Survey of the Effects of Estrogenic Compounds on the Risk of Parkinson's Disease

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor impairments and other non-motor symptoms. Its global prevalence is increasing, with men displaying higher incidence than women. Notably, earlier menopause in women is associated with elevated PD risk, implicating estrogen in a neuroprotective role. Given the widespread use of estrogenic compounds as part of hormone replacement therapy in women undergoing menopause—when PD risk rises—estrogen and other similar estrogenic hormones have been proposed as potential agents for symptom alleviation or risk reduction. This review synthesizes evidence from human studies on the effects of estrogenic compounds on Parkinson's disease, complemented by data-science analysis of published findings. Human studies yield inconsistent results: some indicate heightened risk with exposure to estrogenic compounds, while others suggest neuroprotection, with ethnicity as the only consistent modulator. These divergent outcomes highlight the need for further investigation to clarify the therapeutic potential of estrogenic compounds, as well as the underlying mechanisms in Parkinson's disease.

Introduction

Background

Parkinson's disease is the second most prevalent neurodegenerative disease in the world, with a European study noting that around 1–2% of individuals above the age of 65 are affected[1]. In addition, Parkinson's disease is increasing in prevalence as life expectancy increases worldwide, especially in the developed world; Parkinson's disease is the fastest-growing neurodegenerative disease in the world[1].

There are numerous risk factors for Parkinson's disease. One of the most significant risk factors for Parkinson's disease is sex; studies suggest that males are 1.5 to 2 times more likely to get Parkinson's disease than females are[2,3]. Unique risk factors exist for women; a higher number of pregnancies and a younger age of menopause are linked with an increased risk of Parkinson's disease[2]. Other risk factors potentially attributable to Parkinson's disease, based on a study done in the Southern United States, include pesticide exposure, chemical exposures from military activities, and blows to the head from sports or combat; the former was somewhat more prevalent in women, while the latter two were strongly associated with men[4].

The symptoms for Parkinson's disease can be divided into motor symptoms and non-motor symptoms (such as memory problems, taste loss, and fatigue), with non-motor symptoms sometimes appearing several years before the more obvious motor symptoms of Parkinson's arise[5]. This adds a unique challenge in diagnosing and treating Parkinson's disease, especially if the mental conditions induced by Parkinson's disease are misdiagnosed.

This study focuses on estrogen, a common compound in hormonal medicine. One way in which estrogen is affected is in hormone replacement therapy for menopausal women, where estrogen levels are increased to alleviate symptoms of menopause. Estrogen therapy's effect on non-menopausal health conditions has been mixed so far, with some observations from the United Kingdom, Australia, and New Zealand showing that starting estrogen therapy many years after the start of menopause may increase health risks, especially circulatory conditions such as Venous thromboembolism[6]. It is also possible that other estrogenic hormones, such as progestin, can provide altered but nevertheless related effects as well, based on observations in the United Kingdom[7].

In women, estrogen levels constantly fluctuate during the menstrual cycle and decline after menopause. However, these estrogen cycles can be substantially influenced by geographical origin, ethnicity, and other personal factors such as smoking and alcohol consumption, based on observations in Utah and California[8].

Since women have a lower incidence of Parkinson's disease and since women who have an earlier onset of menopause have an increased risk of developing Parkinson's disease, it is possible that estrogen provides some protective effect against Parkinson's disease[9]. In addition, estrogen may have a long-term protective effect on neurons, potentially through inter-

actions with neurotransmitter systems and other parts of the brain, especially in regions of the brain with many estrogen receptors, such as the hippocampus and amygdala[10]. Interestingly, a study performed on Californian teachers found that women with higher lifetime levels of estrogen may have lower Parkinson's disease rates than men or women with lower lifetime levels of estrogen[11]. This supports the notion that estrogen, and potentially other estrogenic compounds, provide a more chronic protective effect on neurons.

Regardless, it is very likely that the effectiveness of these hormones as a treatment for Parkinson's disease is at least somewhat dependent on other factors. One study performed internationally reported that estrogens may increase the risk of short-term and long-term mechanical complications and revisions[12]. Due to the old age of many Parkinson's patients, as well as the debilitating motor symptoms caused by Parkinson's that may increase the risk of bone breakage, a further weakening of the skeletal system from treatments may be deemed as unacceptable, meaning that estrogenic treatments may be unable to be used feasibly within the context of Parkinson's disease.

