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Association of Estrogen in the Risks of Parkinson's Disease in South Korean Women

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the death of neurons, resulting in symptoms such as shaking, stiffness, and impaired balance. Research suggests a potential link between estrogen, a female sex hormone, and PD risk, with studies indicating that estrogen may play a protective role against the disease. However, most research on this topic has been conducted on European populations, leaving the role of estrogen in PD risk among Asian women, particularly in South Korea, unclear. This study contributes to understanding the potential protective role of estrogen in PD by focusing on South Korean women. A case-control study design was employed, comparing responses from women with PD to healthy controls. The study investigated various reproductive life events, including menstruation, menopause, and hormone replacement therapy, using a questionnaire administered to participants in South Korea. Results revealed that PD patients were significantly older than controls, with differences in reproductive lifespan and age at menopause. Women who underwent surgical menopause showed an increased risk of PD, while hormone replacement therapy and oral contraceptive usage did not show consistent associations with PD risk. The study concludes that estrogen is neither a protective nor a risk factor for PD in South Korean women. This research contributes to the understanding of PD risk factors among South Korean women and highlights the need for further exploration into non-genetic gender-specific symptoms and societal influences on PD risk, aiming to reduce underrepresentation and medical discrimination in PD research.

Introduction

Parkinson's disease is a neurodegenerative disorder "characterized by the death of neurons" (Latif et al., 2021). Due to the lack of production of functioning cells critical to the production of dopamine, Parkinsonism causes "shaking, stiffness, and difficulty with balance and coordination" (National Institute on Aging, 2022). Typically, this disease develops in people after the age of 60, with fewer instances of onset before the age of 50 (Mayo Clinic, 2023).

Currently, there is no permanent cure, but symptoms are primarily treated and maintained with a dopamine replacement agent, levodopa (Gandhi & Saadabadi, 2024). The risk of developing Parkinson's Disease is "twice as high in men than in women" (Cerri et al., 2019). Given the observed sex-related differences, literature suggests that the presence of the female sex hormone estrogen may act as a potential protective factor against Parkinson's disease (Rao et al., 2023). Animal studies have also indicated that estrogen influences dopamine synthesis, a crucial neurotransmitter in Parkinson's disease, suggesting a potential protective role against Parkinson's disease (Shulman, 2002).

There is considerable research into whether estrogen is a protective factor or not, but most of this work has been conducted on European samples as "over 80% of genome-wide association studies have been conducted on individuals of European ancestry" (Schumacher-Schuh et al., 2022). The role of estrogen as a pro-

tective factor in South Korea remains undetermined, as historically, different races have remained geographically isolated (Hunley et al., 2009). Due to the lack of racial diversity in South Korea, specific genotypes could have been preserved through common ancestry (Kittles & Weiss, 2003). Consequently, samples from European ancestry might not represent shared genetic variations and risk factors in South Korea (Hunley et al., 2009; Kittles & Weiss, 2003; National Institute on Aging, 2022; Yuk & Jeong, 2023). For example, while eurocentric research reported the ratio of Parkinson's disease prevalence by gender to be 2:1 male to female, in South Korea the ratio is closer to 1:1.6 male to female, indicating a higher prevalence in women (Park et al., 2019).

Our study contributes to scholarly discourse by examining the potential protective role of estrogen in preventing the onset of Parkinson's disease, focusing on South Korean women and evaluating estrogenic variables (Schumacher-Schuh et al., 2022). The proposed approach involves administering a questionnaire to women with and without Parkinson's disease in South
Korea.

Literature Review

Role of Estrogen in Parkinson's Disease

Estrogen is a crucial component of women's reproductive life (Yu et al., 2022). It is generally accepted that a high level of estrogen in women contributes to their longer lifespan compared with men (Yu et al., 2022). The start of menstruation is called "menarche" and is marked by "rapid increase in the level of estrogen" that leads to early puberty (Yu et al., 2022). The reproductive lifespan is "between puberty and menopause in women" (Yu et al., 2022). During perimenopause, the estrogen level decreases slowly and fluctuates unpredictably (Yu et al., 2022). When women experience menopause and the production of estrogen is reduced drastically (Yu et al., 2022). A woman's ovaries make most of their estrogen" and thus, the shortening of the estrogen lifespan using surgical menopause impacts women's long term health negatively (Yu et al., 2022).

A recent review from Poland compared the reproductive lifespan events in 76 females affected with Parkinson's disease and the non-Parkinsonism control group of 74 subjects (Nitkowska et al., 2014). The result of the study found that women with Parkinson's disease exhibited a shorter reproductive lifespan, earlier menopause, and increased surgical menopause instances compared to control subjects (Nitkowska et al., 2014). A surgical menopause is a procedure to remove the uterus and ovaries, more common for women aged 40 to 50 (National Health Service, 2022). Surgical menopause before menopause was shown to increase risk of Parkinsonism by 68%, which indicated the association between estrogen deficiency and risk of Parkinson's disease (Marras & Saunders-Pullman, 2014; Nitkowska et al., 2014). Another research study by K. Kompoliti, et al. observed 10 menstruating women with Parkinson's disease over 5 consecutive weeks to assess motor Parkinsonism with estrogen levels (Kompoliti et al., 2000). Consistent with the argument for the protective role of estrogen, this study found that Parkinsonism worsens during the premenstrual period, where estrogen is presumed at its lowest (Kompoliti et al., 2000). Lastly, postmenopausal women showed a higher likelihood of developing Parkinson's disease, implying that a decrease in estrogen levels may increase the risk of Parkinsonism (Nitkowska et al., 2014). There are consistent observations of the link between early menopause (natural or surgical) and increased Parkinson's disease risk throughout literature (Lv et al., 2017). Additional hypothesis links the lifetime average estrogen level to Parkinson's disease susceptibility, exploring variables like age at menarche, age at menopause, reproductive lifespan, and type of menopause (surgical vs. natural) (Lv et al., 2017; Nitkowska et al., 2014).

