REVIEW ARTICLE

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Self-Perception of Reproductive Health, Mental Health, and Quality of Life in Females With Classical Congenital Adrenal Hyperplasia: A Systematic Review

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Abstract

Background. Classical Congenital Adrenal Hyperplasia (C-CAH) is a congenital disorder characterized by a loss of 21-hydroxylase enzymes. Consequently, androgen levels increase, resulting in varying degrees of psychological and physiological masculinization. This systematic review aims to examine existing research on females with C-CAH and identify challenges related to reproductive self-perception, mental health, and overall quality of life.

Methodology. This systematic review was conducted based on the PRISMA 2020 guidelines, studies were retrieved from PubMed, EBSCO, Science Direct, and ProQuest, and screened according to predefined eligibility criteria. Quality assessments of included studies were done using the Newcastle-Ottawa Scale (NOS) for case-control studies, adapted NOS for cross-sectional studies, and Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I).

Results. Eleven studies determined to have low risk of bias involving 523 participants were included. All 11 studies addressed self-perception of reproductive health, evaluating gender and sexual-related issues, with outcomes such as atypical gender identity and sexual orientation, gender dysphoria, and sexual satisfaction impairment. Adverse perceptions and experiences related to virilized genitalia were commonly reported. Four studies examined mental health issues, comprising anxiety, social phobia, ADHD, sexual distress, and signs of depression. Finally, females with C-CAH have reduced QoL compared to healthy females, mainly due to impacted general health and pain.

Conclusion. Females with C-CAH demonstrated impaired reproductive self-perception, including sexual satisfaction and gender-related difficulties, alongside psychological concerns including anxiety, social phobia, and maladaptive coping behaviors, with reduced quality of life related to general health and pain.

Key words: congenital adrenal hyperplasia, females, mental health, quality of life, self-perception, reproductive health

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a genetic disorder that causes deficiencies in the steroidogenic enzymes.[1] The most common enzyme deficiency in CAH is 21-hydroxylase deficiency (21OHD) accounting for more than 90% of cases.[1–3] 21OHD is classified into two forms: classical and non-classical.[1,4] Unlike the non-classical form (NC-CAH), the classical form (C-CAH) comprises the salt-wasting and simple virilizing phenotypes and reflects a spectrum of residual 21OHD, rather than a complete loss of enzyme function, making CAH the most prevalent cause of genital virilization.[5] Classical 21OHD occurs in approximately 1 out of every 15,000 births worldwide and is characterized by severe symptoms that include salt-wasting (SW) and ambiguous genitalia.[1,2,5]

The challenges CAH female patients face differ from those experienced by males.[6] In addition to external genitalia virilization, elevated androgen exposure in XX individuals leads to progressive virilization and may influence both psychologically and physiologically, which may affect gender identity, and functionality of reproductive organs.[7] Reports of females with C-CAH conveyed high atypical gender identity, gender dysphoria, cross-gender behaviors, as well as a variety of perceptions surrounding sexual dysfunctions such as sexual satisfaction impairment and stigma.[8–11]

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Due to changes in reproductive health, CAH also affects a patient's quality of life (QoL), potentially lowering quality of life in physical, psychological, and social QoL, such as concerns in romantic relationships, self-esteem, lower marriage rates, and infertility issues.[12,13] In contrast, CAH female patients with positive social support and better understanding of their condition showed improvements in QoL.[13,14] Mental health concerns, namely shame, secrecy, and stigma surrounding ambiguous genitalia in women with CAH can lead to increased psychiatric disorders, including anxiety disorders and depression.[12]

Considering the impacts that CAH potentially creates as addressed above, it is highly important to bring light towards psychological aspects of impacted patients as it is to medical aspects of this condition. Although psychosocial outcomes in the CAH population have been previously reported, existing studies are examined in isolation and have rarely been synthesized through a patient-centered lens that integrates reproductive self-perception, mental health, and quality of life. Existing reviews addressing similar topics included outdated studies, and while a previous systematic review discussed these aspects among males with CAH, none covered all three aspects in females.[15] Therefore, this systematic review aims to address this gap by providing a comprehensive synthesis of reproductive self-perception, mental health, and quality of life outcomes among females with classical CAH.

