Depression in Women: Potential Biological and Sociocultural Factors Driving the Sex Effect

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Abstract

Important sex-related differences have been observed in the onset, prevalence, and clinical phenotype of depression, based on several epidemiological studies. Social, behavioural, and educational factors have a great role in underlying this bias; however, also several biological factors are extensively involved. Indeed, sexually dimorphic biological systems might represent the underlying ground for these disparities, including cerebral structures and neural correlates, reproductive hormones, stress response pathways, the immune system and inflammatory reaction, metabolism, and fat distribution. Furthermore, in this perspective, it is also important to consider and focus the attention on specific ages and life stages of individuals: indeed, women experience during their life specific periods of reproductive transitional phases, which are not found in men, that represent windows of particular psychological vulnerability. In addition to these, other biologically related risk factors, including the occurrence of sleep disturbances and the exposure to childhood trauma, which are found to differentially affect men and women, are also putative underlying mechanisms of the clinical bias of depression. Overall, by taking into account major differences which characterize men and women it might be possible to improve the diagnostic process, as well as treat more efficiently depressed individuals, based on a more personalized medicine and research.

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Introduction

According to cross-national epidemiological research, depression affects women in at least double the percentage of men, regardless of ethnicity and socioeconomic conditions [1]. Depression in women has clinical and course peculiarities that make specific etiopathogenetic factors plausible. Indeed, atypical symptoms such as hypersomnia, hyperphagia, and hyperreactivity of the mood, greater vulnerability to stress, seasonality, longer duration of episodes, higher recurrences, and greater

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chronicity are much more represented in female patients [2]. In addition, several studies reported an earlier age of onset in women [3] and also suicide attempts are more frequent, although women have less lethality, compared to men [4]. Furthermore, comorbidity with anxiety disorders is very frequent in females, while males more often experience substance and/or alcohol abuse [5]. Some reports also suggest a sex-specific responsivity to antidepressant treatment, describing that women respond better to selective serotonin reuptake inhibitor antidepressants, while tricyclic antidepressants are better suited for men [6]. Notably, clinical trials often include women, but sex is rarely considered as a factor to stratify treatment response [7]; therefore, there is an increasing need for these clinical observations to be placed within a new way of looking at medicine, a precise and personalized medicine that captures in sex a specific factor.

Brain Differences

Based on the different clinical phenotypes of depression observed in males and females, it is intuitive to consider the sex differences of human brain as a potential underlying ground. Indeed, for many decades imaging studies have investigated the morphological and functional differences distinguishing human male and female brains, to explain their typical differences of characters and aptitudes.

Firstly, considering the overall brain mass and volume, it has been constitutively recognized that males have a larger brain volume, compared to females, even after correcting for total body size [8]. Interestingly, for many years, most of the studies reported a higher grey-white matter ratio in females, ranging from 4 to 7% [9]; however, grey-white matter ratio has been demonstrated to be a function of brain size itself; hence, when including total brain volume (brain volume excluding meninges and ventricles) as a covariate, the sex differences become greatly reduced, meaning that larger brains bear a larger grey-white matter ratio compared to smaller ones, regardless of sex [10]. These subtle dissimilarities observed when considering general brain macro-aspects cannot explain the fan of nuances that characterize males and females, but differences occurring in specific brain regions might better represent the substrates for the sex-related diversity of many aspects, including the clinical expression of psychiatric symptoms. Indeed, it has been shown, in the general population, that brain regions such as the thalamus, corpus callosum, and cingulum, for the white matter, and parahippocampal, middle frontal and transverse temporal gyri, among others, for the grey matter, are morphologically different between the two sexes [11].

Furthermore, sex-different neural connectivity and functionality might be an important factor contributing to the diverse vulnerability and to the manifestation of different clinical phenotypes in females. Based on decades of research conducted in the general (control) population, regarding structural connectome analyses there is a vastity of heterogeneous, mild, and often not-replicated findings. Indeed, although there are studies that showed some interesting differences between males and females, including greater intra-hemispheric connectivity in males, versus higher inter-hemispheric connectivity in females [12], a critical consideration of such results, in the light of more recent approaches and methodological considerations, highlights that those modest differences can be explained by correcting for brain size [8]. As for the research on functional connectome, in both resting state and task-based analyses, including language, spatial, and emotional-related ones, again overall there is a high heterogeneity, due also to methodological inconsistency and a lack of consensus sex effect [8] able to explain the different vulnerabilities between males and females in developing depression across life.

Switching to studies performed on depressed patients, there are reports of sex-by-diagnosis interactions at the level of grey matter volume of many brain regions: in particular, increase in the left cerebellum and reduction in the right superior/middle temporal gyrus, left middle temporal gyrus, and ventro-medial prefrontal cortex occurred selectively in male patients, while a grey matter volume reduction in the left lingual gyrus and dorso-medial prefrontal cortex occurred selectively in female patients [13]. Interesting results have been also reported when focusing on the hippocampus, a region that has been found affected in patients with mood disorders. Indeed, although in the general population this region does not result to be significantly different in the two sexes [14], in the context of first episodes of depression, male patients showed decreased hippocampal volume compared to male controls, a result that was not found in female patients [15, 16]. However, these findings need to be discussed in the light of how the number and duration of depressive episodes impact on hippocampal features. Indeed, a meta-analysis conducted by McKinnon and colleagues identified statistically significant differences in the hippocampal volume of patients compared to controls, but only among those patients whose duration of illness was longer than 2 years or who had more than one disease episode, regardless of sex [17]. The combination

of these different results might suggest that although the progression of disease is one of the strongest factors affecting hippocampal volume and functionality in both sexes, it is possible that differences existing between males and females when the first episode of depression occurs might differentially influence the progression of their illness as well as their vulnerability.