In Model 1, we illustrated how estrogen may decrease the risk of Parkinson's disease through inhibiting processes that ultimately lead to the loss of dopaminergic neurons and the formation of Lewy bodies. This graph is conceptual in nature.

Significance

No treatment can currently halt the progression of Parkinson's disease[1]. Levodopa, a dopamine precursor, is the main pharmacological treatment for alleviating the symptoms of Parkinson's disease[13]. However, Levodopa administration is associated with several side effects, such as Levodopa-induced dyskinesia (unusual movements induced by Levodopa treatment) and anxiety[14]. In addition, Levodopa seems to only treat the motor symptoms of Parkinson's, while Parkinson's disease also contains many debilitating non-motor symptoms as well[5]. Gut bacteria such as Clostridium sporogenes may break down and deactivate Levodopa residues, which may inhibit Levodopa's effectiveness[15].

Objectives

The objectives of this systemic review of human data are to understand the effects of estrogenic compounds, namely estrogen but also progesterone and other compounds that either act as estrogens or activate estrogen receptors, on the prevalence and severity of Parkinson's disease with regards to humans, especially human women. We chose to focus more on women because women are the primary recipients of estrogenic compounds as part of post-menopausal treatment, when their estrogen production rapidly declines and when their risk
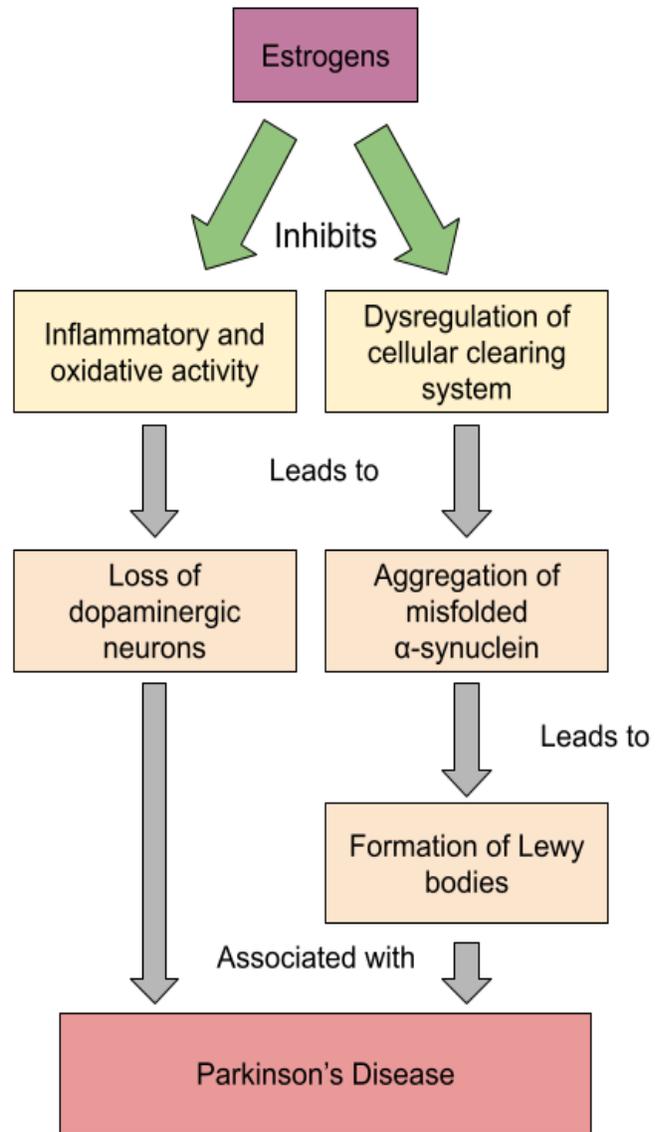
Model 1 Assumed effect of estrogen on the pathogenesis of Parkinson's disease

of Parkinson's disease increases. The studies that we collected serve to provide us data about not only how estrogenic compounds may impact Parkinson's disease, but also about what other factors may alter the impact that these estrogenic compounds may have.

