Movement Disorders
CLINICAL PRACTICE
REVIEW

Unveiling the Role of Sex Hormones and Reproductive Life Factors in Parkinson's Disease

*Roberta Bovenzi, MD,** *Clara Simonetta, MD, Maria Mancini, MD, Veronica Buttarazzi, MD, Alessandro Stefani, MD, PhD, and Tommaso Schirinzi, MD, PhD*

Abstract: Biological sex shapes the risk, presentation, and progression of Parkinson's disease (PD). Nevertheless, the pathophysiological bases remain poorly understood, and sex-specific and hormonal factors are still insufficiently explored in both research and clinical practice. In the first part of this narrative review, we synthesize the most relevant evidence on sex-specific aspects of PD, including epidemiology, genetic bases, motor and non-motor features, and disease progression. We then explore sex-specific biological underpinnings revealed by translational, neuroimaging, and neurophysiological studies. In the second part, we summarize the roles of sex hormones in PD and of reproductive life factors, from menarche to pregnancy, focusing particularly on women with PD. With this review, we aim to highlight a still underexplored dimension of PD and the importance of systematically considering sex, reproductive life, and sex hormones, from experimental research to clinical care. Recognizing and integrating these factors is essential for achieving more individualized and equitable care.

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by nigral degeneration and variable extranigral involvement. Epidemiological data show that PD is more prevalent in males than in females, with substantial sex-related differences in both motor and non-motor manifestations. Overall, women tend to exhibit a more "benign" phenotype and a slower disease progression, suggesting a dual level of protection, both in disease susceptibility and clinical expression.[1] Beyond clinical features, sex-specific differences have been reported at the molecular and systems levels. Nevertheless, although the concept of sex-specificity in PD is increasingly recognized, it remains underestimated in experimental research and in tailored clinical management. Furthermore, the bases of such differences, whether biological, environmental, or social, are not fully elucidated.[2] Although sex hormones are unlikely to be the sole determinants of such dimorphism, compelling evidence supports their contribution, from preclinical studies to real-world observations of the impact of reproductive life factors in women with PD.

In this narrative review, we first summarize the main sex-related differences in PD, encompassing epidemiology, genetics, clinical phenotype, and treatment response, and discuss emerging evidence from translational, imaging, and neurophysiological studies. In the second part we then focus on the role of sex hormones in shaping these differences, reviewing preclinical data on steroidal sex hormones and gonadotropins, and emphasizing the role of the entire hypothalamic–pituitary–gonadal axis in PD in both sexes. Particular attention is then given to the female perspective, exploring how physiological hormonal fluctuations across reproductive life may modulate disease risk, expression, and progression. Through this approach, we aim to highlight the importance of considering not only biological sex but also hormonal and reproductive life factors in understanding PD pathophysiology, with relevant implications for the development of tailored management strategies.

Sex-Specific Clinical Differences in PD

Epidemiology

Both the prevalence and the incidence of PD are reported to be 1.18–2-fold greater in males than in females.[3,4] The male-

Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy

***Correspondence to:** Dr. Roberta Bovenzi, Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier, 00133 Rome, Italy; E-mail: roberta.bovenzi@gmail.com
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to-female ratio progressively increases with age[5] and approaches one in early-onset Parkinson's disease (EOPD), where genetics plays a predominant role.[4]

The male-to-female ratio in PD prevalence appears to have decreased over recent decades, possibly reflecting changes in occupational exposure, diagnostic awareness, and female longevity.[6] Geographical variability has also been reported. Indeed, the male-to-female ratio is higher in Western countries, where men have traditionally held agricultural and industrial occupations associated with greater exposure to pesticides, heavy metals, and head trauma, factors known to increase PD risk.[7] Conversely, in regions such as Middle and South-Eastern Asia, where women are predominantly involved in the agro-alimentary workforce, the sex ratio in PD is more balanced.[4]

Intrinsic biological factors may also contribute to sex differences in PD risk. Metabolic syndrome or cardiovascular risk, both associated with PD risk, are more prevalent among males.[8] Moreover, lifestyle factors such as smoking and caffeine consumption, both "protective" factors, are more common in men and could contribute to the apparent sex gap.[1] Additionally, diagnostic and survival biases may play a role.[9] Finally, underdiagnosis or delayed recognition in women, possibly due to milder phenotypes or lower referral rates to specialized care, may further contribute to the observed differences.[1]

Genetic Bases

Together with sex hormones, and possibly through a crosstalk, the genetic bases of PD may contribute to its sex dimorphism.

Among monogenic forms, variants in *GBA1* and *LRRK2* display sex-related differences in frequency and clinical expression. Some studies report that *GBA1* variants, particularly those classified as severe, occur more frequently in women, whereas *LRRK2*-associated PD (especially carriers of the *G2019S* variant) shows a more balanced male-to-female ratio than idiopathic PD.[10–12] However, large-scale analyses from the International Parkinson's Disease Genomics Consortium and the UK Biobank have not found any significant sex-related genetic differences in PD.[9] Sex might also shape the phenotype of genetic forms, as males with *GBA1*-PD show worse cognitive outcomes and faster progression, suggesting sex-specific vulnerability of cognitive networks.[13] On the other hand, *LRRK*-PD displays less clinical heterogeneity between sexes than idiopathic PD.[14]

Beyond monogenic forms, Mendelian Randomization (MR) studies have explored sex-related genetic pathways in PD. Genetically predicted sex hormone levels differentially influence PD risk in men and women,[15] and genetically predicted age at menopause modulates PD risk in females.[16] Other MR and GWAS studies have identified risk variants showing pleiotropy between PD and reproductive life factors, despite the lack of clear sex-specific differences in allele frequencies at PD loci.[17]

Differences in X and Y-linked gene expression also contribute to the sexual dimorphism of the disease. X-linked parkinsonism, such as *RAB39B*-related PD or X-linked dystonia-parkinsonism (XDP), predominantly affects males, while female carriers usually exhibit incomplete penetrance or milder symptoms. Conversely, the *SRY* gene on the Y chromosome regulates dopamine biosynthesis, indicating a "male-specificity" in dopaminergic metabolism.[18]

Finally, transcriptomic analyses have demonstrated sex-specific regulation of several PD-related genes involved in microglial activation, lysosomal function, and mitochondrial homeostasis,[19] which may reflect hormonal modulation of gene transcription.[20]

Motor Features

Male and female PD patients differ in the clinical phenotype of the disease, ranging from motor to non-motor manifestations.