Overall, although it appears that the pre-existing physiological sex-related brain anatomical and functional diversities are not so evident, there is a reasonable basis to suggest that specific brain regions might represent important elements to consider when investigating biological mechanisms driving the sex effect in the context of clinically diagnosed depression. However, findings at the moment are very heterogeneous, reflecting both the complex dynamics of mood disorders and the existing wide assortment of studies' sampling and methodologies. Moreover, it is important to note that neural correlates of depression in females also depend on age and specific hormonal and reproductivity life stages [18], and therefore, these factors play an important role in the epidemiological differences in the development of depressive symptoms between sexes, determining the onset of specific "subtypes" of depression, some of which are specific for females.

Sexual Hormones and Reproductive Life Stages

Hypothalamic-Pituitary-Gonadal Axis

One of the main biological differences between males and females of all mammary species is definitely represented by levels of circulating sexual hormones, which are produced by gonads and are responsible for the development of primary and secondary sexual characteristics, but also have a fundamental impact on the entire body and the brain. Those chemical messengers have in fact a multitude of actions at the central level, including being involved in neuroplasticity, stress response, and mood regulation; therefore, due to their great impact, reproductive hormonal fluctuations might have a fundamental role also in the development of mental health issues. In particular, among classically female prominent hormones, oestrogens have antidepressant properties and can exert neuroprotective actions by modulating synaptic plasticity, regulating neurogenesis and increasing the expression of neurotrophic factors, including the brain-derived neurotrophic factor (BDNF) [19–21]. Similarly, progesterone exerts its neuroprotective actions by increasing expression of several neurotrophins, including BDNF, and also by activating neuronal proliferation signalling pathways [22, 23].

On these bases, to investigate biological mechanisms involved in the sex effect observed in depressed patients, it is important to explore patterns of sex differences across the lifespan by addressing the peculiarities of specific life stages, some of which represent particularly vulnerable periods for females. In fact, the female reproductive cycle determines the presence of periods characterized by hormonal fluctuations, and biological alterations, in particular in puberty, before the onset of each menstrual period, across the perinatal period and during perimenopause. Although physiological, these biological changes have a great impact on females' whole body, and the brain of some might be unable to quickly respond to the hormonal changes occurring during these life stages and time periods, thereby predisposing them to depression. Either biological, environmental, and psychosocial differences might underlie the higher vulnerability of some females to such still physiological hormonal fluctuations.

Among biological aspects, specific genetic factors might play a role, based also on the familiarity of these conditions [24–26]. Among these, polymorphisms within genes encoding for the oestrogen receptor (ER) alpha and beta, in particular the rs2234693 single-nucleotide polymorphism (SNP) of ER alpha, have been proposed to be involved in the increased vulnerability of some women to "reproductive depression subtypes," as portrayed in a recent meta-analysis by Li and colleagues [27]. In comparison, a limited number of studies investigated the role of ER polymorphisms on depression in males, but these generally reported non-significant associations [28]. Another biological mechanism, potentially explaining the different responses to similar hormonal fluctuations among females, might be associated with the role of transcription factor explicated by the ER [29], which could respond differently to the epigenetic machinery in vulnerable females compared to controls. In addition to these biological potential explanations, also psychosocial and demographic factors might play a role in the different responses of some females during these life stages of reproductive hormonal fluctuations and in turn influence also their biology.

Pubertal Depression

According to a recent metanalytic study addressing the sex effect size of depression diagnosis and of depressive symptoms, by age, across national representative studies [30], considerable sex differences for diagnoses emerge at the age of 12 (the youngest age group available) and reach their peak during adolescence, with an effect size of odds ratio (OR) = 3.02 for age 13–15, similar to depressive

symptoms (Cohen *d* value of 0.47 for age 16). After that age, the effect size was reduced and remained stable across adulthood (ORs between 1.71 and 2.02, *d* = 0.20), but still in the direction of an increased prevalence in females, compared to males.

One biopsychosocial explanation of these findings is that the sex difference observed early in adolescence might be associated with early puberty being disadvantageous for girls, but not for boys, for outcomes such as depression and other behavioural dysregulations, a difference that is then flattened when considering age groups from about a decade older onward. Several reasons might be underlying this effect, including early-pubertal girls encountering more peer sexual harassment, increased peer pressure, early sexual activity, and increased body dissatisfaction, compared to boys and on-time girls [31]. Indeed, early puberty, but not age or puberty state per se, represents a risk factor, among others, for developing depression in young females [32, 33].

From a biological perspective, regardless of sex, the pubertal transition involves visible physical development, refinement of brain morphology, and strong changes in the hormonal milieu, which have been found to be a source of mood sensitivity in peripubertal females [34]. In particular, the reproductive hormones undergo important fluctuations and explicate new functions, which are dissimilar between sexes. In females, the increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) orchestrates ovarian maturation and induces a strong surge of oestrogen; conversely, in males, increased LH levels trigger the testes to secrete more testosterone, and the FSH activates the spermatogenesis. Physiologically, these pituitary hormones increase in both sexes; however, while LH increases in a similar manner, FSH is higher in young females than males during peripubertal transition [35]. In addition, although in both sexes the hypothalamic-pituitary-gonadal (HPG) axis is controlled by the negative feedback of gonadal steroids, females have a second control mechanism based on positive feedback associated with the menstrual cycles, an additional form of variability and changes that is progressively established during this period of transition [36]. Indeed, when the oestradiol level increases above specific levels, it further induces an LH and FSH release, each of which lasts less than 2 days and stimulates ovulation.