Literature Review

Yoo (2020) discussed how a later age of menarche was associated with increased Parkinson's disease risk; an increased age of menopause and an increased fertility length were both as-

sociated with reductions in Parkinson's disease risk; and hormone replacement therapy, oral contraceptives, and female reproductive factors were associated with increases in Parkinson's disease risk[2]. Payami (2023) identified repeated blows to the head and pesticide exposure as preventable risk factors for Parkinson's disease, and race, sex, and genetics as intrinsic risk factors for Parkinson's disease[4]. Pesce (2022) discussed how early and late age at menarche, a higher number of children, artificial menopause (especially at a younger age), and some fertility treatments were associated with an increase in Parkinson's disease risk, and how hormonal therapy was associated with a decrease in Parkinson's disease risk[9]. These three papers all discuss various factors that increase the risk for Parkinson's disease, and all of them include sex as a risk factor. Two of them identify hormonal therapy as a risk factor, but their conclusions are contradictory, with Yoo (2020) associating hormonal therapy with an increase in Parkinson's disease risk, and Pesce (2022) associating hormonal therapy with a decrease in Parkinson's risk[2,9].

Six more papers directly analyze how estrogenic compounds affect Parkinson's disease risk. Currie (2004) associated postmenopausal estrogen therapy with a decrease in Parkinson's disease risk[16]. Simon (2009), on the other hand, found no such beneficial effect from any hormone replacement therapy[17]. Yuk (2023) found an elevated Parkinson's disease risk with tibolone and estrogen that was most apparent in the first years of treatment, as well as a much more consistent increase in risk with regards to an estrogen-progesterone combination[18]. Liu (2020) found little correlation between hormone replacement therapy use and Parkinson's disease risk, even when analyzing both the type of hormone and the duration of hormone usage[19]. Rao (2023) found no correlation between hormone replacement therapy and Parkinson's disease[20]. Lundin (2014) found that esterified estrogen was the only formula of estrogenic hormone replacement therapy associated with Parkinson's disease, and that conjugated estrogen was not associated with Parkinson's disease[21]. All six of these papers focus on a similar subject but tend to differ in terms of formulations of hormones studied, focus on the effect of duration on Parkinson's disease, and conclusions about the overall effect of estrogenic hormones on Parkinson's disease.

Overall, existing literature extensively surveys estrogenic compounds and their effects on Parkinson's disease, but the fairly low level of agreement between the studies and the widely differing focuses on duration and formulation necessitates an organized, systematic review of data that aggregates scattered data to form a more comprehensive view on the effects of estrogenic compounds on Parkinson's disease, as well as a more organized look on how duration of use and formulation may alter their effect. Our systematic review intends to provide this organized view on estrogenic compounds' effect on Parkinson's disease.

Data Collection and Synthesis

Search Strategy and Data Collection

We used databases such as PubMed, ProQuest Research Library, and Medline, along with other academic tools such as Consensus, to find our articles. The main keywords we used were "Parkinson's", "estrogen", and "women". Inclusion criteria included a publication date from the year 2000 or later, with priority being given to more recently written articles; being primary research articles; and having been peer reviewed in order to ensure that the studies that we used are high quality. Exclusion criteria included being irrelevant to the topic of the effects of estrogenic compounds on Parkinson's disease; focusing on Alzheimer's disease; and only containing marginal information about Parkinson's disease. For all of the studies that met our criteria, the methods, results, and discussion within the studies were used to find the data that was needed. We then used this data to make observations about each study. The data that we collected was also organized into tables and figures.

Data Synthesis

After collecting and filtering studies, we organized our quantitative data into three figures in the form of forest plots: one about the effect of estrogenic compounds on the risk of Parkinson's disease, one about how duration of use of estrogenic hormones affects the risk of Parkinson's disease, and one about how the type of estrogenic hormone affects the risk of Parkinson's disease. All three of these forest plots involve analyzing odds ratios, hazard ratios, and/or risk ratios; the type of ratio depicted depends on the studies being analyzed. These figures were made using Copilot. We also recorded qualitative data about each study, such as the main ethnicity studied, whenever it was feasible. Finally, we recorded our results, both quantitative and qualitative, in an organized manner.