First, women's age at onset (AAO) is about two years higher than men's.[3] Moreover, female PD patients more frequently present tremor as the first manifestation and in the course of the disease,[21,22] whereas rigidity and stiffness are more often reported in males.[23] Postural abnormalities such as camptocormia, anterocollis, and Pisa syndrome, together with freezing of gait,[24] all more frequently associated with worse cognitive outcomes,[25] are reported more frequently in males, and the male sex is a recognized risk factor for such complications.[26]

Conversely, in a recent study of patients with EOPD, dystonia, both at disease onset and as a levodopa-induced motor complication, was more frequently observed in females than in males, and sex hormone levels were found to correlate with this feature, suggesting a role for the lower testosterone levels typically seen in women.[27]

As for motor progression, recent data from the Parkinson's Progression Markers Initiative (PPMI) database showed a faster disease progression in terms of both MDS-UPDRS-III and levodopa equivalent daily dose (LEDD) requirements over time in male PD patients compared to females,[28] confirming the results of previous studies finding higher disease progression and mortality rates in males.[29,30] However, other studies have found no differences in disease progression between the two sexes.[31]

Non-motor Features

Several studies have reported sex differences in the overall non-motor symptoms (NMS) burden in PD,[32] with heterogeneous results. A large multicenter study in Italy found that males had a higher prevalence of nearly all NMS compared to females,[33] whereas other studies have found more severe NMS in women.[34]

Regarding specific NMS domains, male PD patients face a higher risk of cognitive impairment and dementia,[13,35] with a specific susceptibility to decreased verbal fluency,[36] and a more frequent physical and verbal aggression and socially inappropriate behavior.[37] Moreover, male PD patients more frequently report sexual dysfunction,[22] hyposmia,[38] and drooling.[7] In contrast, women with PD are more susceptible to neuropsychiatric disturbances such as depression, anxiety, and fatigue,[22] likely reflecting not only biological but also psychosocial factors.

As in the general population, women with PD experience pain more frequently and severely than men,[39] possibly due to

differences in muscle mass, pain processing, and symptom perception.[40] Furthermore, consistent with their greater vulnerability to levodopa-induced complications, females with PD are particularly affected by fluctuation-related and OFF-dystonia pain.[41,42] Female PD patients also display worse gastrointestinal symptoms, including inability to finish a regular meal, nausea, and constipation.[43]

A recent observational study highlighted sex-related differences in cardiovascular autonomic function, showing that males are more prone to orthostatic hypotension and blood pressure variability, whereas females more frequently exhibit symptoms of sympathetic overactivity, such as palpitations and sweating.[44]

Sex differences in sleep have also been observed.[45] Most studies found an overall poor quality and efficiency of sleep in women,[46] who specifically experience more severe sleep disturbances related to nocturnal motor problems, including restless legs syndrome, nocturnal akinesia, OFF-dystonia, painful cramps, and tremor upon waking.[42] Conversely, REM sleep behavior disorder (RBD) shows a male predominance, or at least appears more severe in men, who present more frequent falls from bed and more violent dream content.[47] Moreover, RBD in males has been associated with a higher burden of NMS, including dysautonomia and cognitive impairment, suggesting sex-specific mechanisms underlying sleep disturbances, possibly involving broader multisystem involvement in males and a greater contribution of levodopa-induced fluctuations in females.[42]

Figure 1 provides an overview of symptoms more frequently observed or reported as more severe in women with PD.

Quality of Life (QoL)

Women with PD exhibit a lower QoL and greater disability compared to men, especially regarding bodily discomfort, stigma, and emotional well-being.[48] A cross-sectional study of 569 drug-naïve PD patients showed that female sex, together with disease severity, depression, and fatigue, was identified as an independent predictor of poorer QoL.[48]

Social and cultural influences, as well as differences in healthcare-seeking behavior and access to treatment, are likely to account for a substantial proportion of such sex-specific disparities.[1,49] Women face greater challenges in accessing healthcare services and receive less social support than men, factors that may further influence multiple dimensions of their symptom experience and perceived well-being.[1,49,50]

Fluid Biomarkers

α-Synuclein (α-syn) misfolding plays a crucial role in the pathogenesis of PD. CSF levels of total α-syn inversely reflect both brain accumulation of LBs and synaptic damage, whereas the clinical significance of plasma α-syn remains less clear.[51] One preliminary observational study investigating the influence of sex on α-syn found decreased plasma α-syn concentrations in advanced PD only in men, possibly reflecting greater intracellular accumulation.[52] Moreover, lower plasma α-syn concentrations were correlated with worse cognition, hallucinations, and sleep disturbances in men but not in women.[52] In another study, testosterone levels inversely correlated with CSF total α-syn in male PD patients, suggesting a role of androgens in male vulnerability to PD.[53]

Other fluid biomarkers with potential pathophysiological relevance in PD have also shown sex-specific differences.

Uric acid (UA), the primary product of purine metabolism, is a neuroprotectant that acts as a natural antioxidant and iron chelator.[54] Plasma UA levels are significantly lower in PD patients than in controls and decrease with disease progression and cognitive decline, supporting its potential as a prognostic biomarker.[54] Significant associations between higher UA levels and both lower PD risk and slower motor progression appear stronger in men than in women.[54] Moreover, the neuroprotective effects of UA in women appear to be age-dependent, being evident only at older ages,[55] possibly reflecting the stronger beneficial influence of estrogens during reproductive years.[54]

Elevated homocysteine (Hcy) levels, a byproduct of methionine and folate metabolism, have been associated with PD, although its pathogenic role remains unclear.[56] Higher serum Hcy concentrations are predominantly found in males,[57] and have been differentially associated with greater motor impairment in men and poorer cognition in women.[56]

