Ethnic variation in the onset age of menopause and its consequences on women's health

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Research Article

Abstract

Background: Reproduction is a major determinant of health in women. To investigate whether female reproductive physiology is still evolving in different ethnic populations, the relationship between ethnicity and onset age of menopause was examined. The relationship between menopause and women's health was additionally investigated to reflect on the increased risk of serious health conditions following the hormonal fluctuations associated with menopause.

Methods: All data used to complete the study's statistical analyses were obtained from the Study of Women's Health Across the Nation (SWAN). Women from five ethnicities were included: African American, Chinese, Japanese, Caucasian, and Hispanic. The onset ages of early perimenopause, late perimenopause, and post-menopause were considered, as well as race and diagnoses of stroke, heart attack, osteoporosis, and diabetes. Both ANOVA and Tukey's honestly significant difference (HSD) tests were performed.

Results: We found that the population of Chinese women reached late perimenopause and the population of Japanese women reached both late perimenopause and post-menopause significantly later than African American women. The cohort of Hispanic women reached late perimenopause significantly earlier than most ethnicities, excluding African American women, and reached post-menopause significantly later than all ethnicities. Various associations between the onset of menopause and diagnoses of serious health conditions, including osteoporosis, heart attack, and stroke, were found, individually and in combination with other variables.

Conclusions: The ethnicity-related variation found within the onset age of late perimenopause and post-menopause in the SWAN populations suggests that female reproductive changes are still evolving in different ethnicities. The associations found between menopause and women's health suggest that menopause plays a substantial role in the diagnosis of serious health conditions such as heart attacks, stroke, and osteoporosis. Future studies should consider the impact of both biological (menopause) and non-biological factors on the variation seen in middle-aged women's health and focus on practical applications in women's healthcare.

Background

The field of women's health encompasses a broad array of issues, from physiology to healthcare resources and proper education. An aspect of women's health that has become a relatively recent focus of research is menopause. Menopause is a major determinant of women's health. Menopause occurs when a woman stops menstruating and her ovaries no longer carry functioning follicles to use in reproduction [1]. It is diagnosed after 12 months of amenorrhea, i.e., the absence of menstruation, and traditionally occurs in a woman's 40s or 50s, with an average age of onset of 51 years in the United States [1–3]. The menopausal transition can be separated into distinct phases. One of particular interest for this study is perimenopause, the period preceding menopause when reproductive system changes are

beginning to occur [2]. Common menopausal symptoms are hot flashes, urinary incontinence, urinary tract infections, vaginal atrophy, reduced sexual function, difficulty sleeping, and emotional changes [2, 4]. Given the potential severity and disruptiveness of these symptoms, it is no wonder that menopause and its aspects, symptoms, and associated health conditions have become such an area of interest in the field of women's health.

The evolutionary origins of menopause remain an intriguing area of speculation in the field of evolutionary biology. Current popular hypotheses in this field include the mate choice theory, the lifespan artifact theory, and the grandmother hypothesis [5]. The mate choice theory hypothesizes that male mating preferences for younger females resulted in the accumulation of deleterious mutations affecting female fertility [6]. Natural selection no longer selected for fertility in older females, and eventually mutant alleles, leading to reproductive senescence (i.e., deterioration with age), accumulated and became fixed [5]. The lifespan artifact theory speculates that menopause results from the relatively recent increase in the average human lifespan [5, 7]. After humans became more adept at avoiding predation and curing illnesses, and with increasing industrialization, average lifespan increased [5]. As such, females began to outlive their innate reproductive capacities, a feat their ancestors failed to achieve [5]. Finally, the grandmother hypothesis speculates that menopause evolved from the increased inclusive fitness that arose when women rechanneled their reproductive energy into caring for younger generations and offspring [5]. Kin selection, or the process whereby evolution favours the reproductive success of one's relatives at a personal cost to the individual, is crucial for this theory's rationale [8].

A paper produced by Takahashi et al. [5] combined the advantages of each evolutionary theory above into a novel hypothesis. The theory speculates that, at some point, mating involved only young women, leading to the accumulation of late-onset fertility-diminishing alleles. Human longevity was then extended, allowing reproductive senescence to occur and the fertility-diminishing effects of the accumulated mutations to become apparent. Kin selection was then able to operate, as older non-reproductive women were able to re-channel energy into caring for their grandchildren. The combination of these behavioural patterns and mutations resulted in the menopausal transition [5]. However, regardless of the theoretical basis, the health consequences of menopause remain the same.