Results of Comparative Analyses

Use of HRT: Out of the eleven studies that we collected, one study indicated a correlation between hormone replacement therapy and a reduction in the risk of Parkinson's disease[16]; three studies indicated a correlation between hormone replacement therapy and an increase in the risk of Parkinson's disease[2,17,18]; and four studies indicated no correlation or an inconsistent correlation between the two factors[9,19–21]. Overall, the effect that estrogenic hormones have on the risk of Parkinson's disease is mixed, with some studies reporting an increase in risk while others report a decrease in risk.

Table 1 shows the different conclusions that each study on humans reached regarding the effects of hormone replacement

Table 1 Studies vs. Risk Association

Study	Risk Association	Study Design Type	Total Participants	PD Cases Identified	Follow-Up Duration	Adjustment Variables Used
Currie (2004)	Decrease	Case-control	140	68	None	Age at menarche and menopause, menses duration, number of pregnancies, birth control pill use and duration
Simon (2009)		Cohort	121,701	244	4 years*	Age, pack-years of smoking
Yuk (2023)		Cohort	303,260	0**	7.9 years***	Age and calendar year at inclusion, socioeconomic status, Charlson Comorbidity Index, region of residence, hypertension, diabetes, hyperlipidemia, uterine fibroids, endometriosis, previous hysterectomy, previous adnexal surgery
Yoo (2020)	Increase	Cohort	4,729,546	20,816	2 years****	Age at menarche, age at menopause, number of parities, duration of breastfeeding, duration of HRT, duration of oral contraceptive use, alcohol consumption, smoking, regular exercise, income, BMI, hypertension, diabetes mellitus, dyslipidemia, cancer†
Liu (2014)		Cohort	119,166	410	8–11 years	Age in years at baseline, race, smoking status, caffeine intake
Lundin (2014)	No effect	Case-control	364	137	None	Duration of enrollment in Group Health Cooperative pharmacy database††
Pesce (2022)		Cohort	96,862	1,165	22 years	Age, rural living†††
Rao (2023)		Cohort	304	304	None	Age, disease duration, medication

therapy on Parkinson's disease, as well as additional information regarding each study. Only two of the eight studies were case-control studies. The one study that associated estrogenic hormone usage with a reduced risk of Parkinson's disease also had the lowest number of participants[16]. The study where all of its participants had Parkinson's disease found no correlation between estrogenic hormone usage and Parkinson's disease[20]. Three out of the four studies with more than 100,000 participants found a correlation between estrogenic hormone usage and an increased risk of Parkinson's disease; these three studies also found that less than 1% of their participants had PD cases[2,17,18].

*: Or date of either Parkinson's disease diagnosis, death, stroke diagnosis, loss to follow-up, or end of study 26 years later

**: Study assessed risk and systematically excluded people with Parkinson's disease

***: Between 6.9 and 7.9 years

****: Or until date of incident Parkinson's disease

†: For Model 2; Model 1 was unadjusted, and Model 3 was adjusted for duration for fertility instead of age of menarche and menopause

††: When covariates modified risk estimates by more than 10% and when chi-square statistic was statistically significant, covariates such as smoking, race, coffee consumption, education, history of estrogen-related cancers, and family history of PD were adjusted.

†††: As a baseline; models that included characteristics of menopause and hormonal therapy were adjusted for menopausal status; models including the number of children and breastfeeding were adjusted for nulliparity; in model A1, data regarding age at menarche was adjusted for rural living and childhood silhouette; in model B1, data regarding parity was adjusted for rural living, age at menarche, childhood silhouette, silhouette at 20 years, smoking status, time-varying nulliparity, and parity; in model C1, data regarding menopause was adjusted for rural living, age at menarche, childhood silhouette, silhouette at 20 years, time-varying nulliparity, parity, smoking status, BMI, physical activity, menopausal status, type of menopause, and age of menopause; data for fertility treatments was further adjusted for rural living, age at menarche, childhood silhouette, silhouette at 20 years, and smoking status; post hoc composite score adjusted for baseline rural living