Oral Contraceptives and Hormone Replacement Therapy

Besides the natural estrogen present in bodies, there are other factors that contribute to estrogen levels, such as hormone replacement therapy and oral contraceptives.

Oral contraceptives work by taking estrogen and progestin pills (Cooper et al., 2024). A case report that directly examined a patient in Japan reported that milder Parkinsonism was displayed after taking oral contraceptives for 7 years (Yasui et al., 1992). Another study by Liu et al. analyzed a questionnaire comprising "119,166 postmenopausal women and 410 self identified as patients with Parkinson's disease" (Liu et al., 2014). Consistent with previous research, this study found "a significantly reduced Parkinson's disease risk with long-term oral contraceptive use (>10 years)" compared with those who never took oral contraceptives, but shorter use showed no association (Liu et al., 2014). Contrast to those studies mentioned above, multivariate analysis by Nicoletti et al. showed a significant positive association between use of oral contraceptives and Parkinson's disease through evaluating 200 women with Parkinson's disease and 299 women who served as control subjects (Nicoletti et al., 2011). At this point, however, it is not clear how oral contraceptives are known to be involved in Parkinson's disease since past research shows contradicting results (Rao et al., 2023).

Hormone replacement therapy is a treatment for menopausal symptoms and works by"taking medication to replace the estrogen that the body stops making during menopause" (The North American Menopause Society, n.d.). Benedetti et al. compared the medical records of 72 women with and without parkinson's disease and reported that individuals with Parkinson's disease had used estrogens for "at least 6 months after menopause [8%] less frequently than control subjects" (Benedetti et al., 2001). Consistent with this review, a case control study by Currie et al. obtained data from 68 females with Parkinson's disease and 72 female controls and found that women who did not take postmenopausal estrogen had a 2.5 times greater risk of having Parkinson's disease than women who used hormone replacement therapy (Currie et al., 2004). In contrast, the findings reported by the "Cancer Prevention Study II13 and the Kaiser Permanente Medical Care Program of Northern California" found significant results that hormone replacement therapy was correlated with a higher risk of death from Parkinson's disease and associated with a 2.6 times increased risk of Parkinson's disease (Wang et al., 2014). In further research by the Movement Disorder Society, a meta analysis across 14 studies indicated that hormone replacement therapy and surgical menopause were not found to be significantly associated with Parkinson's disease (Nicoletti et al., 2011; Wang et al., 2014). An alternative study examined incident cases of 178 women with Parkinson's and 189 age matched controls and found increased risk of Parkinson's disease among women only if postmenopausal hormone therapy was used with surgical menopause concurrently (Popat et al., 2005). These conflicting findings may be due to other variables, "including age, estrogen dose and formulation, and timing and length of dosing period" (Shulman, 2002). Overall, data on hormone replacement therapy is contradictory, and currently there is no confirmed role for hormone replacement therapy in the development of Parkinson's disease (Duke University Health System, 2018).

Scholarly discourse has contrasting views on whether oral contraceptives and hormone replacement therapy are protective or pose risks (Marras & Saunders-Pullman, 2014). Despite estrogen's general acceptance as a protective factor in the menstrual cycle, the role of oral contraceptives and hormone replacement therapy remains inconclusive (Currie et al., 2004).

Methods

Participants and Study Design

This study aimed to compare responses from women with Parkinson's Disease and those without it, who served as healthy controls to associate their reproductive life events with risk of Parkinson's disease through a case control study. Starting in mid-November 2023, the president of a Parkinson's disease support group distributed the questionnaire to women with Parkinson's disease in South Korea. An email reminder was sent in late December, and the questionnaire was closed on the first day of February. Concurrently, healthy control participants

were recruited through the social media platform Instagram and word of mouth. For both groups, the inclusion criteria required that participants were Korean women over the age of 50 residing in either South Korea or the United States. In total, we gathered responses from 157 participants, including 134 control subjects and 23 patients with Parkinson's disease.

In our sample, the patients with Parkinson's disease were significantly older than control subjects. Due to the uneven distribution of age, we reran the statistical analysis with matched samples of control subjects similar in age to the Parkinson's disease group with the minimum age set to 56 for the control group. In the restricted sample, the control subjects were reduced to 34 responses.

Materials

We administered the MATA LAB questionnaire, which is an updated version of the Parkinson's Foundation Parkinson's disease GENEration and we used Google Forms as a medium (Rao et al., 2022). The MATA LAB questionnaire discussed menstruation, pregnancy, hormonal disorders/cancer, menopause, and Parkinson's disease experiences. Sample questions included "What age did you start menstruation?" and "How old were you when your period/menses stopped?" (Rao et al., 2022).

The questionnaire was modified to ensure that the participants could complete the survey in a timely manner. Questions with more than two follow-up questions, as well as those focusing on improving or worsening Parkinson's symptoms were excluded due to their inability to include control responses. Participants with Parkinson's disease were asked a total of 16 questions and control participants answered 11 questions. The additional questions for participants with Parkinson's disease accounted for Parkinson's disease-specific symptoms. A sample question included, "Did you use hormone replacement therapy before or after Parkinson's disease diagnosis?" (Rao et al., 2022).

The questionnaire includes checkboxes for 'Yes' or 'No' responses and short answers. We translated the English questionnaire into Korean and had an expert conduct back translation to ensure accuracy.

Before completing the questionnaire, participants provided written consent, and they had the option to choose which questions to answer, minimizing potential risks. The original questionnaire and the modified questionnaire can be found in Appendix C and B, respectively.

The Korean version of the modified questionnaire can be found in Appendix A.