METHODOLOGY

Search strategy

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) guidelines. The study protocol was registered with PROSPERO (CRD420251058613). The PRISMA checklist is provided in (Supplemental Table 1). Published articles were searched across four databases, including PubMed, EBSCO, Science Direct, and ProQuest, from January 2015 to February 2024. The detailed search terms used are presented in (Table 1).

Eligibility criteria

All original articles addressing QoL, mental health, or self-perception of reproductive health including but not limited to their gender identity and their feelings surrounding stigma about their condition or their condition itself, of female patients with classical 21OHD were included. Quantitative, qualitative or mixed methods studies were eligible for inclusion with no age restrictions. Case reports, review articles, protocol studies, irretrievable full texts, and articles published in languages inaccessible to the review team were excluded. Studies without data of interest, studies discussing mixed genders and not displaying separate results, studies with males only, and studies investigating disorders of sexual development or CAH without separate outcomes for classical 21OHD were further excluded.

Study selection and data extraction

Duplicate studies were removed prior to screening. Titles and abstracts of all studies were initially screened based on eligibility criteria prior to full-text assessment. Three independent reviewers (WJT, JVS and MN) assessed retrieved full-text articles of selected studies, with any conflicts resolved through the fourth and sixth author (AFL, LAP). Data were extracted based on a predetermined tabular sheet consisting of (a) authors and year of publication, (b) study location and design, (c) subject population: sample size, and age range or mean age ± SD, (d) comparison group, and (e) study outcomes as described in the eligibility criteria. Extracted data were synthesized.

Quality assessment

Two independent reviewers (JVS and MN) assessed the risk of bias and quality of included studies using the Newcastle-Ottawa Scale (NOS) for case-control studies and adapted NOS for cross-sectional studies from previously published literature.[16] One non-randomized experimental study was assessed using the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) and visualized as traffic light

Table 1. Details of search terms used for every database

No.	Database	Keywords
1.	PubMed	("congenital adrenal hyperplasia"[Title/Abstract] OR "CAH"[Title/Abstract] OR "adrenogenital syndrome"[Title/Abstract]) AND ("women"[Title/Abstract] OR "female"[Title/Abstract] OR "girl"[Title/Abstract]) AND ("psychological"[Title/Abstract] OR "distress"[Title/Abstract] OR "stress"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "qol"[Title/Abstract] OR "emotional"[Title/Abstract] OR "mental disorder"[Title/Abstract] OR "social stigma"[Title/Abstract] OR "lived experience"[Title/Abstract] OR "satisfaction"[Title/Abstract] OR "empower*"[Title/Abstract] OR "attitude*"[Title/Abstract] OR "coping*"[Title/Abstract] OR "network"[Title/Abstract] OR "isolation"[Title/Abstract] OR "relation*"[Title/Abstract] OR "stigma*"[Title/Abstract] OR "social adaptation"[Title/Abstract])
2.	Science Direct	("congenital adrenal hyperplasia"[Title/Abstract] OR "CAH"[Title/Abstract]) AND ("women"[Title/Abstract]) AND ("psychological"[Title/Abstract] OR "stress"[Title/Abstract] OR "quality of life"[Title/Abstract] OR "mental disorder"[Title/Abstract] OR "social stigma"[Title/Abstract] OR "social adaptation"[Title/Abstract])
3.	EBSCOHost	AB (congenital adrenal hyperplasia or CAH or adrenogenital syndrome) AND AB (women or female or girl) AND AB (psychological or distress or stress or quality of life or qol or emotional or mental disorder or social stigma or lived experience or satisfaction or empower or attitude or coping or network or isolation or relation or stigma or social adaptation)
4.	ProQuest	(abstract(congenital adrenal hyperplasia) OR abstract(CAH) OR abstract(adrenogenital syndrome)) AND (abstract(women) OR abstract(female) OR abstract(girl)) AND (abstract(psychological) OR abstract(distress) OR abstract(stress) OR abstract(quality of life) OR abstract(qol) OR abstract(emotional) OR abstract(mental disorder) OR abstract(social stigma) OR abstract(lived experience) OR abstract(satisfaction) OR abstract(empower) OR abstract(attitude) OR abstract(coping) OR abstract(network) OR abstract(isolation) OR abstract(relation) OR abstract(stigma) OR abstract(social adaptation))

plot through the RobVis website.[17] Any disagreements were resolved by the first author (WJT).