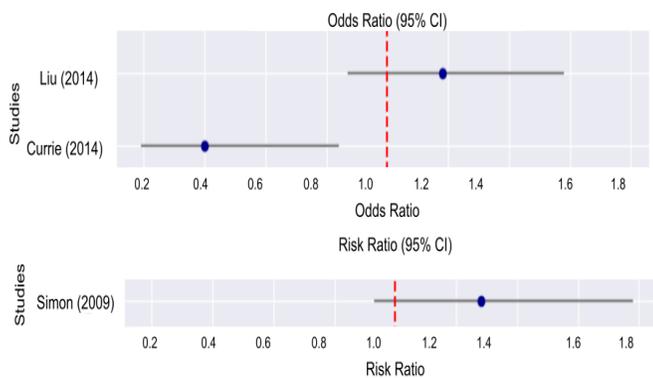In Figure 1, we plotted the odds and risk ratios regarding

Fig 1 Odds and Risk Ratios of Three Studies that indicate Risk Association

Fig 2 The effect of different Estrogenic Compounds on Parkinson's Disease

estrogen's impact on Parkinson's disease from 3 studies done on humans. Each study reported a specific odds or risk ratio, along with the 95% CI ranges of each ratio. For Liu (2014), we used Model 1 adjustment, which means that its odds ratio is adjusted for age, race, smoking, and caffeine. This figure shows that there is an inconsistent correlation between administration of estrogen and the development of Parkinson's disease.

Type of HRT: Overall, the effect of hormones on Parkinson's disease depends on the hormone type; some hormones, such as estrogen, have an inconsistent effect on Parkinson's disease risk, while others, such as progesterone, more consistently affect Parkinson's disease risk in a certain way.

Table 2 describes the hormones used by five of the studies conducted on humans, as well as the distinct effects that these hormones had. Progestin and Progesterone were grouped together for our data analysis, as Progestin is a synthetic hormone that mimics Progesterone. The hormones used in the experiments were all different in terms of amount, kind, and duration, so the data will be affected by the heterogeneity of formulas.

*: For all categories except "Formerly used Estrogen", where a decrease in risk was noted

**: Increase or decrease in risk dependent on duration

***: Later changes to "Increase" as time goes on

In Figure 2, we plotted the hazard and odds ratios associated with the types of estrogen used from four studies along with their 95% CI ranges. We used the Model 1 adjustment for the data from Liu (2014), which means that the data is adjusted for continuous age, race, smoking, and caffeine. The data indicates that estrogen and a combination of estrogen and progesterone have an inconsistent effect on Parkinson's disease, while progesterone consistently increases the risk of Parkinson's disease. Lundin (2014) also indicates that conjugated estrogen decreases the risk of Parkinson's disease, and that a combination of conjugated estrogen and progestin, esterified
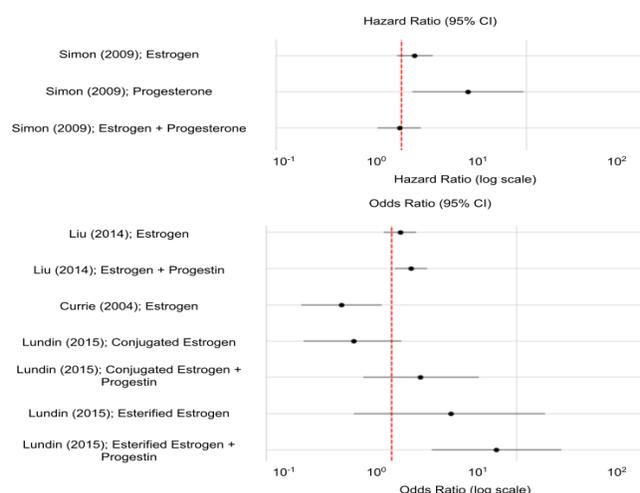
estrogen, and a combination of esterified estrogen and progestin increase the risk of Parkinson's disease [21]. Therefore, Figure 2 shows a correlation that implies that estrogen and a combination of estrogen and progesterone have an unclear effect on Parkinson's disease; conjugated estrogen decreases the risk of Parkinson's disease; and progesterone, esterified estrogen, and a combination of esterified or conjugated estrogen and progestin consistently increase the risk of Parkinson's disease.

Duration of HRT: Overall, the longest and shortest durations tend to result in the highest risk increases for Parkinson's disease, although this tendency is not absolute.

Table 3 shows the results obtained from four of the studies conducted on humans regarding the effects of duration of hormone replacement therapy on the risk level of Parkinson's disease.