Statistical Analysis

We used Jamovi, a 3rd generation statistical spreadsheet chosen for its accessibility, versatility in analysis types, and user-friendly interface, to perform statistical analyses. Descriptive statistics, including mean and confidence intervals (CI), were employed for nominal answers. Categorical data were analyzed by calculating frequencies and percentages for each status, offering an overview of estrogen-related factors within each group. For closed-ended questions, the Binomial proportion test and Goodness of fit were utilized to determine the frequency of yes or no responses within each group. Fisher's exact test was applied to assess potential statistically significant associations between two categorical variables, particularly in cases of unequal sample sizes. Numerical data, such as reproductive lifespan, oral contraceptives usage in years, and age, were analyzed using Welch's T-test. We calculated relative risk, log-odds ratio, and odds ratio to determine whether the factors showed a positive or negative correlation with Parkinson's disease. This method proves to be valuable in my research, particularly for examining an analysis that indicates whether there is an increase or decrease in the likelihood of an event based on specific exposures, such as oral contraceptives, hormone therapy, or reproductive lifespan.

Results

The mean ages of the individuals with and without Parkinson's disease were 65 (standard deviation = 5.11, range: 57-78) and 55.7, respectively (standard deviation = 7.14, range: 50-82). The difference in age between the two groups was significant ($p < .001$). See Figure 1 below for the age distribution in two groups.

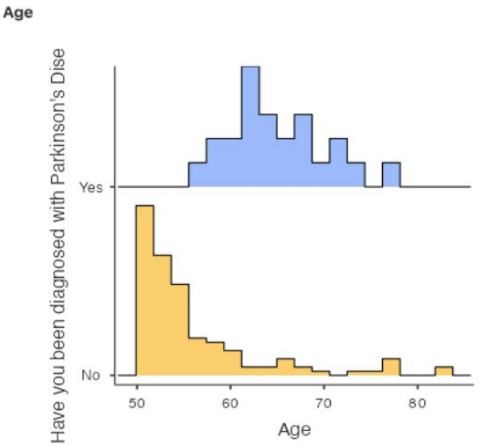

Figure 1. Participant ages separated by group (Parkinson's disease and Control)

The mean age at menopause was 46.8 years for individuals with Parkinson's and 50.2 years for the control group. The mean age at menarche was 14.8 years for both groups. The mean reproductive lifespan was 31.9 years for individuals with Parkinson's and 35.5 years for the control group. These results can be found on Table 1.

Table 1. Welch's T-Test (Parkinson's disease and Control)

		Statistic	df	p
Age	Welch's t	7.611	38.46	<.001
Years of Oral Contraceptives Usage	Welch's t	−0.160	7.28	0.878
Age at Menopause	Welch's t	−1.611	21.50	0.122
What age did you start menstruation?	Welch's t	0.105	24.78	0.918
Years of Reproductive Lifespan	Welch's t	−1.577	20.53	0.130

Note. H_a $\mu_{Yes} \neq \mu_{No}$

Group Descriptives

	Group	N	Mean	Median	SD	SE
Age	Yes	23	65.04	64.0	5.11	1.066
	No	134	55.67	53.0	7.14	0.616
Years of Oral Contraceptives Usage	Yes	5	1.20	0.0	2.17	0.970
	No	21	1.38	0.0	2.69	0.587
Age at Menopause	Yes	21	46.76	49.0	9.60	2.094
	No	96	50.20	50.5	3.94	0.402
What age did you start menstruation?	Yes	21	14.81	15.0	1.60	0.349
	No	131	14.77	15.0	1.35	0.118
Years of Reproductive Lifespan	Yes	20	31.90	34.0	10.00	2.236
	No	95	35.49	36.0	4.35	0.446

Table 2 presents a summary of the frequency and proportions of yes or no responses, categorized by the Parkinson's disease (PD) group and Control group. In the responses gathered from individuals with Parkinson's, 100% were not menstruating, while in the control group, 26.9% were still menstruating. 39.1% of the individuals with Parkinson's and 58.1% individuals from the control group were perimenopausal in our sample. Lastly, 91.3% of the individuals with Parkinson's and 71.2% of the individuals from the control group were menopausal. It is important to note that these questions were asked individually, and participants were able to respond yes to more than one (i.e. they could've answered yes to both perimenopausal and menstruating if they were experiencing distant and irregular menses, or they could've answered yes to both perimenopausal and menopausal if they were on the later stage of perimenopause. This explains why the total percentages add up to over 100%). Surgical menopause was experienced by 27.3% of the individuals with Parkinson's and 16.5% in the control group. These risk factors are revealed to be a statistically insignificant positive correlational variable for Parkinson's disease. Oral contraceptives were reported to be used for an average of 1.4 years by the group of individuals with Parkinson's and 1.5 years by the control group. In the group of individuals with Parkinson's, 23.8% reported a history of oral contraceptives use, while in the control group, 17.6% did. For hormone replacement therapy, 30.4% of the individuals with Parkinson's disease and 14.6% of control subjects reported to have used it.