Finally, neuroinflammation and immune activity, two major drivers of PD pathophysiology, also exhibit sex-related differences.[58] Males with PD exhibit a more pronounced pro-inflammatory profile, with lower lymphocyte counts and higher neutrophil-to-lymphocyte ratios (NLR), whereas females show lower monocyte counts, NLR, and monocyte-to-lymphocyte ratios (MLR). Moreover, immune-based clustering analyses have identified two distinct subgroups in PD: a "high peripheral inflammation" cluster, predominantly composed of male patients and associated with worse clinical features and greater central α-syn burden, and a "low peripheral inflammation" cluster, mainly comprising female patients and associated with milder clinical features and lower central synucleinopathy.[59] These findings align with preclinical evidence suggesting a sexually dimorphic immune response in PD, particularly regarding macrophagic and monocytic populations, which may be relevant to the different risks and progression of PD encountered between sexes.[60]

Neuroimaging

Previous studies have found dimorphic changes in the volume of the basal ganglia and cerebral regions in both patients with PD and aging subjects.[61] Male PD patients exhibit greater cortical and subcortical atrophy than age-matched female PD patients, with greater differences observed in the globus pallidus (GP), as the basal ganglia are among the main brain regions containing sex steroid receptors.[62]

In a recent study using brain MRI and clinical information from the PPMI study, male PD patients exhibited greater atrophy and local anatomical connectivity disruption compared to females from the earliest stages of the disease.[63] Furthermore,

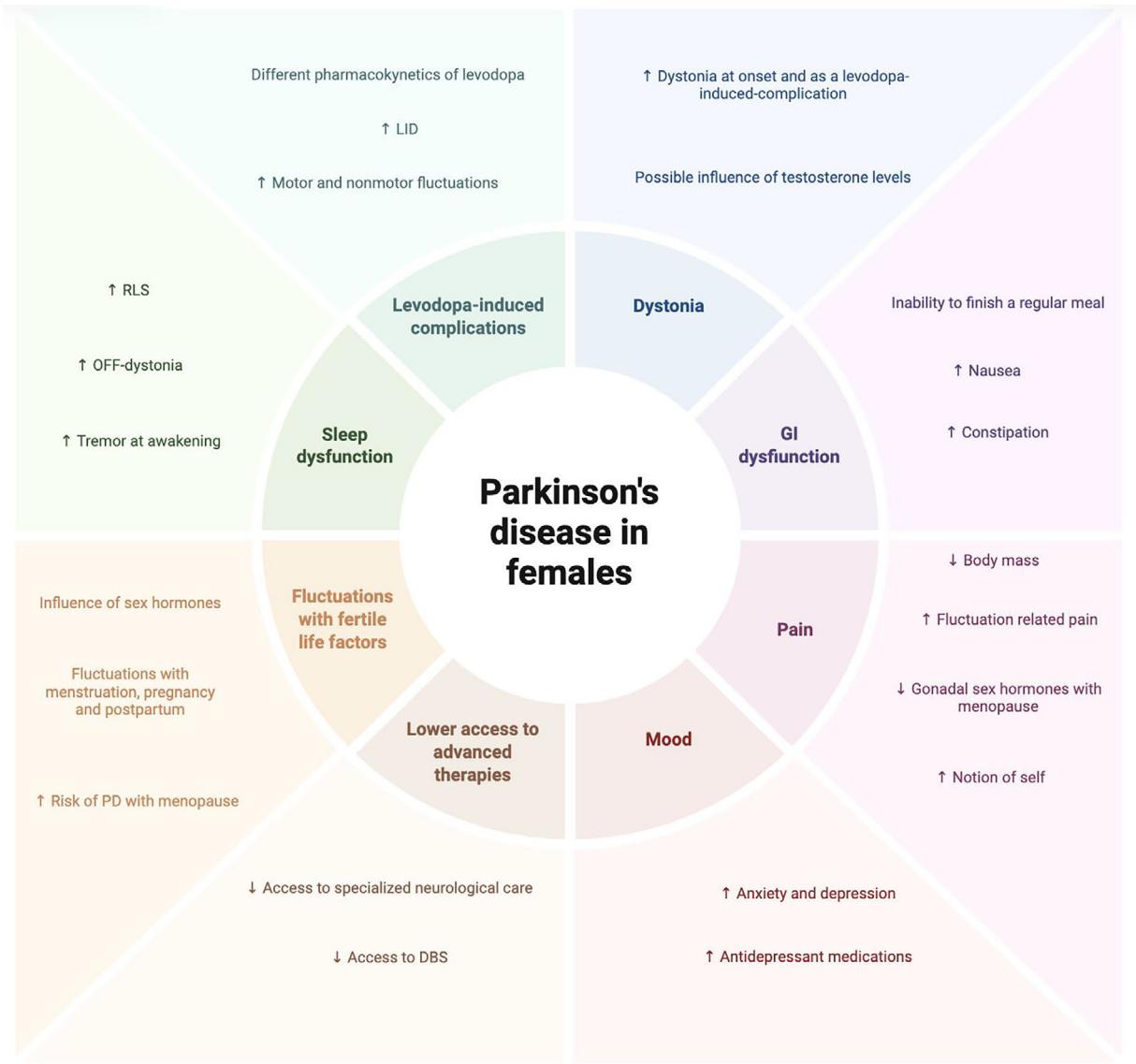

Figure 1. Overview of motor and non-motor symptoms more frequently observed or reported as more severe in women with Parkinson's disease (PD). Women with PD often present with tremor, show a higher susceptibility to levodopa-induced dyskinesias (LID), and more frequently experience sleep disturbances, gastrointestinal dysfunction, and dystonia, both at disease onset and as a levodopa-induced motor complication. Additional features include pain and mood disturbances.

serum testosterone levels have been shown to inversely correlate with GP volumes in male PD individuals,[53] supporting a role for androgens in the greater degree of atrophy observed among males.