RESULTS

A total of 783 studies were identified across all databases. Prior to screening, 288 duplicates were removed, and the remaining 495 studies were screened based on title and abstract. Reviewers obtained 29 studies for full-text assessment and ultimately included 11 studies for qualitative synthesis.[9,13,18–26] The screening process is summarized as a PRISMA flowchart and presented in (Figure 1).

The characteristics and outcomes of the 11 included studies were extracted, comprising a total of 523 participants. An overview of the study characteristics is presented in Table 2. The majority of selected studies were conducted in the United States, followed by the United Kingdom, Turkey, Austria, and India. All included studies were peer-reviewed original articles that comprise a total of 800 samples, including female patients with classical CAH as the focus of study, and a variety of control groups.

Nine studies were cross-sectional studies, with one case-control study, and one non-randomized experimental study. Based on the NOS, seven studies were classified as low-risk studies and three as high-risk (Tables 3 and 4). The

Table 2. An overview of included study characteristics

Studies (year)	Location	Study design	Sample size	Age range (years) / mean (SD)	Comparison group
Schernthaner-Reiter et al. (2019) [9]	Austria	Cross-sectional	35 females	35.1 (12.3)	NC-CAH
Kanhere et al. (2015) [13]	United States	Cross-sectional	89 patients with CAH	NR	None
Gangaher et al. (2016) [18]	India	Cross-sectional	22 females	3.5-32	Female reared as male
Endendijk et al. (2016) [19]	United States	Cross-sectional	54 girls	10-13	NC-CAH
Meyer-Bahlburg et al. (2018) [20]	United States	Cross-sectional	62 women*	18-51	None
Meyer-Bahlburg, Reyes-Portillo et al. (2017) [21]	United States	Cross-sectional	62 women*	18-51	None
Dwiggins et al. (2020) [22]	United States	Case-control study	36 patients with classic CAH; 27 control women	19-67	Unaffected relatives
Spencer et al. (2021) [23]	United Kingdom	Cross-sectional	43 girls and 38 boys with CAH; 41 girls and 31 boys control†	4-11.93	Unaffected relatives
Doktur et al. (2021) [24]	Turkey	Cross-sectional	27 girls and 18 boys	6-18	Male
Hines et al. (2016) [25]	United Kingdom	Non-randomized experimental	43 girls and 38 boys with CAH; 41 female and 31 male controls†	4-11	Unaffected relatives
Meyer-Bahlburg, Khuri et al. (2017) [26]	United States	Cross-sectional	62 women*	18-51	None
Summary			523		

*Meyer-Bahlburg, Khuri et al., Meyer-Bahlburg et al., and Meyer-Bahlburg, Reyes-Portillo et al., were conducted using the same study population.
† Spencer et al., and Hines et al., were conducted using the same study population.
NC-CAH – Non-classical congenital adrenal hyperplasia

Table 3. Modified Newcastle-Ottawa scale quality assessment of cross-sectional studies

Author (year)	Selection				Comparability	Outcome		Results
	Case representative	Sample size	Non-respondents	Ascertainment		Outcome assessment	Statistical test	
Schernthaner-Reiter et al. (2019)	★	☆	☆	★	★☆	★	★	High risk
Kanhere et al. (2015)	★	☆	★	★	★★	★	★	Low risk
Gangaher et al. (2016)	★	★	★	★	★☆	★	☆	Low risk
Endendijk et al. (2016)	★	☆	★	★	★★	★	★	Low risk
Meyer-Bahlburg et al. (2018)	★	☆	★	★	★☆	★	☆	High risk
Meyer-Bahlburg, Reyes-Portillo et al. (2017)	★	☆	★	★	★★	★	☆	Low risk
Spencer et al. (2021)	★	☆	★	★	★★	★	★	Low risk
Doktur et al. (2021)	★	★	★	★	★★	★	★	Low risk
Meyer-Bahlburg, Khuri et al. (2017)	★	☆	★	★	★☆	★	☆	High risk

The amount of stars indicates the number of points one study can achieve within each category. A black star (★) indicates that the study has earned a point, while a white star (☆) means that the study failed to earn a point.