In turn, these sex differences influence also the physiological feedback regulation that sex steroid hormones have also on the hypothalamic-pituitary-adrenal (HPA) axis, altering its modulation and reactivity [37]. In addition to this, as shown from preclinical studies, in males, but not in females, oestradiol increases corticosteroid-binding globulin, probably protecting males to the excitatory effects of oestradiol on the HPA axis, by decreasing the amount of free corticosterone [37]. This effect of higher excitability of the HPA axis exerted by HPG axis activity, together with higher prevalence of some stressful, as well as traumatic, experiences during puberty in females, as previously mentioned among psychosocial factors, further supports a fundamental role of sexual hormones as central mediator of a biological-X-environmental condition of higher vulnerability to pubertal depression in females, compared to males.

Overall, marked differences emerge during early adolescence in terms of vulnerability to depression, representing a narrowed timeframe, where focusing on associated biological changes might provide a fundamental basis for understanding the depression sexual bias. One further important point to consider is that pubertal transition is indeed a phase of elevated brain plasticity and highly sensitive development. Given the high impact that reproductive hormones have on neurons, the aforementioned hormonal changes, along with the other concurrent physiological biological changes, as well as specific puberty-adolescence environmental factors, not only characterize the higher vulnerability for females in this specific phase of their lives, but can also have substantial consequences on their pubertal neurodevelopment, priming their brain for long-term effect. In summary, the combination of all these risk factors operating in a time window of sensitivity might be responsible for the higher vulnerability to depression of females also in later years and throughout life.

Premenstrual Dysphoric Disorder and Premenstrual Syndrome

A great percentage of females, although considerably variable depending on nationality, experiences, during the luteal phase of menstrual cycle, physical, psychological, and/or behavioural changes, which fall under the definition of premenstrual syndrome (PMS) [38]. However, 3–8% of females of reproductive age experience even more severe psychological symptoms, including irritability, depressed mood, anxiety, decreased interest in usually enjoyable activities, difficulties in concentration, lethargy, appetite, and sleep disturbance, meeting the diagnostic criteria for premenstrual dysphoric disorder [39, 40]. All these traits are common symptoms to major depressive disorder; however, the main difference is represented by the periodicity, the occurrence of these symptoms during the luteal phase, and the improvement within a few days after the onset of menses.
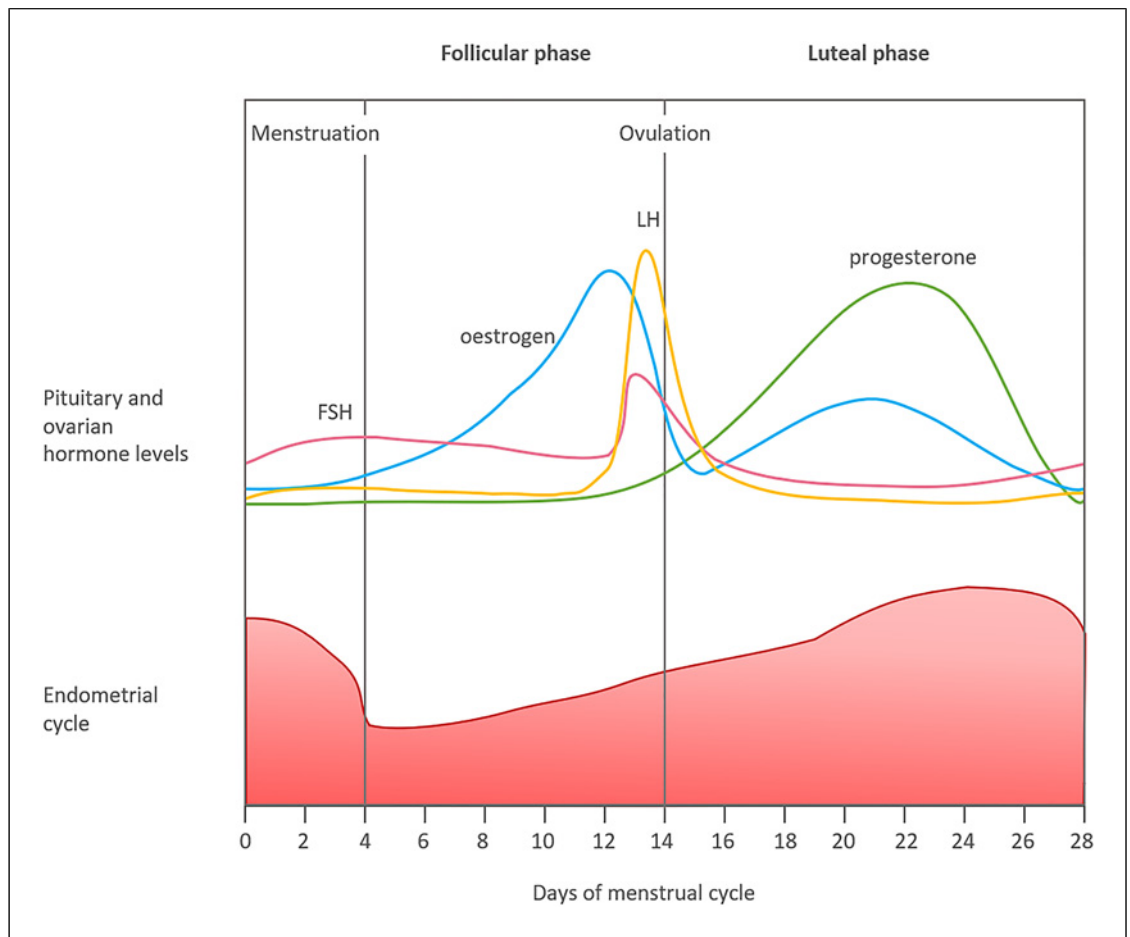
Fig. 1. Pituitary and ovarian hormonal fluctuations and endometrial phases of the menstrual cycle.