Table 2. Binomial Test (Parkinson's disease and Control)

	Level	Count	Total	Proportion	p
Have you used hormone replacement therapy? (PD group)	Yes	7	23	0.304	0.093
	No	16	23	0.696	0.093
Have you used hormone replacement therapy? (Control)	Yes	19	130	0.146	<.001
	No	111	130	0.854	<.001
Have you ever used oral contraceptives? (PD group)	Yes	5	21	0.238	0.027
	No	16	21	0.762	0.027
Have you ever used oral contraceptives? (Control)	Yes	23	131	0.176	<.001
	No	108	131	0.824	<.001
Are you still menstruating? (PD group)	No	23	23	1.000	<.001
Are you still menstruating? (Control)	Yes	36	134	0.269	<.001
	No	98	134	0.731	<.001
Are you perimenopausal? (PD group)	Yes	9	23	0.391	0.405
	No	14	23	0.609	0.405
Are you perimenopausal? (Control)	Yes	75	129	0.581	0.078
	No	54	129	0.419	0.078
Have you experienced menopause? (PD group)	Yes	21	23	0.913	<.001
	No	2	23	0.087	<.001
Have you experienced menopause? (Control)	Yes	94	132	0.712	<.001
	No	38	132	0.288	<.001
Did you undergo a surgical menopause? (PD group)	Yes	6	22	0.273	0.052
	No	16	22	0.727	0.052
Did you undergo a surgical menopause? (Control)	Yes	20	121	0.165	<.001
	No	101	121	0.835	<.001

Table 3 illustrates a supplementary question directed specifically to individuals with Parkinson's disease regarding the onset of Parkinson's disease symptoms in relation to their reproductive lifespan. No statistically significant differences were noted in the onset of Parkinsonism compared to the onset of symptoms during regular menses, perimenopause, or one year or more after the last menstrual period ($p > .05$). The responses of individuals with Parkinson's regarding the timing of onset to the menstrual cycle were statistically significant, with notable differences between responses concerning menstruation and menopause ($p < .001$ for both). However, there were no statistically significant differences observed in instances of perimenopause affecting Parkinson's disease risk ($p > .05$).

Table 3. Parkinsonism Onset Proportions

Proportions - When did your Parkinson's onset start?

Level		Count	Proportion
While going through perimenopause	Observed	10	0.455
	Expected	7.33	0.333
One year or more after last menstrual period	Observed	9	0.409
	Expected	7.33	0.333
While having regular periods	Observed	3	0.136
	Expected	7.33	0.333

χ^2 Goodness of Fit

χ^2	df	p
3.91	2	0.142

As seen in Table 4, all the individuals with Parkinson's disease that identified to have used hormone replacement therapy used them before their Parkinson's diagnosis.

Table 4. Proportions Test in Relations to Parkinson's Diagnosis

Proportions - Did you use hormone replacement therapy...

Level		Count	Proportion
Before PD diagnosis	Observed	8	1.00
	Expected	4.00	0.500

Information on the frequencies of the different types of hormone replacement therapy for both Parkinson's disease group and the control group can be found in Table 5.

Table 5. Fisher's Exact Test (Parkinson's disease and Hormone replacement therapy)

Contingency Tables

	Have you been diagnosed with Parkinson's Disease?		
What type of Hormone replacement therapy?	Yes	No	Total
Estrogen	4	14	18
Progesterone	1	2	3
Progestin	0	1	1
Other	3	3	6
Total	8	20	28

χ^2 Tests

	Value	df	p
χ^2 continuity correction	2.14	3	0.544
Fisher's exact test			0.617
N	28		

Table 6 presents a summary of the proportions of hormone types used by participants. In the Parkinson's disease group, 50% used estrogen, 12.5% used progesterone, and 37.5% used other hormones. Conversely, in the control group, 70% used estrogen, 10% used progesterone, 5% used progestin, and 15% used other forms.

Table 6. Proportions for types of hormone replacement therapy used (Parkinson's disease and Control)

Proportions - Type of HRT (Control)

Level	Count	Proportion
Other	3	0.1500
Estrogen	14	0.7000
Progesterone	2	0.1000
Progestin	1	0.0500

Proportions - Type of HRT (PD group)

Level	Count	Proportion
Other	3	0.375
Estrogen	4	0.500
Progesterone	1	0.125

To evaluate the associations of oral contraceptives, hormone replacement therapy, surgical menopause, and instances of current menstruation, perimenopause and menopause with the risk of Parkinson's disease, we calculated relative risk, log-odds ratio and odds ratio with 95% CI.

The pooled relative risk was 1.44 (CI: 0.575-3.58) for oral contraceptives use (ever versus never), 1.75 (CI: 0.776-3.82) for surgical menopause, 2.12 (CI: .971-4.63) for hormone replacement therapy (ever versus never), .513 (CI: .237-1.11) for perimenopause, 3.68 (CI:
.904-15) for instances of menopause.

The pooled odds ratio was 1.53 (CI: 0.509-4.63) for oral contraceptives use (ever versus never), 1.99 (CI: 0.692-5.75) for surgical menopause, .0568 (CI: .00336-.96) for menstruation, 2.53 (CI: .92-6.97) for hormone replacement therapy (ever versus never), .454 (CI: .181-1.13) for perimenopause, 4.29 (CI: .959-19.2) for instances of menopause.

The pooled log-odds ratio was .429 (CI: -.676-1.53) for oral contraceptives use (ever versus never), .69 (CI: -.369-1.75) for surgical menopause, -2.87 (CI: -5.69–0.0408) for menstruation, .929 (CI: -.835-1.94) for hormone replacement therapy (ever versus never), -.789 (CI: -1.7- .119) for perimenopause, 1.46 (CI: -.0423-2.96) for instances of menopause.

Restricted Sample

In the subset control group, the mean age is 65 (standard deviation = 5.11, range: 57-78) and 65.5 (standard deviation = 7.74, range: 57-82) in the Parkinson's disease group and control group, respectively. No significant differences were observed in years of oral contraceptives usage, instances of surgical menopause, hormone replacement therapy, and its types, menopause, age at menopause, age at menarche, and years of reproductive lifespan. The null hypothesis is still accepted for oral contraceptives usage, surgical menopause, hormone replacement therapy usage, and experience of perimenopause. However, statistically significant differences are no longer observed in instances of menopause.