Table 4. Newcastle-Ottawa scale quality assessment of case-control studies

Author (year)	Selection				Comparability	Outcome			Results
	Representativeness	Selection	Definition	Demonstration		Ascertainment	Same Method	Non-response	
Dwiggins et al. (2020)	★	★	★	★	★	★★	★	☆	Low risk

The amount of stars indicates the number of points one study can achieve within each category. A black star (★) indicates that the study has earned a point, while a white star (☆) means that the study failed to earn a point.

non-randomized study was classified to have a moderate risk of bias based on ROBINS-I (Figure 2).

This paper investigates three main domains: (1) self-perception of reproductive health including gender identity, sexual orientation, sexual satisfaction, gender-typical preferences, and perceptions surrounding patients' genital appearance, (2) mental health, and (3) quality of life, with all outcomes summarized in (Table 5).

DISCUSSION

Self-perception of reproductive health

All included studies addressed diverse issues in relation to sex, gender identity and perceptions surrounding patients' genital appearance. Three studies acknowledged that female patients with C-CAH are overall more likely to have atypical sexual orientation.[9,20,22] Dwiggins et al., showed significant differences compared to healthy females, with a higher proportion of participants reporting bisexual or homosexual orientation. Similarly, the study of Schernthaner-Reiter et al., also demonstrated slightly higher homosexual gender identity among females with C-CAH compared with females with NC-CAH. Some participants from Meyer-Bahlburg et al.,'s interview revealed that frequent misgendering made them restrict their sexual life to women partners only. Dwiggins et al., also reported significantly lower sexual satisfaction compared to healthy controls because of a higher number of reconstructive surgeries done due to the severity of the condition. In contrast, in the study of Schernthaner-Reiter et al., NC-CAH females reported higher sexual satisfaction albeit by non-statistically significant levels. Beyond sexual orientation, five studies

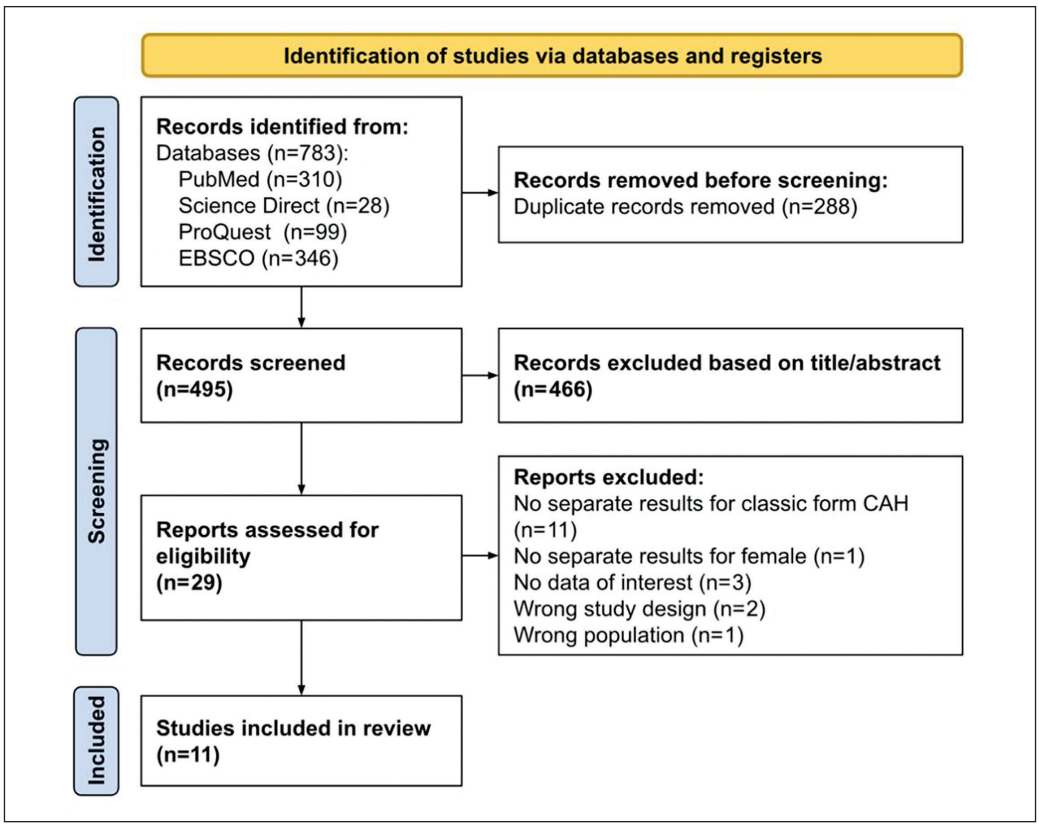

Figure 1. A PRISMA 2020 flowchart for literature search and screening.