Throughout menopause, the ovaries' hormone levels fluctuate; less estrogen is produced, severely increasing the risk of various health conditions in middle-aged women. The most common health conditions affected by these changes are heart disease, stroke, osteoporosis, diabetes, thyroid problems, and urinary incontinence [9, 10]. Before menopause, women have a lower risk of heart disease than men, but with lower estrogen levels after menopause, cholesterol can build up in the artery walls leading to the heart [9]. By the time women reach the age of 70, they have the same risk of heart disease and stroke as their male counterparts at that age [9]. Estrogen is a hormone that protects against bone loss, so a decreased level can also cause bone mass to decrease more rapidly, leading to an increased risk of osteoporosis [9, 10]. Estrogen and progesterone affect how cells respond to insulin, and so as their levels fluctuate over the menopausal transition, so do blood sugar levels [11]. As a result, uncontrolled high blood sugar can lead to complications related to diabetes [11]. Certain perimenopausal symptoms may

also be related to thyroid dysfunction, as the fluctuations in estrogen during menopause influence the level of thyroid-binding globulin that is released [12]. Finally, lower estrogen levels have been shown to weaken the urethra, leading to urinary incontinence in about half of post-menopausal women [9]. Therefore, middle-aged women are not only experiencing the disruptive symptoms of menopause but the potential risk of more serious health conditions as well.

The Study of Women's Health Across the Nation (SWAN) is a United States-based, multi-centre longitudinal study designed to examine the health of middle-aged women through the examination of changes occurring during the menopausal transition [13]. Changes include physical, biological, psychological, and social differences [13]. The study was initiated in 1994, with 16 follow-up visits occurring to date since baseline data was collected in 1997 [13]. The women who participated in the study self-identified as one of five ethnicities: African American, Japanese, Chinese, Caucasian, or Hispanic [13]. The objectives of the study have been summarized as follows: (1) to characterize the symptoms, hormonal patterns, and bleeding patterns of menopause; (2) to investigate the hormonal and bleeding characteristics related to changes in bone mineral density, cardiovascular marker status, carbohydrate metabolism, and body composition during menopause; (3) to examine the relationship between psychosocial factors, personality characteristics, and behaviours as they relate to the age of onset, symptoms, and physiological changes of menopause; (4) to determine what changes are the result of menopause, and not age-related changes; and (5) to describe and quantify the cultural and ethnic differences among women regarding menopause and aging in general [14]. Through this multi-disciplinary focus, SWAN has created an extensive and comprehensive cross-examination of women's health during the transitional period of menopause [15], supporting research regarding various aspects of women's health.

While SWAN data has been used extensively to produce and publish results regarding women's health, almost none of these papers use the data as a tool to examine the evolutionary origins of menopause, particularly across different races and their effect on women's health. An exception to this is an earlier study by Chan et al.[16] that used a set of incomplete SWAN data (i.e., data from baseline up until the tenth follow-up visit in 2008) to examine the relationship between race and the onset of menopause. The focus was to reflect on whether menopause continues to evolve and, if so, if it could de-evolve or disappear entirely. The following menopausal characteristics were examined between and within ethnicities: onset age of perimenopause, onset age of menopause, duration of perimenopause, and variation in serum hormone concentrations [16].

The study's results showed no significant differences in the age of perimenopausal and menopausal onset between ethnicities, although a similar window of menopausal age was noted within populations. These findings may indicate the role of similar mating behaviours and patterns between ethnicities. Significant variation was observed in serum hormone concentrations. Specifically, the rate of increase of follicle-stimulating hormone and testosterone differed significantly in Hispanic and African American women compared to the remaining ethnicities during menopause. These findings led Chan et al. to conclude that menopause is a relatively young and continuously evolving trait [16].

Chan et al. used partial data from SWAN's collection of annual surveys. We decided to revisit the results of Chan et al. [16] using complete SWAN data. The aim of the present study was to reanalyze the SWAN data for variation and evolution of menopause and its effect on women's health. As such, this study's two objectives are to analyze the relationship between (1) ethnicity and the onset of menopause and (2) menopause and women's health.