Discussion

In our sample, individuals without Parkinson's disease exhibited a longer reproductive lifespan, an earlier age at menarche, and a later age at menopause. As expected, our data revealed a significant decrease in the prevalence of Parkinson's disease for those who are still menstruating, with a 94% reduction in risk. However, the observed differences may be influenced by age. Notably, we observed a 54.6% decrease in Parkinson's disease

risk for individuals experiencing perimenopause and a triple increase in risk for those who have undergone menopause. The Parkinson's disease group was significantly older than the control group, with a mean difference of almost 10 years ($p < .001$). This prompts consideration of potential implications for the validity of the results. It's possible that the control group may not be old enough to have developed Parkinsonism, as Parkinson's disease is uncommon in individuals younger than 50, with the average age of diagnosis being around 60 (Johns Hopkins Medicine, 2023). The mean age at menopause for the Parkinson's disease group in our data (46.8) appears to be younger than the United States national average age at menopause (49.9) and the South Korean national average age at menopause (49.3) (Appiah et al., 2021; Kim et al., 2023). Additionally, we found that the average reproductive lifespan in the United States (37.1) exceeded that of both the Parkinson's disease group (31.9) and the control group (35.5), as well as the average reproductive lifespan of the South Korean population (34.1) (Appiah et al., 2021; Kim et al., 2023). These comparisons provide additional insights suggesting that our study sample is consistent with the average Korean sample and aligns with previous research indicating that earlier menopause is a risk factor. Reduced estrogen levels may contribute to the higher prevalence of Parkinson's disease in South Korea compared to the United States (Appiah et al., 2021; Kim et al., 2023).

Next, we investigated the potential contribution of surgical menopause as a risk factor in Parkinson's disease. Our study revealed a 99% increase in the risk of Parkinson's disease associated with surgical menopause. This finding aligns with existing research, suggesting a connection between increased Parkinson's disease risk and the removal of ovaries, leading to a subsequent decline in estrogen levels (Marras & Saunders-Pullman, 2014; Nitkowska et al., 2014). However, these observed differences did not meet our threshold for statistical significance ($p > .05$). Future research should consider this question with a larger sample size.

Previous research has found mixed results on the relationship between oral contraceptives with Parkinson's disease risk (Marras & Saunders-Pullman, 2014). In our sample, individuals from both the control and Parkinson's disease groups who reported oral contraceptives usage had an average duration of approximately 1.45 years, which is too short for oral contraceptives to exhibit a protective factor for Parkinson's disease (Liu et al., 2014). My initial hypothesis was that estrogen and oral contraceptives would be a protective factor against the development of Parkinson's disease. This expectation was based on the idea that oral contraceptives usage is less common in South Korea and these factors could explain the elevated prevalence of Parkinson's disease among women compared to men in South Korea, in contrast to the global average (Park & Kim, 2021; Park et al., 2019). However, this hypothesis was rejected, as we observed that oral contraceptives users are 53% more likely to correlate with Parkinson's disease risk. Limitations included recruitment of a convenience sample, which might have contained greater or fewer oral contraceptive users than expected based on population prevalence rates, and a comparatively brief duration of oral contraceptives usage, may account for these unexpected findings. Alternatively, these results could be interpreted to suggest that while oral contraceptives may demonstrate protective effects in other countries, the opposite effect may be observed in South Korea due to unique contributing factors. Variations in the concentrations of progesterone and estrogen in oral contraceptives, as well as differences in predominant oral contraceptive formulations in South Korea, could potentially account for this difference. Such an interpretation would explain the higher prevalence of Parkinson's disease among women compared to men in South Korea, deviating from global patterns (Park et al., 2019).

In our study, hormone replacement therapy was a correlational factor associated with an increased Parkinson's disease risk. Considering the role of hormone replacement therapy in alleviating postmenopausal symptoms, the increased risk may stem from co-occurring factors such as low estrogen levels prompting the need for hormone replacement therapy (The North American Menopause Society, n.d.). Previous research also indicated the importance of variables such as the timing of hormone replacement therapy usage (Shulman, 2002). For example, hormone replacement therapy is known to prevent dementia, symptoms that individuals with Parkinson's disease commonly experience, if it starts within the first five years of menopause (Ali et al.,

2023; National Institute on Aging, 2022). However, these differences did not meet our threshold for statistical significance ($p > .05$).

It is possible that the inconclusive results observed across the data reflect differences between healthcare systems. South Korea may diagnose women earlier and have better screening practices for women, which could impact the onset of symptoms and the timing of diagnosis, consequently leading to a higher reported prevalence of Parkinson's disease among women compared to the global average. However, detailed data regarding diagnostic practices and screening protocols were not available for analysis in this study. Further research should consider different healthcare systems to better understand the inconsistency in the role of estrogen in Parkinson's disease prevalence.

Limitations and Future Research

The study's limitations included a recruitment of a convenient sample as participants were not randomly selected and the questionnaire was distributed in a targeted website. There was no equal opportunity and random sampling and population based. There was also an uneven distribution between the two sample groups. Moreover, relying on online communication with individuals in South Korea raises concerns about the reliability of self-reported data, in addition to the difficulty in reaching this geographically distant group. Additionally, the study overlooks environmental factors specific to residing in South Korea, as responses were collected from Koreans living in both South Korea and the United States. Future studies could consider replicating this research with an additional inclusion criteria, specifically targeting residents of South Korea to better account for fitting environmental factors. An oversight in survey design was noted, particularly in the categorization of participants based on menstruation status. Instead of posing independent questions for menstruation, perimenopause, and menopause, a forced-choice option could have been done to result in percentages that sum up to 100.

Future research should address hormone replacement therapy and oral contraceptives further. Specifically, examining the age at which hormone replacement therapy was initiated and its correlation with the onset of Parkinson's disease could provide valuable insights (Shulman, 2002). Different brands of oral contraceptives have different doses of estrogen, which is crucial to consider (Hatcher, 2018). The duration of oral contraceptive use may have a potential impact on Parkinson’s disease (Michael J. Fox Foundation, n.d.).