As for molecular imaging studies, SPECT imaging studies have reported higher DAT binding in women in both healthy controls and PD patients, with a more prominent effect in the caudate than in the putamen.[64] Whether these results reflect higher baseline striatal dopaminergic function in females remains debated. A higher DAT availability in women may also be related to increased dopamine transmission or turnover.[64] Finally, higher striatal, and especially caudate, FDOPA uptake has been described in both healthy and PD women through PET imaging studies as well.[65]

Brain Connectivity

Overall, PD patients exhibit greater disruptions in morphometric and functional connectivity (FC) than HC,[61] with more profound alterations in males. In an fMRI study, De Micco et al found that male PD patients showed abnormal spectral composition in the slow-5 band of the sensory-motor (SMN) and dorsal attention (DAN) networks, with SMN changes predicting disease severity at follow-up.[66] Conversely, females presented an

"overconnected" SMN, possibly reflecting an increased baseline dopaminergic drive.[66] Similarly, an FDG-PET study reported widespread alterations of the nigro-striato-cortical network in males, with relative sparing of the mesolimbic pathway. In contrast, females exhibited greater mesolimbic changes and only partial nigrostriatal-cortical reconfiguration.[67]

In a study using local field potentials (LFP) to investigate sex-related differences in the oscillatory activity of the human subthalamic area in PD, females displayed higher spectral power in the alpha/low-beta (8–20 Hz) band off-therapy and higher power in the high-gamma (60–90 Hz) and 300 Hz bands after dopaminergic stimulation,[68] suggesting an overall more preserved connectivity.

Finally, a recent high-density EEG-based FC study in early-stage PD identified sex-specific patterns that were influenced by circulating sex hormones.[69] Notably, testosterone levels correlated with altered fronto-parietal connectivity in males, whereas estradiol levels correlated with enhanced interhemispheric connectivity in females,[69] confirming a central role of sex hormones in modulating PD-related functional changes.

Management and Treatment

Biological sex and gender influence the multidisciplinary care of PD patients.[70] Women with PD are referred to clinical settings and movement disorder specialists less readily than men,[71] and receive less social support and caregiving resources,[1] with relevant implications for overall QoL.

Regarding pharmacological treatments, sex-related differences in pharmacokinetics, therapeutic response, and side-effect profiles have also been reported.

Levodopa (LD) remains the most effective drug in the treatment of PD; however, its prolonged use leads to motor complications such as fluctuations and levodopa-induced dyskinesias (LID). Female sex, along with LD dose, disease duration and severity, and younger AAO, are established risk factors for LD-related complications.[72] Wearing-off phenomena and dyskinesias occur earlier and more frequently in women,[73] likely due to sex-specific profiles of LD pharmacokinetics and metabolism. Overall, LD bioavailability is higher in women,[74] only partly due to lower body weight[75] and likely influenced by sex-specific differences in COMT- and MAO-mediated metabolism.[76] Nonetheless, only a few studies have investigated sex differences in the response to COMT and MAO inhibitors. A multicenter Italian study on opicapone, a COMT inhibitor, found no sex differences in the long-term rate of discontinuation of the drug among sexes. However, there were sex-specific differences in the causes of discontinuation: hypotension and psychiatric disorders were numerically more prevalent in males, while disabling dyskinesia and lack of efficacy were more frequently reported in females.[77] Conversely, a post hoc analysis of the SYNAPSES study[78] revealed that the MAO-B inhibitor safinamide improved motor symptoms and complications in both sexes, with good tolerability and no need to adjust concomitant dopaminergic therapy.[23]

Regarding dopamine agonists (DA), only one study investigating the pharmacokinetics of pramipexole found no differences between the sexes.[79] However, when treated with DA, men are more at risk of developing impulse control behaviors (ICBs).[80] Furthermore, biological sex seems to have a prognostic value, as male sex has been associated with more persistent ICBs in a large-scale prospective study.[81] In terms of the content, females are less likely to report compulsive sexual behaviors and, instead, more likely to develop binge eating and shopping habits.[7]

Among treatments for NMS, antipsychotics are more frequently prescribed in male PD patients, possibly mirroring higher rates of aggressive behavior,[82] whereas antidepressants are more common among women, consistent with their higher prevalence of mood disorders.[82]

In the context of neurosurgical approaches, deep brain stimulation (DBS) of the STN and GPi represents an effective option for managing motor complications not adequately controlled by pharmacotherapy. Although STN-DBS provides comparable motor benefits in both sexes[32] and greater QoL improvement in women,[83] implantation procedures are performed up to twice as often in men, a ratio that exceeds the epidemiological differences between the sexes.[83] Studies on DBS and MRgFUS thalamotomy and pallidotomy have shown that women are not only treated less frequently, but also at later disease stages, suggesting a tendency to postpone invasive therapeutic procedures.[84,85] The causes of these discrepancies are not fully understood; however, factors related to gender inequality in access to care cannot be ruled out.[86]

Sex-specific differences in other device-aided treatments (DAT) have also been reported. Females with advanced PD are overall underrepresented in infusion therapy trials.[87] Nonetheless, in our Centre, female patients showed higher compliance with LCIG, possibly due to gender-specific psycho-behavioral traits.[49]

Ultimately, women with PD appear to exhibit a better response to transcranial magnetic stimulation (TMS), possibly due to a greater cortical compensation capacity or delayed maladaptive sensorimotor changes,[88] as demonstrated by functional studies.

Sex Hormones and Reproductive Life Factors in PD

Estrogens

Preclinical Models

Estrogens are the main female sex hormones, produced by the ovaries in women and, in lower concentrations, through the aromatization of testosterone in men.

In preclinical models, estrogens, particularly estradiol (E2), have demonstrated neuroprotective and pro-dopaminergic properties in several central and peripheral nervous system regions.[89] E2 administration reduces dopaminergic depletion induced by several neurotoxicants, such as methyl-4-phenyl-1,2,3,6-tetrahydropyridine

(MPTP), 6-hydroxydopamine (6-OHDA), and methamphetamine.[89] This neuroprotective effect is abolished in the presence of tamoxifen, a potent anti-estrogenic agent.[90] The mechanisms and cellular targets of this protective influence are heterogeneous. Estrogens promote dopaminergic neuronal plasticity, exert antiapoptotic and antioxidant actions, prevent the entry of neurotoxicants by down-regulation of DAT, and ultimately halt α-syn aggregation.[89] Estrogens also exert anti-inflammatory effects by inhibiting NF-κB activity, attenuating microglial activation, and promoting microglial polarization toward the cytoprotective M2 phenotype.[91]

In addition to their neuroprotective actions, estrogens enhance dopamine synthesis and release, reduce dopamine reuptake, and act as direct agonists at striatal D2 receptors,[7] thereby exerting a symptomatic effect.[89] E2 supplementation in ovariectomized animal models induces an increase in the synthesis and release of dopamine in the striatum as well as the density of dopamine receptors.[92] Other hypothesized pro-dopaminergic mechanisms include the downregulation of MAO and COMT enzymes involved in dopamine metabolism,[89] which likely contributes to the sex-related differences observed in LD pharmacokinetics.