The biological mechanisms underlying this disorder are definitely related in some way with the gonadal sex hormone changes occurring in the female body, characterized by the rapid decrement in the levels of steroid reproductive hormones, such as oestradiol and especially progesterone, whereas levels of pituitary gonadotropins, such as the FSH and LH, remain relatively low and stable in this phase [41] (shown in Fig. 1). Indeed, both oestradiol and progesterone have neuroprotective roles [42, 43]; moreover, their sudden decrease can determine important effects at the level of neurotransmitter systems, such as that of serotonin, γ-aminobutyric acid, and dopamine, which can contribute to menstrual-related psychological symptoms in vulnerable females [44]. However, the fluctuating levels of gonadal sex hormones cannot fully explain the development of this type of disorder, and the reason why some females are more vulnerable than others, since hormonal levels have not been found to be significantly different between affected and healthy ones, with relation to the same timeframe of the menstrual cycle [40]. Interestingly, PMS has a strong heritability, and genetic variations at the level of ER sequence have been proposed to be potentially contributing to an aberrant response to hormonal fluctuations [25, 45], and therefore to determine the different vulnerabilities of some women; however, no clear evidence of this correlation is available.

In this context, an important point to discuss is the use, by some women, of hormonal contraceptives, since these influence the levels and fluctuations of circulating reproductive hormones, which in turn might alter the vulnerability to develop depressive symptoms. An adequate discussion should consider differently the various contraceptive administration routes (oral, transdermal, vaginal), composition (combined oestrogenic and progestinic, or progestinic only), and dosage. In general, considering the more recent literature on the topic, from randomized controlled trials, it appears that in females

already suffering from PMS or premenstrual dysphoric disorder the use of oral combined contraceptives does not specifically improve premenstrual depressive symptoms, but improves overall premenstrual symptomatology [46]. As for the general female population, collected results from a recent review point toward a trend for hormonal contraceptives determining an impairment in different aspects of mood-related features, such as emotion recognition and reactivity, reward processing, and stress response, although not limited to the premenstrual phase [47]. Available literature, based on decades of research on the association between use of oral contraceptives and mood symptoms, is very heterogeneous, but in general it seems like the occurrence of depressive symptoms is one of the main reasons for discontinuing hormonal contraceptive use, although the newest generations of these drugs have reduced the percentage of these side effects [48], potentially characterizing a publication bias that needs to be further investigated.

Perinatal Depression

Depression across the perinatal period is a serious and often underdiagnosed medical issue, affecting about 10–15% of females [49]. Indeed, although according to available limited direct comparative studies, the prevalence of depression does not result to be statistically different between pregnant women and non-pregnant women of childbearing age [50], the rate for depression in pregnancy being underdiagnosed and therefore untreated is very high, reaching up to 70–80% [51], higher compared to non-pregnant women of childbearing age [52]. The etiopathology behind this condition remains to be fully elucidated, but is likely to be multifactorial. Psychosocial factors, including lack of support, history of abuse, and high perceived stress, significantly increase the risk for antenatal and postnatal depression [53]; however, dysregulations affecting biological systems, especially those extensively embroiled in the pregnancy, have also been found to play a major role in perinatal depression [54]. Of relevance, during gestation a woman's body undergoes very drastic, but still physiological, changes, including those that involve her hormonal patterns, immune system, and metabolism [55]. These substantial physical adjustments, combined with the challenges and stress of this life-changing experience, can ultimately affect the mental health of vulnerable females.

In the context of pregnancy, labour, and breastfeeding, reproductive hormones undergo considerable fluctuations, which might hold a pivotal role in the onset of perinatal mental health disorders [56–58]. Indeed, pregnancy is characterized by an astonishing increase across the trimesters, followed by a drastic drop at labour, in the levels of oestrogens and progesterone, two classes of hormones with neuroprotective and antidepressant properties [59]. Due to their positive action on the brain, it has been traditionally proposed that their drastic drop during delivery is one of the triggers for postpartum mood symptoms, including the mild and temporary symptoms of *baby blues*, but also more severe manifestations of postpartum depression [58]. Although this theory still holds strong and has been confirmed by some elegant interventional studies [60–62], many other observational studies report null or contradicting results in the association between postpartum depression and low levels of gonadal hormones [63–65]. Additionally, it does not explain why not every new mother develops postpartum symptomatology, nor why depression can occur during gestation, too. Overall, fluctuations of reproductive hormones surely play a great role in pregnancy-related depression, but cannot fully explain incidence of the disorder; therefore, other factors and biological systems must contribute to its aetiology.