Likewise, future research should thoroughly explore the gender-associated risks of sociocultural symptoms that might explain observed sex differences in prevalence of Parkinson’s disease. More variables influencing estrogen levels, such as pregnancy, menstrual symptoms in Parkinson's disease patients, sexual activity, breast cancer, and natural estrogen intake, were not addressed due to time constraints (Rao et al., 2023). These unexamined variables may exert a more substantial influence on estrogen levels than those investigated in our study. Investigating the role of estrogen in either serving a protective or risk through research opens further exploration into non-genetic gender-specific symptoms. This includes societal gender norms, stigma, and cultural and social roles influencing treatment and diagnosis (Currie et al., 2004; Maffoni et al., 2017). For example, women experience misdiagnosis, and delayed diagnosis, influencing factors like higher mortality rates and a faster progression of Parkinson's disease (Cerri et al., 2019; Criado-Perez, 2021). It is possible that there is a shorter time window between symptom onset and diagnosis of Parkinson’s disease for South Korean women due to the different healthcare system. Addressing these issues could contribute to reducing the underrepresentation of women in Parkinson's disease research, initiating a discourse on the harmful effects of solely focusing on men's symptoms, and promoting better representation and support for women, who are less likely to have a specialist or a caregiver in their family (Kim & Woo, 2022; Morris, 2001).

Conclusion

Given the absence of well-established prevention methods for Parkinson's Disease, understanding the risks is valuable in this field. The current study found that Parkinson's disease is more prevalent among women who have undergone surgical menopause, used hormone replacement therapy and oral contraceptives, and experienced menopause. A closer examination of each variable reveals significant differences, suggesting protection during menstruation, non-significant protective results for perimenopause and non-significant risk results for menopause. Due to the contradicting results on the role of estrogen from the variables investigated, our study concluded that estrogen is neither a protective nor a risk factor for Parkinson's disease.

The significance of my research lies in expanding our understanding of Parkinson's disease within a group that has been underrepresented in the Parkinson's disease literature, namely Asian women. This becomes crucial in acknowledging the existence of sex-specific symptoms in Parkinson's disease, an understanding essential for properly supporting patients and ensuring a high quality of life tailored to their diverse lifestyles. The research opens for further exploration into non-genetic gender-specific symptoms, such as societal gender norms and stigma. Addressing these issues could contribute to reducing the underrepresentation and medical discrimination of women in Parkinson's disease research.

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References

Ali, N., Sohail, R., Jaffer, S. R., Siddique, S., Kaya, B., Atowoju, I., Imran, A., Wright, W., Pamulapati, S., Choudhry, F., Akbar, A., & Khawaja, U. A. (2023). The Role of Estrogen Therapy as a Protective Factor for Alzheimer's Disease and Dementia in Postmenopausal Women: A Comprehensive Review of the Literature. *Cureus*, *15*(8), e43053. https://doi.org/10.7759/cureus.43053

Appiah, D., Nwabuo, C. C., Ebong, I. A., Wellons, M. F., & Winters, S. J. (2021). Trends in Age at Natural Menopause and Reproductive Life Span Among US Women, 1959-2018. *JAMA*, *325*(13), 1328–1330. https://doi.org/10.1001/jama.2021.0278

Benedetti, M., Maraganore, D., Bower, J., McDonnell, S., Peterson, B., Ahlskog, E., Schaid, D., & Rocca, W. (2001, October 12). *Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: An exploratory case-control study*. International Parkinson and Movement Disorder Society. https://doi.org/10.1002/mds.1170

Cerri, S., Mus, L., & Blandini, F. (2019). Parkinson's Disease in Women and Men: What's the Difference? *Journal of Parkinson's Disease*, *9*(3), 501–515. https://doi.org/10.3233/JParkinson's disease-191683

Cooper, D. B., Patel, P., & Mahdy, H. (2024). Oral Contraceptive Pills. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK430882/

Criado-Perez, C. (2021). *Invisible women: Data bias in a world designed for men.* Abrams Press.

Currie, L., Harrison, M., Trugman, J., Bennett, J., & Wooten, F. (2004, June). *Postmenopausal Estrogen Use Affects Risk for Parkinson Disease*. JAMA Neurology Network. https://jamanetwork.com/journals/jamaneurology/fullarticle/786007

Duke University Health System. (2018, March 30). *Neurology and Women's Health, Part 5: Parkinson's and Movement Disorders*. Neurology and Women's Health, Part 5:

Parkinson's and Movement Disorders. https://neurology.duke.edu/news/neurology-and-womens-health-part-5-parkinsons-and-m ovement-disorders

Gaenslen, A., Swid, I., Liepelt-Scarfone, I., Godau, J., & Berg, D. (2011). The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. *Movement Disorders*, *26*(4), 653–658. https://doi.org/10.1002/mds.23499

Gandhi, K. R., & Saadabadi, A. (2024). Levodopa (L-Dopa). In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK482140/

García-Ramos, R., Santos-García, D., Alonso-Cánovas, A., Álvarez-Sauco, M., Ares, B., Ávila, A., Caballol, N., Carrillo, F., Escamilla Sevilla, F., E. Freire, Gómez Esteban, J. C., Legarda, I., López Manzanares, L., López Valdés, E., Martínez-Torres, I., Mata, M., Pareés, I., Pascual-Sedano, B., Mir, P., & Martínez Castrillo, J. C. (2021). Management of Parkinson's disease and other movement disorders in women of childbearing age: Part 1. *Neurología (English Edition)*, *36*(2), 149–157. https://doi.org/10.1016/j.nrleng.2020.05.015

Gong, D. K. (n.d.). *Intro | "If you lie down you die, if you walk you live."* Korean Parkinson's Disease Association. Retrieved October 19, 2023, from http://www.kpda.co.kr/