Figure 2 summarizes the roles of the main hormones of the HPG axis in PD.

Human-Based Evidence: Reproductive Life Factors

In addition to preclinical evidence, epidemiological observations on female reproductive factors highlight the role of female sex hormones, particularly estrogens, in PD pathophysiology.

Hormonal levels change throughout a woman's reproductive lifespan, influenced by menstrual cycles and pregnancies. Menopause, defined as the cessation of spontaneous menses after 12 months, marks the end of the fertile life of a woman and is characterized by elevated gonadotropins and low E2 and progesterone levels.[93]

Increasing evidence correlates menopause and other reproductive life factors with PD risk and progression. Both incidence and prevalence are higher in postmenopausal than in premenopausal women of the same age.[94] Early menopause (<46 years) has been associated with an increased risk of PD,[95] with a 7% risk rise for each year decrease in age at menopause.[16] Not only the age at

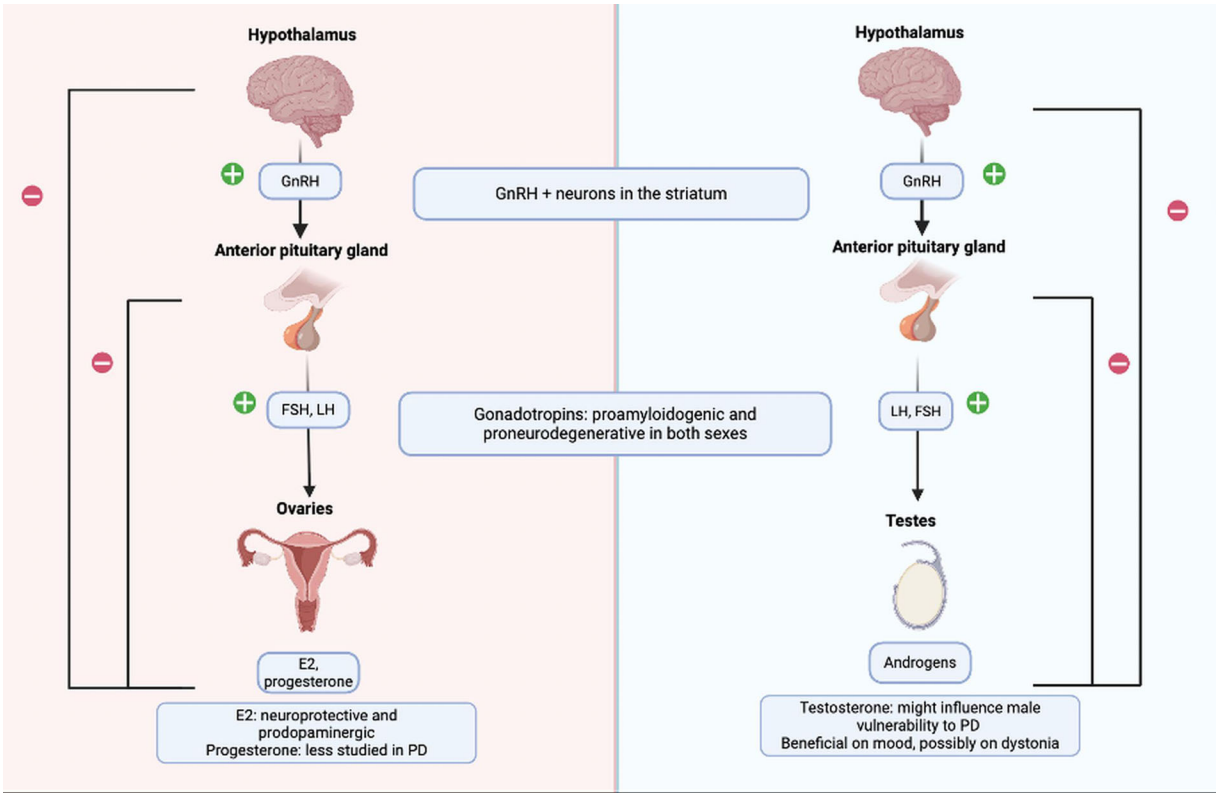

Figure 2. Schematic representation of the hypothalamic–pituitary–gonadal (HPG) axis in females (left) and males (right), and its potential implications in Parkinson's disease (PD). Estrogens exert neuroprotective and pro-dopaminergic effects, while progesterone is less studied in PD. In males, androgens may influence vulnerability to PD pathology, albeit could be beneficial to mood and specific motor manifestations such as dystonia. Gonadotropin-releasing hormone (GnRH) neurons in the striatum and peripheral gonadotropins may mediate age-dependent amyloidopathy and cognitive impairment, suggesting a broader role of the HPG axis in neurodegeneration.

menopause but also its type may play a role, as oophorectomy, whether unilateral or bilateral, and hysterectomy alone increase the risk of the disease.[96] Menopause, especially when surgical, is associated with a higher risk of cognitive impairment and dementia as well.[97]

Conversely, a longer fertile lifespan is associated with a reduced PD risk, whereas a fertile lifespan shorter than 36 years has been linked to an increased risk.[98]

Not only the duration but also the timing of estrogen exposure seems to be determining, as delayed menarche has been associated with delayed PD onset (5-month delay per 1-year increase in menarche age).[21] In a recent study, postmenopausal patients with lower lifetime estrogen exposure showed significantly reduced putaminal DAT uptake and required higher medication dosages, indicating greater nigrostriatal system impairment.[99]