In this perspective, the endocrinological milieu of reproductive hormones established during pregnancy also guides an important remodelling of the immune system of expectant women, shifting the balance from higher levels of type 1 T helper (Th1) cells, which are responsible for a pro-inflammatory response, to predominantly higher levels of type 2 T helper (Th2) cells, which in contrast are responsible of the more tolerogenic environment [66], to keep protecting the maternal body from pathogens, simultaneously avoiding alienation of the semi-allogenic foetus [67]. Alterations in this finely regulated Th1/Th2 bias, represented, for example, by an abnormal increase of the Th1 pro-inflammatory activity during pregnancy, might play a fundamental role in the development of perinatal depression, consistent with the neuroinflammatory theory of depression [68]. However, results are very heterogeneous, and other biological mechanisms can be potentially involved, in a complex, intercorrelated manner, reflecting the uniqueness of this period of women's life.

Among other biological systems, the HPA axis also undergoes, during the perinatal period, important remodelling, highly influenced by reproductive hormone fluctuations [69, 70]. However, also in this regard, heterogeneous results have been collected in the literature, since both hypercortisolaemia and hypocortisolaemia have been associated with depressive symptomatology by differently designed studies, suggesting a dysregulation of the HPA axis without a clear aetiology [71, 72].

Furthermore, metabolism and related factors may also play a role. In particular, a variety of observational and interventional studies have proved the important impact of omega-3 long-chain polyunsaturated fatty acids (L-PUFAs) on perinatal depression incidence [73–75], which is lower in those countries with high intake of seafood, which is rich in these compounds, and in those subjects taking supplements [76]. These molecular components are particularly important since they represent a strategic node linking nutrition, immune system, and brain development and functioning [77–79]. Maternal levels of omega-3 L-PUFAs, such as the eicosapentaenoic acid and docosahexaenoic acid, undergo a progressive decrease during pregnancy, to supply the growing foetus of these components, necessary for the nervous system development [80]. Also, the decrease, during pregnancy of omega-3 L-PUFAs levels, might not return to normal before many months after delivery, especially if women decide to breastfeed [81]. In addition, omega-3 L-PUFAs are also important beneficial modulators for the gut microbiota [82–85], which in turn bidirectionally modulates the activity of hormonal axes (including those of oestrogen, cortisol, and other neurosteroids), of the immune system, and of brain functionality via the gut-brain axis. Following this line of research, several studies have tried to investigate the effect of probiotics in modulating depressive symptomatology in pregnant women. Although this new line of intervention has brought up to still weak positive results, as shown in a recent meta-analysis [86], the alterations observed at the level of the omega-3 L-PUFAs and gut microbiota in the context of perinatal depression might partially support the role of nutrition as one of the environmental factors influencing the vulnerability to develop depressive symptoms experienced only in a percentage of pregnant females [87] and confirm the overall complexity of the pathology and the implication of multiple systems. On these bases, alterations of these biological components might play a key role in the vulnerability for psychiatric disorders in this life period and potentially aggravate the risk associated with other biological, as well as non-biological, variables.

Perimenopausal Depression

Between the approximate age range of 42–52 years old, women approach the perimenopause, a time defined by the World Health Organization as "the period immediately prior to the menopause, when the endocrinological, biological, and clinical features of approaching menopause commence, and until at least the first year after the final menstrual period" [88], which can last for 3–9 years.

Among most characteristic traits of this phase, there are: an important decrease in sex steroid levels, vasomotor symptoms (commonly called hot flashes), vaginal dryness, and loss of libido [89]. In this context, the risk of developing depressive symptoms is increased, although a clear association with raised depression diagnosis has not been proved yet [90].

While men also experience a similar phase, called andropause, this happens later in life compared to women (from 50 years old onward) and with different and less pronounced biological, physical, and psychological features: unlike the rapid decreases in hormonal levels that occur in women during menopause, total testosterone levels in men remain more stable over the years [91, 92]. Moreover, men can be potentially fertile up until the eighth decade of life, experiencing only a limited androgen deficiency, which can occasionally be accompanied by weakness, fatigue, sexual dysfunction, depression, anxiety, irritability, insomnia, memory impairment, and reduced cognitive function [93]. The milder biological changes reported in men's andropause might also potentially explain the lower vulnerability for depressive symptoms observed in males, compared to the higher percentage of females suffering of depression during this phase of reproductive decline; however, comparative studies are difficult due to the different setting age for these life stages between sexes.

Overall, when assessing sex differences in the context of depression, it is important to consider them in the perspective of different reproductive phases. Indeed, reproductive transitional life stages represent for some women periods of high risk for the onset or exacerbation of depressive symptoms, thus determining the development of different specific biotypes of depression, alongside the overall higher prevalence of depression in females. All these subtypes have in common to occur in reproductive transitional stages, with significant sex hormone fluctuations serving as their primary defining feature.

Stress and HPA Axis

Depressive disorders have been frequently associated with a dysregulation in one of the major stress response systems, the HPA axis. Neuroendocrine research confirms in fact that depressed patients show altered levels and responsivity of cortisol, due to an altered activation of the HPA axis, although results are very heterogenous [94]. It is important to note, however, that this biological system is also characterized by sexual differences,

markedly influenced by sex hormones based on a complex HPA-HPG axis mutual interaction. In particular, both androgens and oestrogens can regulate stress responsiveness via regulation of cortisol receptors activity; however, while testosterone seems to have an inhibitory role in the HPA axis function, studies on oestrogens and progesterone suggest a sensitizing function [95, 96]. On these bases, monthly hormonal fluctuations and oral contraceptive use can further influence women's cortisol response [97–99]. For these reasons, sex-related HPA axis differences might be involved in the diversity of depressive phenotypes between males and females.