Hatcher, R. (2018). *Contraceptive Technology* (21st ed.). Ayer Company Publishers, Incorporated. https://books.google.com/books/about/Contraceptive_Technology.html?id=qsz8twEACA AJ

Hunley, K. L., Healy, M. E., & Long, J. C. (2009). The global pattern of gene identity variation reveals a history of long-range migrations, bottlenecks, and local mate exchange: Implications for biological race. *American Journal of Physical Anthropology*, *139*(1), 35–46. https://doi.org/10.1002/ajpa.20932

Johns Hopkins Medicine. (2023, October 13). *Young-Onset Parkinson's Disease*. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/parkinsons-disease/you ngonset-parkinsons-disease

Kenborg, L., Lassen, C. F., Ritz, B., Andersen, K. K., Christensen, J., Schernhammer, E. S., Hansen, J., Wermuth, L., Rod, N. H., & Olsen, J. H. (2015). Lifestyle, Family History, and Risk of Idiopathic Parkinson Disease: A Large Danish Case-Control Study. *American Journal of Epidemiology*, *181*(10), 808–816. https://doi.org/10.1093/aje/kwu332

Kenton, W. (2023, June 28). *Goodness-of-Fit*. Investopedia. https://www.investopedia.com/terms/g/goodness-of-fit.asp

Kim, A., & Woo, K. (2022). Gender differences in the relationship between informal caregiving and subjective health: The mediating role of health promoting behaviors. *BMC Public Health*, *22*(1), 311. https://doi.org/10.1186/s12889-022-12612-3

Kim, H.-Y. (2017). Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. *Restorative Dentistry & Endodontics*, *42*(2), 152–155. https://doi.org/10.5395/rde.2017.42.2.152

Kim, H., Jung, J. H., Han, K., Lee, D.-Y., Fava, M., Mischoulon, D., & Jeon, H. J. (2023). Ages at menarche and menopause, hormone therapy, and the risk of depression. *Science Direct*, *83*, 35–42.

Kim, S., Park, H.-J., Park, M. J., & Kim, H. S. (2020). Reliability and Validity of the Korean Short-form Eight-item Parkinson's Disease Questionnaire (Parkinson's diseaseQ-8). *Journal of Health Informatics and Statistics*, *45*(2), 147–156. https://doi.org/10.21032/jhis.2020.45.2.147

Kittles, R. A., & Weiss, K. M. (2003). Race, Ancestry, and Genes: Implications for Defining

Disease Risk. *Annual Review of Genomics and Human Genetics*, *4*(1), 33–67. https://doi.org/10.1146/annurev.genom.4.070802.110356

Kompoliti, K., Comella, C. L., Jaglin, J. A., Leurgans, S., Raman, R., & Goetz, C. G. (2000). *Menstrual-related changes in motoric function in women with Parkinson's disease | Neurology* [November 28, 2000]. Neurology Journals. Retrieved December 5, 2023, from https://doi.org/10.1212/WNL.55.10.1572

KPDA. (2023, October 11). 여의도국회의사당집회—*YouTube*. https://www.youtube.com/watch?v=ogE-GVELcAg

Latif, S., Jahangeer, M., Razia, D., Ashiq, M., Ghaffar, A., Akram, M., Allam, A., Bouyahya, A., Garipova, L., Shariati, M., Thiruvengadam, M., & Ansari, M. (2021, June 21). *Dopamine in Parkinson's disease—ScienceDirect*. Science Direct. https://doi.org/10.1016/j.cca.2021.08.009

Liu, R., Baird, D., Park, Y., Freedman, N. D., Huang, X., Hollenbeck, A., Blair, A., & Chen, H. (2014). Female reproductive factors, menopausal hormone use, and Parkinson's disease. *Movement Disorders*, *29*(7), 889–896. https://doi.org/10.1002/mds.25771

Lv, M., Zhang, Y., Chen, G.-C., Li, G., Rui, Y., Qin, L., & Wan, Z. (2017). Reproductive factors and risk of Parkinson's disease in women: A meta-analysis of observational studies. *Behavioural Brain Research*, *335*, 103–110. https://doi.org/10.1016/j.bbr.2017.07.025

Maffoni, M., Giardini, A., Pierobon, A., Ferrazzoli, D., & Frazzitta, G. (2017). Stigma Experienced by Parkinson's Disease Patients: A Descriptive Review of Qualitative Studies. *Hindawi*, *2017*, 7. https://doi.org/10.1155/2017/7203259

Marras, C., & Saunders-Pullman, R. (2014). The Complexities of Hormonal Influences and Risk of Parkinson's Disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *29*(7), 845–848. https://doi.org/10.1002/mds.25891

Mayo Clinic. (2023, May 26). *Parkinson's disease—Symptoms and causes*. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/parkinsons-disease/symptoms-causes/syc-20376055

McKinney, K., Hinshaw, K., Ross, D., Whitehead, M., Stevenson, J., Panico, S., Galasso, R., Celentano, E., Frova, L., Capocaccia, R., & Berrino, F. (1996). Use Of Hormone Replacement Therapy. *BMJ: British Medical Journal*, *313*(7058), 686–687.

Michael J. Fox Foundation. (n.d.). *Sexual & Reproductive Health | Parkinson's Disease*. The Michael J. Fox Foundation for Parkinson's Research. Retrieved February 20, 2024, from https://www.michaeljfox.org/news/sexual-reproductive-health

Morris, M. (2001). GENDER-SENSITIVE HOME AND COMMUNITY CARE AND CAREGIVING RESEARCH: A SYNTHESIS PAPER. *Health Canada Women's Health Bureau*, 88.