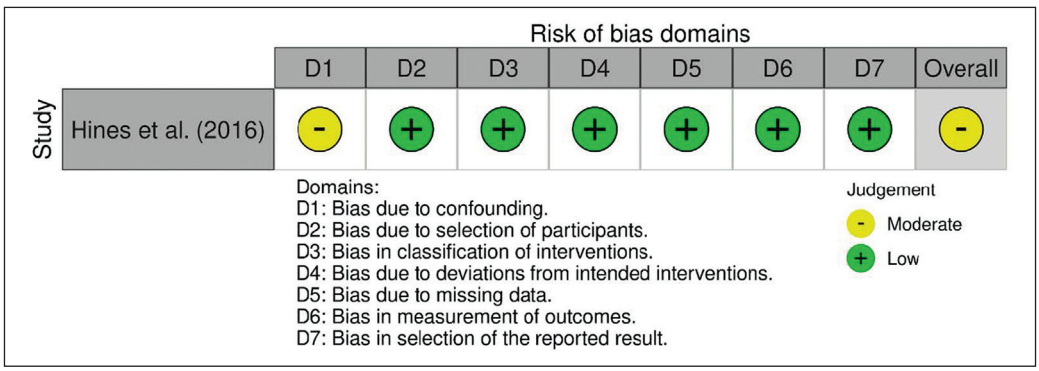

Figure 2. Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) quality assessment.

Table 5. An overview of included studies and outcomes of investigated domains

Studies (year)	SPRH	QoL	Mental health
Schernthaner-Reiter et al. (2019)	More identified as homosexual (p = 0.062) Higher sexual satisfaction (p = 0.636)		Lower sexual distress (p = 0.063)
Kanhere et al. (2015)	Showed cross-gender behavior (51.8%) Dissatisfaction with genital appearance Childhood and adult perceptions are in accordance (p = 0.02)	Reduced QoL	
Gangaher et al. (2016)	Higher rate of gender dysphoria.		Showed subsyndromal depression
Endendijk et al. (2016)	More cross-gender behavior (p <0.05) Higher masculine gender identity (p >0.05)		
Meyer-Bahlburg et al. (2018)	Adverse emotion and experiences. Showed homosexuality. Dissatisfaction with genital appearance.		Showed substance abuse
Meyer-Bahlburg, Reyes-Portillo et al. (2017)	Doubts on current gender identity. Adverse emotions and experiences.		
Dwiggins et al. (2020)	Less likely to be heterosexual (p = 0.013). Changed gender identity. Lower sexual satisfaction (p = 0.017).	Reduced QoL (p <0.05)	
Spencer et al. (2021)	More cross-gender behavior (p <0.001).		
Doktur et al. (2021)	Higher rate of gender dysphoria (p = 0.23). More cross-gender behavior (18.5%).		Higher rate of anxiety disorder (p = 0.22) Higher rate of social phobia (p = 0.33) Lower rate of ADHD (p = 0.052)
Hines et al. (2016)	Reduced female-type preferences (p <0.10).		
Meyer-Bahlburg, Khuri et al. (2017)	Adverse emotions and experiences. Dissatisfaction with genital appearance.		

SPRH – Self-perception of Reproductive Health; QoL – Quality of Life; ADHD – attention-deficit/hyperactivity disorder

reported effects on gender identity; some manage to make adjustments and find comfort in their current gender identity, whereas experience gender dysphoria.[18,19,21,22,24] No atypical gender identity or gender dysphoria was reported among control groups.[19,22,24] Females with NC-CAH demonstrated only slightly higher masculine gender identity scores, likely reflecting lower prenatal androgen exposure and less severe genital virilization. Gangaher et al., reported that participants reared as female have higher rates of gender dysphoria and dissatisfaction with their female identity, compared to those reared as male.[18] In interviews conducted by Meyer-Bahlburg, Reyes-Portillo et al., some participants reported that parental and societal stigma contributed to doubts about being female; however, open discussions regarding their condition helped alleviate those concerns.[21]

Three studies examining the relationship between prenatal androgen exposure and gender-typed behaviors demonstrate consistent findings.[19,23,25] Girls with C-CAH exhibited significantly more male-typical preferences and behaviors than unaffected girls and girls with NC-CAH, whereas boys with C-CAH did not differ from unaffected boys. Consistent with these findings, Kanhere et al., reported that many affected girls preferred male-typical play activities. However, a substantial proportion expressed neutral preferences regarding playmates, suggesting that environmental influences such as sibling gender, may also contribute to behavioral development.