In this perspective, different studies have reported a greater HPA axis response after exposure to psychological stressors in males, compared to females (controlled for their cycle phase and use of hormonal contraceptives) [100, 101], and, interestingly, this was maintained also when taking into account depressive symptoms, which predicted for a flatter cortisol response curve in females, compared to males [102]. However, females are considered to subjectively experience more stress than males and report more somatoform symptoms and show higher stress vulnerability. Overall, the sexually different interactions between the HPA and HPG axes may lead to differential onset, magnitude, and resolution of endocrine responses in males and females during stressor exposure, and ultimately expose the two sexes to a diverse vulnerability and clinical features of depression.

Immune System and Inflammation

When investigating biological substrates potentially responsible for the sex differences in depression, the immune system represents a putative target. Indeed, a large part of the existing research in the field of biological psychiatry has focused its attention on the bidirectional correlation between inflammation/immune activation and psychiatric illnesses, laying the bases for the neuroimmune theory of depressive disorder [103]. Inflammation plays a key role in initiating depression among a subset of individuals, and depression also has inflammatory consequences; however, the exact mechanisms of this intercorrelation are yet to be completely explained [104]. Moreover, inflammation affects behaviour in a transdiagnostic way spanning from mood disorders, schizophrenia, neurodegenerative disorders, and medical illness, and those findings are not consistent across all affected patients. Indeed, only subgroups of depressed patients have been found to exhibit increased levels of C-reactive protein (CRP), peripheral blood chemokines and cytokines (interleukin (IL)-6 and tumour necrosis factor-α the most studied), microglia activation, and monocytes trafficking to the brain [105–107]. The underlying involvement of inflammation might be therefore a fundamental attribute in order to explain the nuances of clinical phenotypes of depression in the perspective of biological sex.

Indeed, similar to depression, autoimmune diseases have a higher female prevalence: females have a twofold to ninefold greater risk of specific autoimmune diseases compared to males, including lupus, Hashimoto's thyroiditis, and rheumatoid arthritis [108], and conversely having an autoimmune disorder represents a risk factor for developing a mood disorder [109]. In fact, the immune system is characterized by marked sex differences in immune cell number, ratio, and activity. In particular, females have a higher number of different peripheral immune cell types, including Th2 cells, B cells, and neutrophils, and show a more robust response to infections, with increased phagocytic capacity and higher production of specific cytokines [110]. Furthermore, at the central level, the morphology, the number, and the functionality of microglial cells, which act as "*macrophages of the brain*" have been shown to be sexually dimorphic, in relation to specific brain areas and stages of brain development, based mainly on preclinical studies on rodents [111–114], but also supported by clinical studies in Alzheimer disease post-mortem brains [115]. Interestingly, the X chromosome contains more immune-related genes than any other chromosome, and some of these genes, including those coding for the CD40LG protein (expressed on T cells), the toll-like receptor 7 [116], and the CXCR3 chemokine receptor, defy X-inactivation mechanisms, leading to a double dose of the gene product in females [117, 118]. In this perspective, due to the great involvement of immune modulation in the development of mood disorders, these sex differences in components of the immune system may contribute to sex diversity in depression.

Interestingly, in a recent study, depressed women were reported to have increased levels of IL-6 compared to depressed men, and higher IL-8 and interferon-γ, and decreased levels of IL-5, compared to healthy women, from a panel of pro- and anti-inflammatory serum cytokines. Within the male comparison, on the other hand, no significant difference was identified between depressed and controls [119]. Along with these results, in another study, CRP levels were found to be significantly positively associated with depressive symptoms in females, but not in males [120]. Taken together, these findings suggest an increased reactivity of the female immune system in the

context of depressive symptoms, which could be an underlying causative mechanism to their general higher vulnerability. However, other biological systems might also be involved in the etiopathology of this disorder and related complications.

Metabolism and Obesity

Being overweight and/or obese are medical conditions which are widely spread in high-income countries, but also dramatically on the rise in low- and middle-income ones. It has been largely demonstrated that pathological excessive weight can lead to many severe health implications, including diabetes, cardiovascular diseases, and cancer, but, in addition to these, it has been shown how obesity and being overweight represent also risk factors for the development of depressive symptomatology [121].

Since the causes of obesity are both biological and social, the epidemiology of this disease can vary greatly by demographic factors. Overall, the prevalence of obesity is higher in females, compared to males, although the magnitude of this difference varies among countries and ethnicities [122]. Sociocultural differences play a major role in the increased vulnerability of women, based on, for example, the higher likelihood of men to do physical jobs, or the higher acceptance of being overweight for women, in some still developing countries, since this physical form is more relatable with maternity and nurturing. On the contrary, in already developed countries, there is an increasing pressure on women to be thin in order to conform to the generally accepted standard of beauty. This view, and the consequent stigma addressing overweight females, might be an underlying cause for the increased incidence of comorbid depression in overweight and obese females, compared to male counterparts from the same weight categories [123]. Accordingly, findings from a recent study suggest that, in the context of major depressive disorder, depression severity is positively associated with multiple obesity measures, including body mass index, total body fat, and visceral fat mass, only in depressed women, while these associations are not found in depressed men [124]. Although sociocultural differences across countries play a fundamental role to be accounted for, it is interesting to consider that a worldwide survey from 2008 estimated that the relationship between total obesity and depressive disorder is also moderated by sex, since, in the pooled OR from the different countries assessed, it resulted significant only among females [125].