National Health Service. (2022, October 11). *Hysterectomy*. Nhs.Uk. https://www.nhs.uk/conditions/hysterectomy/

National Institute of Standards and Technology. (n.d.). *1.3.6.6.18. Binomial Distribution*. National Institute of Standards and Technology. Retrieved February 20, 2024, from https://www.itl.nist.gov/div898/handbook/eda/section3/eda366i.htm

National Institute on Aging. (2022, April 14). *Parkinson's Disease: Causes, Symptoms, and Treatments*. National Institute on Aging. https://www.nia.nih.gov/health/parkinsons-disease/parkinsons-disease-causes-symptomsand-treatments

Nicoletti, A., Nicoletti, G., Arabia, G., Annesi, G., De Mari, M., Lamberti, P., Grasso, L.,

Marconi, R., Epifanio, A., Morgante, L., Cozzolino, A., Barone, P., Quattrone, A., & Zappia, M. (2011). Reproductive factors and Parkinson's disease: A multicenter case–control study. *Movement Disorders*, *26*(14), 2563–2566. https://doi.org/10.1002/mds.23951

Nitkowska, M., Czyżyk, M., & Friedman, A. (2014). Reproductive life characteristics in females affected with Parkinson's disease and in healthy control subjects – a comparative study on the Polish population. *Neurologia i Neurochirurgia Polska*, *48*(5), 322–327. https://doi.org/10.1016/j.pjnns.2014.08.004

Park, H., & Kim, K. (2021). Trends and Factors Associated with Oral Contraceptive Use among Korean Women. *Healthcare*, *9*(10), 1386. https://doi.org/10.3390/healthcare9101386

Park, J.-H., Kim, D.-H., Kwon, D.-Y., Choi, M., Kim, S., Jung, J.-H., Park, Y.-G., & Han, K. (2019). Trends in the incidence and prevalence of Parkinson's disease in Korea: A nationwide, population-based study | BMC Geriatrics | Full Text. *BioMed Central*, *320.* https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-019-1332-7

Rao, S. C., Li, Y., Lapin, B., Pattipati, S., Ghosh Galvelis, K., Naito, A., Gutierrez, N., Leal, T. P., Salim, A., Salles, P. A., De Leon, M., & Mata, I. F. (2023). Association of women-specific health factors in the severity of Parkinson's disease. *Npj Parkinson's Disease*, *9*(1), Article 1. https://doi.org/10.1038/s41531-023-00524-x

Risks and Benefits of Hormone Replacement Therapy (hormone replacement therapy) on JSTOR. (1996). Retrieved February 20, 2024, from https://www.jstor.org/stable/25066175

Schneider, D. G., & Lauber, M. (2020). *The Chi-Square Test.* https://dlf.uzh.ch/openbooks/statisticsforlinguists/chapter/chi-square-test-significance-2/

Schumacher-Schuh, Artur Francisco, Bieger, A., Okunoye, O., Mok, K. Y., Lim, S.-Y., Bardien, S., Ahmad-Annuar, A., Santos-Lobato, B. L., Strelow, M. Z., Salama, M., Rao, S. C., Zewde, Y. Z., Dindayal, S., Azar, J., Prashanth, L. K., Rajan, R., Noyce, A. J., Okubadejo, N., Rizig, M., … Global Parkinson's Genetics Program (GP2). (2022). Underrepresented Populations in Parkinson's Genetics Research: Current Landscape and Future Directions. *Movement Disorders: Official Journal of the Movement Disorder Society*, *37*(8), 1593–1604. https://doi.org/10.1002/mds.29126

Shirley Ryan AbilityLab. (2014, January 29). *Parkinson's Disease Questionnaire—39.* Shirley Ryan AbilityLab. https://www.sralab.org/rehabilitation-measures/parkinsons-disease-questionnaire-39

Shulman, L. M. (2002). Is there a connection between estrogen and Parkinson's disease? *Parkinsonism & Related Disorders*, *8*(5), 289–295. https://doi.org/10.1016/s1353-8020(02)00014-7

Tenny, S., & Hoffman, M. R. (2024). Relative Risk. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK430824/

The North American Menopause Society. (n.d.). *Hormone Therapy: Benefits& Risks*. The North American Menopause Society. Retrieved February 20, 2024, from https://www.menopause.org/for-women/menopauseflashes/menopause-symptoms-and-tre atments/hormone-therapy-benefits-risks

Wang, P., Li, J., Shi, Q., Wen, H., & Du, J. (2014, December 31). *Hormone replacement therapy and Parkinson's disease risk in women: A meta-analysis of 14 observational studies—PMC*. National Library of Medicine. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4317144/

Yasui, M., Kihira, T., Ota, K., Funahashi, K., & Komai, N. (1992). [A case of parkinsonism induced by an oral contraceptive]. *No to Shinkei = Brain and Nerve*, *44*(2), 163–166.

Yu, Z., Jiao, Y., Zhao, Y., & Gu, W. (2022, December 2). *Level of Estrogen in Females—The*

Different Impacts at Different Life Stages. Multidisciplinary Digital Publishing Institute. https://www.mdpi.com/2075-4426/12/12/1995

Yuen, K. K. (1974). The Two-Sample Trimmed t for Unequal Population Variances. *Biometrika*, *61*(1), 165–170. https://doi.org/10.2307/2334299

Yuk, J.-S., & Jeong, S. H. (2023). Association Between Menopausal Hormone Therapy and Risk for Parkinson's Disease. *Journal of Parkinson's Disease*, *13*(8), 1357–1367. https://doi.org/10.3233/JParkinson's disease-230230

Zhao, Y. J., Wee, H. L., Chan, Y.-H., Seah, S. H., Au, W. L., Lau, L. N., Pica, E., Li, S. C., Luo, N., & Tan, L. (2010). *Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times—Zhao—2010—Movement Disorders—Wiley Online Library*. *25*(6), 710–716.