Overall, females with C-CAH demonstrated greater masculinization across several sexual- and gender-related domains. They were more likely to report same-sex attraction, male-typical preferences and behaviors, dissatisfaction with female gender identity, and gender dysphoria than control groups. These findings support the role of prenatal androgen exposure and virilization in shaping psychosexual development. Non-significant findings in some studies may reflect limited statistical power resulting from relatively small and unequal sample sizes. Nevertheless, these observations are consistent with findings reported more than two decades ago, despite the inclusion of a small number of participants whose diagnosis of classical 21OHD was not confirmed.[27] Likewise, a study comparing C-CAH to other androgen excess disorders also showed significantly higher homosexuality and lower sexual satisfaction in C-CAH females.[28]

This review also highlights the perceptions and experiences of females with C-CAH regarding their condition, particularly their genital appearance. According to the three of four studies addressing this topic, there is a relatively high occurrence of affected females who demonstrate dissatisfaction towards their genital appearance, wishing they looked better or wanting a different genital appearance.[13,20,26] In two of the three interview-based studies by Meyer-Bahlburg et al., participants described their genitalia as abnormal, different, or strange and reported feelings of fear and discomfort related to their appearance.[20,26] Across all three interview studies, many participants expressed discomfort when their genitalia were visible to others, particularly during medical examinations, sexual activity, changing clothes in the presence of other women, or wearing swimwear. Negative self-perceptions were often compounded by stigma and reactions from others, contributing to feelings of nervousness, avoidance, shame, and secrecy that may adversely affect mental health. Dissatisfaction with genital appearance and genital self-consciousness may also contribute to impaired sexual satisfaction, and potentially influence gender identity and

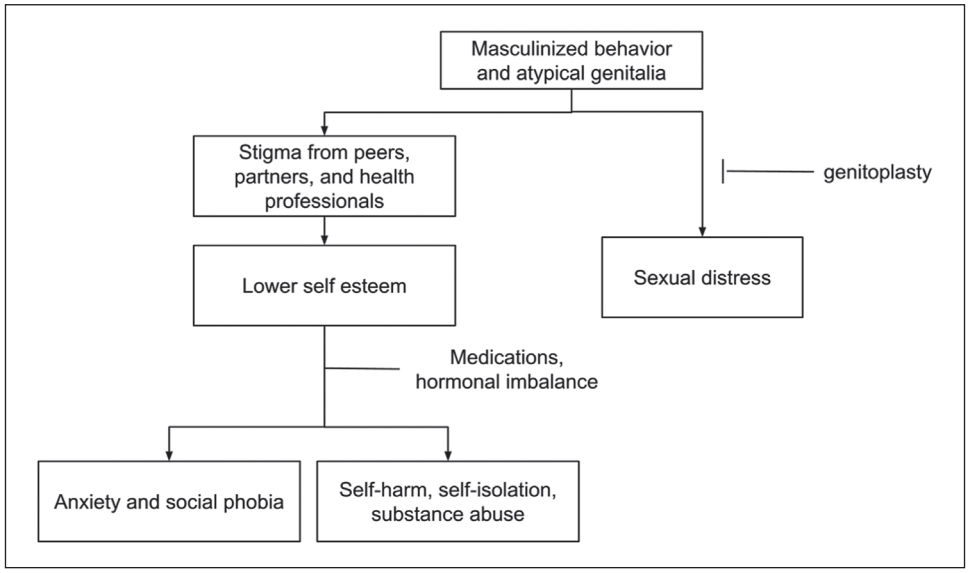

Figure 3. Mental health implications of C-CAH in female patients.

sexual orientation, as supported by previous research demonstrating significant associations among these factors.[29]

Taken together, females with C-CAH experience challenges related to sexuality, gender identity, and perceptions of virilized genitalia that are closely interconnected. Variability in outcomes likely reflects the influence of multiple biological and environmental factors, including prenatal androgen exposure, parental support, sibling sex, societal attitudes, and stigma. Medical interventions, such as genital reconstructive surgery and hormone replacement therapy, may also influence these outcomes. Consequently, supportive family environments and appropriate psychosocial care are important in helping affected individuals cope with gender- and sexuality-related concerns.