*: Estrogen and Tibolone showed a greater increase in risk for durations of less than 3 years than Estrogen + Progesterone

**: Estrogen + Progesterone showed a greater increase in risk for durations of 3 years of greater than Estrogen or Tibolone

***: Decreased before adjustment; increased after adjustment

In Figure 3, we plotted the hazard ratios, odds ratios, and risk ratios associated with specific time intervals from four studies, along with their 95% CI ranges. We used Model 1 for data adjustment of Liu (2014), which means that its data is adjusted for continuous age, race, smoking, and caffeine. We used Model 3 for data adjustment of Yoo (2020), which means that its data is adjusted for duration of fertility, parity, duration of breast feeding, duration of HRT, duration of oral contraceptive use, alcohol consumption, smoking, regular exercise, in-

Table 2 Effect of Hormone Formulation(s) on risk

Study	Type of Hormone	Risk Correlation
Currie (2004)	Estrogen only	Decrease
Liu (2014)	Estrogen	Increase*
	Estrogen + Progesterone	
Yuk (2023)	Estrogen	No effect**
	Estrogen + Progesterone	
	Tibolone	
Yoo (2020)	Estrogen, Progesterone (Distinguishment was not made in data)	Decrease***
Simon (2009)	Estrogen	Increase
	Progesterone	
	Unknown Hormone	
	Estrogen + Progesterone	Decrease

come, body mass index, hypertension, diabetes mellitus, dyslipidemia, and cancer. The data shows that while hormone use generally increases the risk of Parkinson's disease, the highest risks tend to appear at the shortest and longest periods of use.

Impact of Ethnicity: Out of 8 studies, 3 of them reported data on ethnicity. Liu (2014) reported that 91.0% of its non-PD subjects were non-Hispanic White, while 93.2% of its PD subjects were non-Hispanic White; 7.9% of its non-PD subjects were of another ethnicity, while 5.9% of its PD subjects were of another ethnicity[19]. Lundin (2014) reported that 93% of both its case and control groups were non-Hispanic White; this study did not provide data for other ethnicities[21]. Pesce (2022) noted that data on skin color may indicate that it used a mostly White study base, but due to restrictions on collecting ethnicity data due to French law, the study was unable to precisely verify ethnic data; as such, we did not count it as having reported data on ethnicity[9]. Both Liu (2014) and Lundin (2014) concluded that there was no overall effect on risk from Parkinson's disease. Yuk (2023) reported in its discussion that all of its subjects were of Korean ancestry[18]. It concluded that there was some increase in the risk of Parkinson's disease when estrogenic hormones were administered. Yuk (2023) found an increase in risk for the first 3 years, and cited in its discussion a study that indicated that Asian women may have different susceptibilities to Parkinson's disease[18].

These factors suggest that ethnicity may affect how estrogenic compounds affect Parkinson's disease, and ultimately their effectiveness in mitigating the risk and severity of Parkinson's disease.
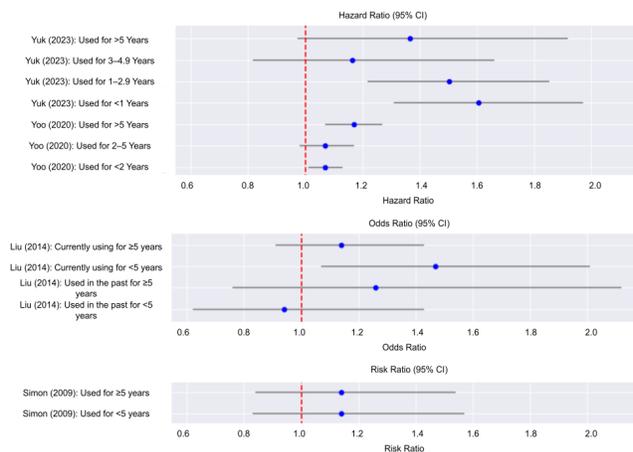

Fig 3 Effect of Duration on Parkinson's Disease

Table 3 Effects of duration of hormone replacement therapy on risk of Parkinson's disease in humans

Study	Duration	Risk Change
Simon (2009)	Fewer than 5 years	No effect
	More than 5 years	
Liu (2014)	Used in the past for fewer than 5 years	Decrease
	Used in the past for greater than 5 years	Increase
	Currently using for less than 5 years	
	Currently using for more than 5 years	
Yuk (2023)	Fewer than 1 year, 1–2.9 years	Increase*
	3–4.9 years, more than 5 years	Increase**
Yoo (2020)	2 or fewer years	
	2–5 years	Increase***
	5 or fewer years	

Conclusions and Discussion

Key Findings

Our analysis reveals complex and often contradictory effects of estrogenic hormones on PD risk and severity.