Methodology

Sample population

SWAN's eligibility criteria were as follows: women aged 42–52 years; no surgical removal of the uterus and/or both ovaries; no current use of exogenous hormone preparations affecting ovarian function; at least one menstrual period in the past 3 months; and self-identification with one of the ethnic groups designated at each study site [14]. Enrollment took place between 1996 and 1997, with a total of 3,302 pre-menopausal women enrolled [15]. The study included African American, Caucasian, Chinese, Hispanic, and Japanese women [13].

The eligibility criteria used will differ those used in the Chan et al. study [16]. All 3,302 women enrolled in SWAN will be considered in this study.

Menopausal stages

The onset ages of early perimenopause, late perimenopause, and post-menopause were examined for each ethnicity in SWAN. The variable "STATUS" was used to indicate the menopausal status of the participants. Those who were in early perimenopause responded to the variable with "(4) Early Perimenopause" (i.e., women who have had bleeding in the previous 3 months, but with noticeably inconsistent menstrual cycles). Women in late perimenopause responded to the variable with "(3) Late Perimenopause" (i.e., women who have experienced a menstrual cycle in the previous 12 months, but not in 3 months prior to their visit). Finally, post-menopausal women responded to the variable with "(2) Natural Post" (i.e., women who have not experienced a menstrual cycle during the previous 12 months) [16]. The age at which each participant reached these stages was extracted and used for statistical analysis to test for statistically significant relationships between the age at which women entered these stages of menopause and other variables.

Ethnic populations

Regarding the SWAN variable "RACE", a participant's response of "1", "2", "3", "4", or "5" was used to indicate Black/African American, Chinese/Chinese American, Japanese/Japanese American, White/White non-Hispanic, and Hispanic ethnicity, respectively. We will be using "ethnicity" and "race" interchangeably.

Health conditions affected by menopause

Stroke, heart attack, osteoporosis, and diabetes will be considered the health conditions most affected by menopause; as such, they will be used to investigate statistical significance between menopause and

women's health. The following variable names will be used, corresponding to the SWAN codebook: "STROKE", "HEARTAT", "OSTEOPR", and "DIABETE". A response of "1" indicates that the participant has not been told that they have this condition by a medical professional; a response of "2" indicates that they have been told. It should be noted that thyroid problems and urinary incontinence were not considered in this analysis. Furthermore, diagnoses of heart attacks, osteoporosis, and diabetes were not reported in the baseline data and so were first incorporated in the visit 1 dataset.

Datasets and statistical analysis

The variables examined in this study were compared across ethnicity to determine statistical significance. Data from the baseline visit and the first 10 annual visits were uploaded into *R*, a programming software [17]. The desired variables from each visit were extracted into one document, containing each participant's SWAN identification number and age, menopausal status, and health condition status at each visit. All statistical tests were completed in *R*.

To conduct the statistical analyses required, data from one visit was selected to represent the study's population, and so the proportion of each ethnicity was compared for every visit. The later datasets were preferred since they captured the most recent and accurate participant responses available. Visit 10, which represented the most recently available data, was insufficient for statistical use, as no Hispanic women reported data at this visit. However, visit 9 included a proportionate number of Hispanic women to the other ethnicities. Therefore, the data responses from visit 9 were used in all statistical testing.

To compute the statistical significance between age of early perimenopausal, late perimenopausal, and post-menopausal onset with race and stroke, heart attack, osteoporosis, and diabetes, both one-way and two-way ANOVA tests were completed. Calculated p-values of *p < 0.05* were considered statistically significant. Additionally, Tukey's HSD test was completed for each onset age. This *post-hoc* analysis tested differences among the sample means of all races for significance. Statistically significant differences between races corresponded to 95% confidence intervals that did not contain 0 for the difference in mean onset ages.