The relationship between PD risk and parity seems to be more complex. While some studies found a protective effect of pregnancy, with the birth of one child delaying the onset of PD by 2–3 years,[29,100] others found that both the number and longer cumulative length of pregnancies were linked to an increased PD risk.[96,98] Indeed, while the E2 neuroprotective and pro-dopaminergic properties are well established, the role of estriol (E3), the dominant estrogen during pregnancy,[101] remains unclear. Furthermore, outside of pregnancy, multiparous women have lower circulating E2 levels than nulliparous ones, leading to lower lifetime estrogen exposure and potentially contributing to an increased PD risk, as suggested by the large E3N cohort study.[96]

Reproductive life factors might also affect PD clinical severity. Cereda and colleagues found that the UPDRS motor score at onset was inversely associated with age at menopause, fertile life length, and lifetime estrogen exposure, whereas delayed menarche was associated with a tremor-dominant phenotype.[21] Other studies found that higher lifetime estrogen exposure relates to milder motor symptoms,[99] or that a short reproductive lifespan is associated with faster disease progression.[31]

Despite strong demographic evidence, only a few studies have assessed estrogen levels in PD. In our cohort, we found that higher E2 levels correlated with better motor functioning (MDS-UPDRS parts III and IV) in both male and postmenopausal PD patients, suggesting that estrogens may act as neuroprotective and pro-dopaminergic agents independently of biological sex.[93] Similar findings were then observed in EOPD patients, where lower E2 levels in females were associated with greater motor impairment and more frequent motor complications.[27]

In EOPD, women face unique challenges related to menstruation, pregnancy, and breastfeeding.[102] Most studies report deterioration of PD symptoms during the week prior to menstruation.[101] The first evidence dates back to 1986, when Quinn and Marsden found that 11 of the 12 assessed women experienced worsening of symptoms during menses.[103] Later reports described improvement with acetazolamide[104] or hormonal therapy.[105] In a survey conducted on 17 PD patients, 60% reported a worsening of symptoms during menses.[106] Similar findings were recently observed in a cohort of genetic Parkin-PD patients.[107]

No significant issues related to fertility, conception, or childbirth have been reported in women with PD.[108] Pregnant PD women were less likely to undergo a cesarean section (15% vs 32%) and to present spontaneous abortion (5% vs 15%) than the general American population.[101]

Managing movement disorders during pregnancy represents a major challenge since the effects of pharmacological treatments on the fetus are mostly unknown.[109] Most evidence reports the safety of LD monotherapy during pregnancy,[107,110] while information on other agents is scarce.[111] Amantadine, instead, appears to be teratogenic.[112] Recently, the MDS Scientific Issues Committee has provided recommendations for the management of PD during pregnancy, which, however, fall beyond the scope of our review.[113] Regarding the effects of pregnancy on the clinical course of PD, the literature remains conflicting but generally points toward a worsening of symptoms during pregnancy and the postpartum period,[110] often exacerbated by medication reduction or withdrawal.[114] Besides hormonal influences, altered pharmacokinetics, changes in diet, variations in intestinal absorption, and physical and psychosocial factors may contribute to the modification of PD features during pregnancy.[101]

Finally, compelling evidence on the neuroprotective and pro-dopaminergic action of estrogens has led to investigating its therapeutic efficacy in various clinical trials, with conflicting results. A recent meta-analysis has shown that estrogen replacement therapy (ERT) in postmenopausal women significantly reduces the risk of developing PD.[115] However, the ERT effect appears to vary according to the formulation and dosage of the hormone therapy, the duration and timing of administration, and some factors of reproductive life, such as the presence of natural or surgical menopause.[99] Notably, ERT has been demonstrated to be protective in the immediate postmenopausal period,[116] but not in advanced menopause, laying the basis for the "critical window hypothesis,"[117] which emphasizes the importance of the timing of estrogen exposure.[21,118–121] The total period of estrogen deprivation after menopause might be a pivotal factor in the influence of exogenous estrogen effects on neurodegeneration as well.[99,122] As for their possible symptomatic effects, studies in women with PD have shown conflicting results, and ERT is reported to either improve motor function[123,124] or worsen it.[125] In conclusion, regarding potential therapeutic implications of estrogens in PD, there is currently insufficient evidence to support routine use. Furthermore, long-term postmenopausal ERT is associated with the risk of cardiovascular events, stroke, breast cancer, and pulmonary embolism,[126] further challenging its use.

Figure 3 summarizes the influence of reproductive life factors on PD.

Progesterone

Progesterone is a steroid hormone produced by the ovaries, placenta, corpus luteum, and in minor concentrations by the