Human studies show inconsistent outcomes: of 8 reviewed, one reports reduced risk with exposure to estrogenic hormones, three indicate increased risk, and four show no effect or mixed results. Ethnicity emerges as the only consistent modulator, with divergent findings between reported East Asian and European populations. Hormone type also influences severity; progesterone, esterified estrogen, and esterified or conjugated estrogen combined with progestin generally exacerbate symptoms; conjugated estrogen alone is linked with alleviating symptoms; and estrogen and a combination of estrogen and progesterone have an unclear effect.

Implications

The observed ethnic divergence between East Asian populations and non-Hispanic White populations represents an informative finding that is supported by existing observations. Brakedal (2022) noted in its introduction that lower male/female sex ratios for Parkinson's disease are reported from Asian populations[1]. Liu (2004) found in its study in Utah and California that Asian women had a much longer menstrual cycle than Caucasian women, which implies that Asians and non-Hispanic Whites may have different responses to certain drugs such as hormone replacement therapies[8]. However, the effect of ethnicity on the effectiveness of treatments for Parkinson's disease is understudied, largely because non-White ethnicities are not well-represented in many studies of Parkinson's disease. For example, Park (2023) found that Genome-wide association studies (GWAS), which apply to diseases such as Parkinson's disease, are disproportionately conducted among White populations; at the time of the study, there was no GWAS data for the Korean population afflicted with Parkinson's disease despite Korea having the fastest-aging society in the world, paired with a rapidly rising prevalence of Parkinson's disease[22].

Hormone formulation also has practical implications; women at an elevated Parkinson's disease risk who are considering hormone replacement therapy for menopause may benefit from estrogen-only regimens over those including progesterone, given the latter's association with an increased risk and severity of Parkinson's disease.

Additionally, timing of therapy appears at least somewhat influential, with evidence for a potential "critical window" where hormone administration yields protective effects, outside of which risk may rise. Lord (2008) noted how past studies indicated that using estrogen or a combination of estrogen and progesterone may provide beneficial effects on the brain if a certain duration was not exceeded; long-term usage of a combination of estrogen and progesterone was linked with negative effects on the brain[10]. These findings are supported by our data, which links the highest and lowest durations of usage with the largest increase in Parkinson's disease risk, although the studies that we used to observe duration broadly linked estrogenic hormones with an increase in Parkinson's disease risk. Liu (2004) states based on data from past studies how the "timing hypothesis" states that the timing of estrogen treatment relative to the stage or type of menopause may crucially affect estrogenic hormones' effect on Parkinson's disease[19]; our data provides some support for this hypothesis.

Collectively, these insights underscore factors—ethnicity, formulation, and timing—that likely modulate estrogen's therapeutic potential in PD and identify promising directions for targeted interventions.

Future Directions

Current studies predominantly focus on European and East Asian cohorts, limiting generalizability to African, Hispanic, and other populations. As such, judging from the potential for estrogenic hormones to have different effects on Parkinson's disease depending on the ethnicity of the patient, more investigations regarding ethnic differences in the effect of estrogenic hormones on Parkinson's disease should be conducted, especially on underrepresented groups such as people of African and Hispanic ethnicity.

In addition, we recommend further studies that search for the validity of a "critical window" with regards to using estrogenic hormones in order to alleviate the symptoms of Parkinson's disease, as while some evidence exists for this hypothesis, there is still a lack of definitive data or proof regarding the existence or lack thereof of this "critical window".

Further studies on estrogenic compounds' effect on Parkinson's disease are essential to resolve existing contradictions and establish estrogenic hormone based strategies as viable PD interventions.

As a result of this research, we believe that our study would provide a useful comparison of results from a variety of studies that all observe the effect of estrogenic compounds on Parkinson's disease for future studies studying estrogenic compounds and their effects on Parkinson's disease to use and reference. Our paper currently only holds research value, but it could be used to suggest or to guide a suggestion for a standard guideline for estrogen therapy for people with Parkinson's disease.

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