In addition to the sociocultural differences, biological mechanisms might also be involved in the sex-driven bias of obesity and potentially represent a link also with the increased vulnerability to depression in females. In this perspective, there is a consistent sexual dimorphism regarding the distribution of body fat, mainly guided by levels of gonadal hormones, with males and oestrogen-deficient post-menopausal females showing accumulating abdominal and visceral fat, whereas pre-menopausal females display more gluteo-femoral fat [126]. Furthermore, metabolism and energy homeostasis are differentially regulated in the two sexes: females have lower daily energy expenditure, tend to lose body fat less consistently after high physical activity, and have higher energy intake after exercise, compared to males [127, 128]. The observed android and gynoid metabolic differences might represent a substrate of increased vulnerability in women for obesity and depression, based also on interaction with other biological systems.

Indeed, similar to depression, obesity is also linked to an increased systemic inflammatory status, since the adipose tissue from obese individuals releases pro-inflammatory cytokines, creating chronic systemic inflammation [129]. Multiple studies have shown that many individuals with obesity and/or major depression express high levels of pro-inflammatory cytokines, and further analyses have allowed to demonstrate that the pro-inflammatory profile of some depressed patients can be partially related to obesity [130]. Therefore, since the association between body fat and CRP is stronger in females [131], plus they generally have a higher relative adiposity percentage compared to males [126] and are at higher risk for autoimmune disorders characterized by aberrant inflammation, it is possible to suggest that the spiralling interaction among obesity, inflammation, and stress might be partially responsible for the increased vulnerability to depression for females.

Interestingly, one recent large study tried to uncover the causal role of high BMI on depression, in an attempt to disjoin the sociopsychological component of obesity. In particular, their approach was based on the use of data of genetic variants associated with high BMI and with or without its adverse metabolic profile, and further analysed the results in males and females separately [132]. Their model resulted in a genetic profile of higher BMI, with or without adverse metabolic profile, to be strongly associated with higher odds of depression, especially in females. Although these findings are far from explaining the specific aetiology of this association, and its biological basis, it is clear that there is a bidirectional correlation between obesity and depression and that biological sex might be a fundamental covariate. As reported in a recent systematic review from Blasco and colleagues [133], the results from
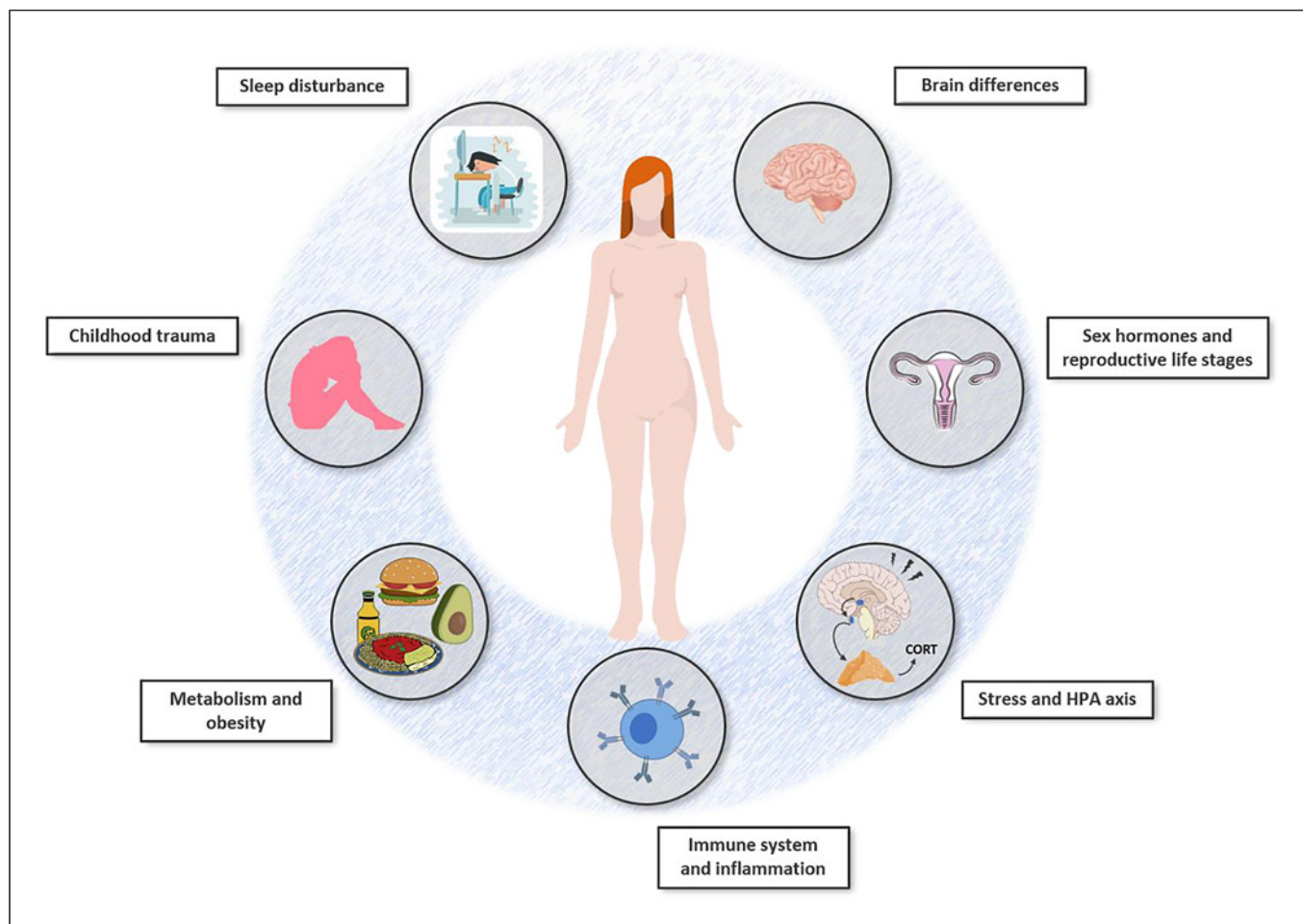
Fig. 2. Biological systems and risk factors potentially involved in the different prevalence and clinical phenotype of depression in women, compared to men.

collected studies confirmed that depression is a risk factor for obesity, but also obesity is a risk factor for depression, especially in females [134]. Another study from 2022 confirmed a sex-based different association between metabolically healthy obesity and depression [135]; however, the effect of sex in this correlation has not been strongly confirmed in overall literature, as reported in other studies with negative findings for sex mediation [121].