Mental health

Four studies included in this review examined mental health outcomes and have been summarized in (Figure 3).[9,18,20,24] Although statistically insignificant, the elevated rates in anxiety disorders and social phobia showed by Doktur et al., are described as a cause of the lower self-esteem in female patients with C-CAH. The findings in this study are consistent with other studies included in this review, which reported reduced self-esteem among participants who experienced stigma from peers, partners, or even health professionals due to their masculinized behavior, atypical genitalia, or chronic medication use., which may increase their susceptibility to psychiatric disorders.[20,21,26] The findings related to attention-deficit/hyperactivity disorder (ADHD) were generally consistent with population-based studies showing a higher prevalence of ADHD among males.[30] The lack of statistical significance may reflect insufficient statistical power due to the small sample size rather than a true absence of association. Alternatively, it may indicate that males and females with CAH experience comparable psychological burdens related to chronic disease management and long-term treatment. The findings regarding sexual distress were supported by other studies included in this review.[9,18,20] Although C-CAH is considered to be more severe than the non-classical form, the study showed a lower distress in females with C-CAH. Sexual distress is often found in female patients with C-CAH as a consequence of their dissatisfaction and negative self-perceptions due to their severely impaired sexual function. However, factors other than disease severity may contribute to these outcomes. For example, genitoplasty has been associated with impaired sexual function in some studies, yet most females with C-CAH in the study by Schernthaner-Reiter et al., had undergone reconstructive surgery, whereas those with NC-CAH generally had not. These findings suggest that reconstructive surgery may alleviate some aspects of sexual distress in selected patients. This interpretation is supported by similar studies showing high level of satisfaction after corrective surgery, allowing patients to live free from the 'intersex individual' label, resulting in reduced distress.[31,32]

The distress caused by peer pressures and stigma was further supported by one sample from Gangaher et al., examining psychological aspects in females with CAH. Though the aim of the study was not specifically to measure mental health, it reported attempted self-harm performed by one participant as a result of being ridiculed by her peers. Moreover, interviews done by Meyer-Bahlburg et al., showed a shift in behavior where one patient distanced herself from men due to her impaired sexual function and inability to meet both her and her partner's sexual needs. She experienced feelings of hopelessness, leading her to avoid relationships with men and, instead, turn to alcohol. She also inquired whether the interviewer had identified substance abuse or addiction among other females with C-CAH.

Generally, these findings suggest that females with C-CAH have several mental health problems, mainly anxiety disorders, social phobia, sexual distress and present coping mechanisms like self-harm, self-isolation, and substance abuse which are often signs of depression. These outcomes are likely influenced by both biological factors, including hormonal imbalances, and psychosocial factors, such as stigma and concerns about social acceptance. Genitoplasty may contribute positively to psychological well-being in some individuals (Figure 3).

However, given that only four studies addressed mental health outcomes, and one relied primarily on qualitative interviews, further research is needed to better characterize the psychological challenges faced by females with C-CAH and to identify appropriate supportive interventions.

Quality of life

Patients with CAH face lifelong physical and psychosocial challenges that can significantly impact their quality of life (QoL).[33] The chronic nature of CAH necessitates lifelong treatment, frequent healthcare visits, and ongoing management of reproductive and sexual health concerns, all of which may adversely affect psychosocial well-being. Concerns regarding fertility, transmission of the condition to offspring, and long-term health outcomes may further contribute to reduced QoL.[34] Overall, CAH appears to have a greater impact on females than males, largely due to excess androgen exposure and its associated consequences.[33] Untreated female patients may experience hirsutism, acne, voice deepening, anovulation, and menstrual irregularities, ambiguous genitalia, precocious puberty, obesity, and short stature in adulthood.[33,34] Greater degrees of virilization, particularly with the classical form of CAH, have been associated with a lower quality of life.[33]