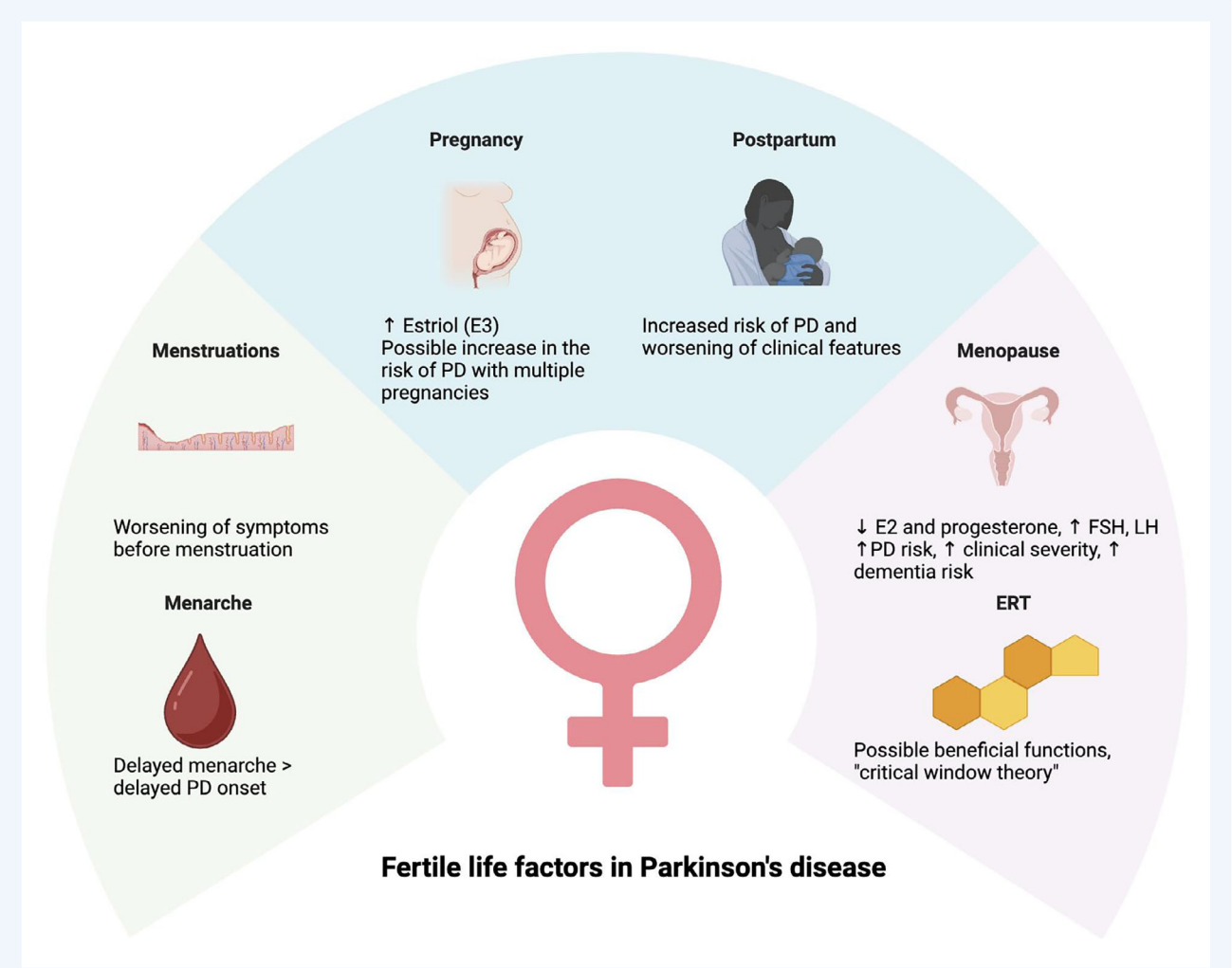

Figure 3. Schematic overview of the main reproductive life events and their potential influence on Parkinson's disease (PD). Menarche: delayed menarche has been associated with a delayed PD onset. Menstruations: symptoms may worsen before menstruation. Pregnancy: increased estriol (E3) levels rather than estradiol (E2) levels; possible rise in PD risk with multiple pregnancies. Postpartum: increased risk of PD and worsening of clinical features. Menopause: reduced E2 and progesterone levels, and increased gonadotropins (FSH, LH) are linked to increased PD risk, greater clinical severity, and higher dementia risk. Estrogen replacement therapy (ERT): possible beneficial effects, particularly under the "critical window theory."

Leydig cells of the testis. Within the CNS, it can be locally synthesized by neurons and glial cells and, being comparably expressed in both sexes, exerts pleiotropic neuroprotective actions, including attenuation of inflammation and reactive gliosis, promotion of neurogenesis, and myelin regeneration.[127]

While the neuroprotective role of estrogens has been extensively investigated, the potential effects of progesterone have received comparatively less attention.[128] Preclinical studies on both PD toxic and trauma models have demonstrated a neuroprotective effect of progesterone on dopaminergic neurons, possibly mediated by its immunomodulating activity.[129] Moreover, whereas the absence of ovarian hormones increases phosphorylated tau (p–T) levels in the hippocampus of ovariectomized rats,[130] progesterone administration appears to prevent tau hyperphosphorylation in animal models, supporting its role in maintaining neuronal integrity.[131]

However, to date, no studies have tested the effects of administering progesterone alone in patients with PD, and its role in PD remains unclear.[128]

Testosterone

Testosterone is one of the major androgenic sex steroid hormones, synthesized primarily by the testes and, to a lesser extent, by the ovaries in females. It can be converted into dihydrotestosterone (DHT) via the enzyme 5α-reductase or into E2 through aromatization.[53] Androgens act through specific membrane and intracellular receptors broadly expressed within the CNS, particularly in the basal ganglia.

Currently, in PD, the available literature remains unbalanced toward women, estrogens, and female reproductive factors, and evidence regarding the role of androgens remains inconsistent across preclinical and clinical studies.[132] More robust findings

come from Alzheimer's disease (AD), where female sex is a risk factor for disease development. Experimental studies demonstrate that testosterone administration reduces neuronal toxicity and amyloid-β accumulation,[133] while clinical observations indicate that lower circulating testosterone levels correlate with greater amyloid load and earlier disease onset.[133,134]

In healthy men, testosterone levels decrease with age, and a correlation between serum testosterone levels and depression, fatigue, and worse QoL is well documented.[135] While testosterone deficiency is observed in approximately 20–25% of the elderly population over 60 years,[136] small studies have reported a higher prevalence in male PD patients, ranging from 35%[137] to 47%.[138] However, a recent large-scale study found higher testosterone and E2 levels in male PD patients compared with controls, possibly related to alterations of the brain–gonadal axis associated with PD pathology, as suggested by correlation analyses between sex hormones and clinical and biochemical parameters. Specifically, E2 levels correlated with better motor functioning, whereas testosterone correlated positively with CSF total α-syn and negatively with right GP volume, suggesting a link between higher testosterone availability and greater PD neuropathology.[53]

Supporting a detrimental role of androgens, experimental models have shown that castration attenuates 6-OHDA–induced nigrostriatal dopaminergic damage,[139] whereas testosterone or DHT replacement, unlike E2, fails to confer neuroprotection in MPTP or 6-OHDA models.[140] In reserpine-treated animals, testosterone administration further worsens behavioral manifestations and nigrostriatal damage by aggravating toxicant-induced oxidative stress.[141] Similarly, testosterone supplementation failed to improve motor outcomes in PD trials,[142] and androgen deprivation therapy for prostate cancer does not increase PD risk,[143] suggesting limited neuroprotective, or even detrimental, androgenic effects. Conversely, in preclinical models, 5α-reductase inhibitors, by reducing the conversion of testosterone to the more potent androgen DHT, may exert neuroprotective and antidyskinetic effects. Moreover, recent epidemiological studies have reported an increased risk of prostate cancer among PD patients, suggesting a possible shared pathogenic background involving both hormonal and genetic factors[144] and again pointing toward a potential neurotoxic effect of androgens on the nigrostriatal dopaminergic system and a possible contribution to male vulnerability to the disease.