The findings discussed so far provide a solid basis for the involvement of the investigated biological mechanisms in explaining why women have a twofold higher lifetime risk of developing depression, compared to men. On the other hand, although very promising, the differences in the mentioned systems and the different life stages are commonly shared also by females who otherwise do not develop depressive symptoms. The com-

bination of these biological factors of vulnerability, together with a genetic unfavourable background, might be synergistically involved. However, other factors of environmental and psychosocial nature, with a close impact on the biology of both males and females, are worth to be mentioned. Some of these will be briefly described in the next section.

Other Risk Factors

Childhood Trauma

Traumatic events experienced during childhood represent known risk factors for the development of depression at any point during life, in both males and females [136]. It is important to note that incidence of childhood trauma, regardless of type, is not statistically different

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between the two sexes; however, specific types of traumatic experiences, especially sexual abuse and assault, have 3 to 4 times higher rates in young girls compared to boys [137]. Interestingly, a recent study showed notable differences in the association between childhood maltreatment and depressive symptoms in an allostatic load model, with significant results in females only, although allostatic load was not significant as mediation factor [138].

Current research is still focused in trying to reveal the causative link between childhood trauma and the development, even decades later, of depression. Childhood adversities yield a myriad of deleterious and long-term effects on brain circuitry, inflammation, stress responsivity, cognitive functions, and general health, all of which can ultimately contribute to the onset of depressive symptomatology [139, 140]. From a biological point of view, excessive psychological stress appears to cause sensitization of the immune system and an excessive immune response to further stressors, which can lead to excitotoxicity and can interfere with normal neural development patterns in such a fundamental and delicate period for brain development, like childhood [140, 141]. Indeed, both the central nervous system and the immune system develop in concert in the early stages of life, up until adolescence. On these bases, early traumatic experiences and strong stressors have a deep impact on both systems, which, as previously discussed, are particularly vulnerable in females.

Sleep Disturbances

When considering common symptoms of depression, sleep disturbances are among the major complaints, affecting up to 90% of patients, with an increased prevalence in women [142]. However, more recently, a growing interest has been focused in demonstrating that sleep disorders, and particularly insomnia, not only are core symptomatic manifestation of depression, but also can represent an independent risk factor for subsequent depression [143]. Indeed, a bidirectional relationship exists between depression and sleep health; however, the mechanisms by which sleep disturbances can act as biological risk factors for depression are still unclear. Observational and experimental manipulation studies have shown that sleep disturbances are associated with an increase in the inflammatory state, in particular an increase in the circulating levels of CRP, IL-6 and tumour necrosis factor, activation of the nuclear factor-kB transcription control pathway and of signal transducer, and activator of transcription family proteins [144]. Epidemiologically, females are at higher risk for developing specific sleep disorders, including insomnia, restless leg syndrome, and idiopathic hypersomnia, compared with males; therefore, this higher vulnerability may pose them at a further sex-specific risk for developing a depressive disorder during their life [145, 146].

Conclusion

Decades of epidemiological research have revealed important sex-related differences in the onset, prevalence, and clinical phenotype of depression. Underlying this disparity, there are social, behavioural, and educational factors, which are dependent on the cultural environment; however, biological factors undeniably play a role in the sex effect of depression. Sexually different biological systems might represent the underlying ground for these disparities, including cerebral structures and neural correlates, reproductive hormones, stress response pathways, the immune system and inflammatory reaction, metabolism and fat distribution, and many other systems which are found to be differentially regulated and functioning between males and females (shown in Fig. 2). In this review, we have tried to dissect the role of each of these systems separately, to provide a comprehensive overview of biological factors potentially playing a role in the sex difference of depression. However, it is clear that all of the mentioned systems are profoundly interconnected, and therefore, it is necessary to take into consideration their multidirectional influence on each other, especially among stress, glucocorticoids, the immune system, and reproductive hormones, which are known to heavily modulate each other. Also, sociocultural and epidemiological differences need to be accounted as covariates of biological factors.

Based on all these observed differences, it is important to develop a medicine and research that takes into account sex, with a particular focus also on specific age and life stages of individuals. Indeed, females experience during their life specific periods of particular vulnerability, which can be associated with unique biological alterations, and that are not found in males. In this way, it might be possible to tackle this medical issue in a more efficient manner and improve also the diagnostic process, by allowing, for example, a better distinction of frequent physiological traits of these periods of the reproductive life, from actual symptoms of psychiatric disorders. Ultimately, this might lead to identify specific biomarkers and develop personalized therapies, through the lens of biological sex.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.G.D.B. and P.L. wrote the first draft of the manuscript. C.M. and A.C. reviewed the first draft and finalized the paper. All authors contributed to and have approved the final manuscript.

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