Studies by Dwiggins et al., and Kanhere et al., evaluated quality of life in females with C-CAH using a 36-item Short Form Survey (SF-36) questionnaire which measures eight health-related quality of life (HRQoL) domains including physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health perception. Both studies showed lower QoL across all domains compared to healthy controls, particularly in general health and pain, with increased dyspareunia and pelvic pain likely contributing to these findings.[13,22] Urinary dysfunction had minimal impact on QoL, though patients with clitorectomies reported worse control.[35] Importantly, family support, positive childhood experiences, and broader psychosocial support were associated with better QoL outcomes in early adulthood. This may partly explain why differences in some SF-36 domains were not statistically significant. Thus, the quality of life in female patients with C-CAH are multifactorial. However, these findings should be interpreted cautiously because only two studies examined QoL outcomes, both of which had relatively small sample sizes. Furthermore, important confounding factors, including surgical history, degree of virilization, hormonal control, and mental health status, may have influenced the reported outcomes.

To our knowledge, this is the first systematic review to comprehensively examine reproductive self-perception, mental health, and quality of life among females with C-CAH. Our findings manage to bring emphasis on those aspects that are often overseen, providing insights useful for determining the most suitable care tailored to specific challenges encountered by females with C-CAH. However, there are certain limitations in this review. The included studies are highly heterogeneous in outcome measurements and patient demographics, limiting direct comparisons and the strength of the conclusions. Nevertheless, such heterogeneity is expected, given the rarity of the condition.

Limitations

This systematic review has several limitations that should be considered when interpreting the findings. First, the included studies generally involved small and unequal sample sizes, reflecting the rarity of classical CAH but nonetheless limiting the generalizability of the results to the broader CAH population. Second, substantial heterogeneity was present across the included studies in terms of outcome measures, study populations, age ranges, and comparison groups. Variations in assessment instruments, along with differences in patient demographics and clinical characteristics, limited direct comparisons across studies and hindered the synthesis of definitive conclusions. Given this heterogeneity, we did not perform a meta-analysis and instead synthesized the findings narratively. In addition, the evidence base was dominated by cross-sectional studies conducted largely in Western settings and focused primarily on adolescents and adults. This does not imply that these age groups are inherently less well adjusted; rather, psychosocial concerns are more readily identified and reported during adolescence and adulthood, and clinic-based recruitment may preferentially capture individuals experiencing distress. Consequently, well-adjusted females with CAH and good clinical control may be underrepresented. Moreover, most studies compared females with CAH to healthy controls rather than examining differences within the CAH population, for instance, disease severity, treatment history, or adequacy of hormonal control, which may introduce selection bias and limit clinical interpretability. Consequently, the findings should be interpreted cautiously, and future research using standardized outcome measures, more diverse and representative cohorts, and within-CAH comparisons is warranted to improve comparability, external validity, and clinical relevance.

CONCLUSION

Females with C-CAH demonstrated impaired self-perception of reproductive health in several domains, including reduced sexual satisfaction, dissatisfaction with

genital appearance, doubts regarding gender identity, and gender dysphoria. They also appeared to be more vulnerable to mental health problems, particularly anxiety disorder, social phobia, and social distress, alongside behaviors suggestive of maladaptive coping, such as self-isolation, self-harm, and substance abuse. In addition, females with C-CAH generally showed lower quality of life, especially in the domains of general health and pain, including dyspareunia and pelvic pain. The multifactorial nature of these issues highlights the need for broad and coordinated support from families, local communities, and healthcare professionals. Considering the heterogeneity and small number of included studies, future research should prioritize longitudinal designs, and the inclusion of more diverse and well-adjusted CAH populations, and standardized outcome measures. Further comparative analyses within CAH subgroups, considering disease severity, hormonal control, surgical history, sex of rearing, and sociocultural context, are also essential to better inform individualized and multidisciplinary care for females with C-CAH.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
WJT: Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript, Project administration; **MN:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **JVS:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **AFL:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **SRW:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript; **LAP:** Conceptualization, Methodology, Validation, Acquisition of data, Formal analysis, Interpretation, Writing – original draft preparation, Writing – review and editing, Visualization, Final approval of manuscript, Supervision.

Data Availability Statement
Datasets generated and analyzed are included in the published article.

Author Disclosure
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None.

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