In apparent contrast with these findings, other studies have shown positive correlations between androgen levels and better mood or QoL in male PD patients,[145] and associations between low testosterone levels and apathy.[138] Okun et al. reported that depression and motivational symptoms, while refractory to conventional treatments, responded to testosterone replacement therapy (TRT).[137,142,146] Nevertheless, other studies have failed to confirm associations between testosterone and specific NMS, such as fatigue and apathy,[136] suggesting that testosterone's effects may stem from general mood and energy enhancement rather than on disease-specific mechanisms.[132]

Finally, limited evidence suggests a protective role of testosterone against dystonia in PD. In a cohort of EOPD patients, lower testosterone levels in females were associated with higher dystonia prevalence,[27] possibly mirroring androgenic modulation of GABAergic transmission,[147] a pathway central to dystonia pathophysiology.[148]

Gonadotropins

Gonadotropins are a family of three hormones: FSH, or follicle-stimulating hormone; LH, or luteinizing hormone; and hCG, or chorionic gonadotropin. FSH and LH are produced by the pituitary gland in both sexes, while hCG is produced by the chorion and the placenta during pregnancy.

Increasing evidence is linking gonadotropins to the development of AD and PD-dementia,[149] suggesting that the entire HPG axis plays a role in neurodegeneration, particularly in amyloidopathy, a copathology found in around 30% of PD cases and closely correlated with worse cognition.

LH drives APP processing toward the amyloidogenic pathway in vitro.[150] Elevated LH levels correlate with plasma Aβ40 and Aβ42 concentrations in individuals with subjective memory complaints[151] and with a higher risk of AD among men.[152] Similarly, preclinical studies indicate that FSH blockade inhibits amyloidogenesis[153] supporting the emerging hypothesis that FSH may act as a key mediator linking female sex and menopause to AD.[154]

In PD patients, higher gonadotropin levels have been found to correlate with increased amyloid burden, reflected by lower CSF Aβ42/Aβ40 ratios, and poorer cognitive performance in both sexes.[53,93] However, while these associations disappeared in men after adjusting for age, likely due to the slow and progressive nature of andropause, they persisted in postmenopausal women, who experience a sharp increase in gonadotropin concentrations in response to the estrogen decline of perimenopause. Similarly, gonadotropin levels, specifically FSH in males with PD and LH in postmenopausal females with PD, directly correlate with increased pathological β-FC in different cortical areas,[69] suggesting a role in bradykinesia as well.

As for hCG, evidence is limited; however, in animal toxic models, hCG administration appears to exert neuroprotective effects by alleviating dopaminergic cell death, likely driven by a down-regulation of LH in the substantia nigra.

Overall, these findings suggest that the age- and menopause-related rise in FSH and LH levels may act as a relevant physiological modulator of neurodegeneration in the aging brain in both sexes, particularly with respect to cognition and possibly bradykinesia.[69]

Finally, a population of neurons secreting gonadotropin-releasing hormone (GnRH), traditionally known for its hypothalamic expression, has recently been identified within the striatum, where it may exert local regulatory effects.[154] While this finding supports the notion that sex hormones play roles extending beyond reproduction, the specific contribution of GnRH/GnRH receptor signaling to neurodegenerative processes and basal ganglia function remains to be elucidated[154].

Conclusions

PD is a heterogeneous and multifactorial disorder in which diverse molecular and pathophysiological mechanisms converge on nigrostriatal degeneration. This heterogeneity translates into substantial variability across individuals, and biological sex represents one of its key modulators. From genetic and molecular pathways to immune responses, neuropathological features, and clinical phenotype, PD exhibits sex differences, a reality that must be acknowledged in research and clinical practice. Epidemiological data indicate that women are protected from developing PD, at least in Western populations, and typically experience a slower disease progression, possibly reflecting the influence of estrogens during the fertile years. This epidemiological pattern aligns with preclinical and clinical evidence showing that estrogens, particularly E2, modulate dopaminergic neurotransmission and exert anti-inflammatory and antioxidant actions, ultimately preventing nigral dopaminergic degeneration. However, this apparent biological advantage contrasts with the lower QoL observed in women with PD, likely influenced by social and psychosocial factors such as reduced access to specialized care, lower social support, and a greater likelihood of being caregivers rather than care recipients. Conversely, men with PD tend to experience faster cognitive and motor decline, raising questions about the role of androgens in shaping disease trajectories. Finally, the role of gonadotropins, well characterized in AD, remains to be clarified in PD, where preliminary evidence points to their contribution to amyloid copathology and cognition in both sexes. While hormone-based therapeutic strategies have yielded inconsistent and inconclusive results due to issues related to dosage, formulation, timing, and adverse effects, these insights nonetheless highlight the potential for personalized, sex-informed management approaches. This perspective extends from the optimization of conventional pharmacological treatments (eg, addressing the higher risk of dyskinesias and pain in women, or cognitive deterioration in men) to the tailoring of sleep and neuropsychiatric care, and even to the design of disease-modifying interventions considering sex-specific immune, genetic, and electrophysiological profiles.

Importantly, the clinical management of women of reproductive age with PD requires particular attention to the hormonal fluctuations across the menstrual cycle, pregnancy, and postpartum, all of which can significantly influence symptom control and treatment response.

At the same time, clinical research directions that integrate sex-specific features and sex hormone assessments with molecular, neuroimaging, and neurophysiological biomarkers, as well as preclinical investigations into how these hormonal factors influence the molecular pathways implicated in PD pathology, are urgently needed to clarify their contribution to disease vulnerability, phenotype, and progression.

Ultimately, hormonal factors and their physiological fluctuations should be regarded not as isolated modulators, but as part of a broader biological and gender dimension that shapes every aspect of PD. Recognizing and integrating these dimensions, from experimental research to clinical decision-making, is essential for achieving more individualized and equitable care.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

R.B.: 1A, 1B, 1C, 3A
C.S.: 3B
M.M.: 3B
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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. COI_disclosure.