dilator only (n=36); Surgery (n=8)	Compared with a standardization sample, MRKH patients reported greater physical QoL, but poorer scores on the mental QoL component and greater anxiety. No differences for depression. Poor sexuality (especially sexual esteem)
Pastor et al, 2017 (Czech Republic)	To investigate sexual wellbeing and partners' perspective among MRKH patients with a neovagina	42	45 healthy; patients' sexual partners	Mixed-methods. FGSIS; semistructured and structured interviews	Laparoscopic Vecchietti vaginoplasty	MRKH patients reported poorer genital image than healthy controls. 97% of men at first did not recognize the artificial vagina. Infertility was not considered a reason for relationship breakup by 83% of men
Patterson et al, 2014 (UK)	To investigate young women's subjective experience of MRKH syndrome	5	—	Qualitative. Semistructured interview	—	Although the diagnosis was considered as a private experience, mothers were heavily involved. Women reported sensitivity to difference and intimacy problems. Female identity and self-esteem were compromised by the disease
Sabatucci et al, 2018 (Italy)	To evaluate long-term sexual function and QoL after vaginoplasty	39	—	Quantitative. PGWBI	Modified Abbé-McIndoe technique using autologous in vitro cultured vaginal tissue	Patients reported greater QoL compared with their pre-intervention condition as well as with the median standardized profile of the general population

Weijenborg et al, 2019 (The Netherlands)	To examine sexual and psychological wellbeing in MRKH patients	54	79 healthy	Quantitative. SES; FGSIS; SCL-90; HADS; RSES; MMQ (subscale relationship satisfaction); Sexual and Physical Abuse Questionnaire (three questions)	Vecchietti (n=1); Davydov (n=5); McIndoe (n=5); Williams (n=1); cutaneous groin flaps (n=1); unspecified (n=2)	MRKH patients reported longer relationships, less frequent abuse experiences, poorer sexual esteem and genital image, but similar psychological health condition compared with controls. Psychological factors (especially sexual esteem) predicted sexual dysfunction
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Abbreviations: BDI (Beck Depression Inventory); BSI (Brief Symptom Inventory); CAIS (Complete Androgen Insensitivity Syndrome); CISS (Coping Inventory for Stressful Situations); CTMLA (Cohen Test for Life Management Ability); EDI (Eating Disorder Inventory); FEMu (Questionnaire on Attitudes toward Motherhood); FGSIS (Female Genital Self-Image Scale); FUSS (Feelings of Inadequacy in Social and Sexual Situations); HADS (Hospital Anxiety and Depression Scale); IIP-32 (Inventory of Interpersonal Problems); MMQ (Maudsley Marital Questionnaire); MSQ (Multidimensional Sexuality Questionnaire); NEO-FFI (NEO Five Factor Inventory); PBI (Parental Bonding Instrument); PCOS (Polycystic Ovary Syndrome); PGWBI (Psychological General Well Being Index); PHQ (Patient Health Questionnaire); RSES (Rosenberg Self-Esteem Scale); SCL-90 (Symptom Check-List); SES (Sexual Esteem Subscale of the MSQ); SF-12 (Short Form-12 Health Survey); STAI (State-Trait Anxiety Inventory); WHOQoL-BREF (World Health Organization Quality of Life - Brief version)

Supplemental Figure 1. PRISMA flow-chart for article selection