Expected limitations

Expected limitations of the study include the limited diversity of ethnicities, study sample size, the menopausal stage definitions, and the selection of a single dataset to be used for statistical testing. All women enrolled in the study at baseline were included in the analysis, differing from the methodology, and therefore results, of Chan et al., which implemented a more restrictive set of eligibility criteria [16]. This study makes a distinction between early perimenopause and late perimenopause, as per the SWAN annual questionnaires. However, many studies do not make this distinction, instead investigating perimenopause as a single stage, which may explain any differing results, or lack thereof, in this study. In addition, while this study refers to the onset of post-menopause as the time when women experience 12 months without a menstrual cycle, many studies refer to this simply as the onset of menopause. To complete the required analyses, data from visit 9 was selected for use. While it was deemed the most accurate and representative set of data available, any results, significant or otherwise, will likely differ

from those produced by another dataset. Finally, following the relevant Chan et al. study limitations, it is also expected that the restrictive eligible age range used by SWAN will be a limitation of this study [16].

Results

Tukey's Honestly Significant Difference Testing

To examine the mean differences between races for the ages of early perimenopausal, late perimenopausal, and post-menopausal onset, three Tukey's HSD tests were completed using the data from SWAN visit 9. In this dataset, 674 African American, 207 Chinese, 254 Japanese, 1203 Caucasian, and 131 Hispanic women reported data. Statistically significant results indicated that the mean onset ages for two ethnic populations differed significantly. A comparison of the distribution of onset ages for each race was constructed and can be seen in Fig. 1. A noticeable amount of variation can be observed within the boxplots for late perimenopause and post-menopause, with the boxplots for early perimenopause being the most consistent with one other.

The first test, which looked at mean differences in race compared to the onset age of early perimenopause, did not produce any significant results (Fig. 2). This aligns with the lack of a significant relationship found between race and onset age of early perimenopause (**Table 2**). None of the 95% confidence intervals produced a statistically significant p-value (i.e., all contained 0 in their interval). The relationships that almost differed significantly were between Hispanic and Japanese ($p = 0.1373378$) and Japanese and African American ($p = 0.1737345$) populations (**Table 3**).

The second Tukey's HSD test examined the mean differences in race compared to the onset age of late perimenopause. Five significant relationships were produced in this case (Fig. 3), aligning with the significant association that was found between race and the onset age of late perimenopause (**Table 2**). Lying to the right of the *0* boundary (i.e., relationships where the mean difference was positive), Chinese and African American populations ($p = 0.0344715$) and Japanese and African American populations ($p = 0.0185633$) differed significantly. To the left of the *0* boundary (i.e., the mean difference was negative), Hispanic and Chinese populations ($p = 0.0005473$), Hispanic and Japanese populations ($p = 0.0003507$), and Hispanic and Caucasian populations ($p = 0.0024939$) differed significantly. It should be noted that the mean differences in Caucasian and African American ($p = 0.1182216$) and Hispanic and African American ($p = 0.1016629$) populations almost differed significantly as well (**Table 4**).

The third Tukey's HSD test, looking at the onset age of post-menopause, also produced five statistically significant relationships (Fig. 4). This observation aligns with the significant association found between race and the onset age of late perimenopause (**Table 2**). The significant differences, which were all positive, were seen between Japanese and African

American ($p = 0.0076733$), Hispanic and African American ($p \approx 0.0000000$), Hispanic and Chinese ($p = 0.0000762$), Hispanic and Japanese ($p = 0.0025965$), and Hispanic and Caucasian ($p = 0.0000002$)

populations. It should be noted that the difference between Caucasian and African American populations was close to differing significantly as well ($p = 0.0630467$) (**Table 5**).

ANOVA Testing

ANOVA tests were completed, crossing age of menopausal onset with race and various health conditions, using the SWAN visit 9 dataset. The first ANOVA test examined the relationships between the age of early perimenopausal onset with age and health condition. Only one significant relationship was revealed, between osteoporosis and age of early perimenopausal onset ($p = 0.00427$). No other relationships were seen to be statistically significant, with the next closest two being between age of early perimenopausal onset and race ($p = 0.07031$) and age of early perimenopausal onset and

race/heart attacks ($p = 0.13689$) (**Table 2**).

The second ANOVA test examined the relationships between the age of late perimenopausal onset with race and all relevant health conditions. In this case, four relationships produced statistically significant results. The relationship between race and onset age of late perimenopause was the most significant relationship ($p = 1.95x10^{-5}$). Statistically significant associations were also seen between the onset age of late perimenopause and osteoporosis ($p = 0.0242$), heart attacks ($p = 0.0183$), and the combination of race, osteoporosis, and stroke ($p = 0.0263$). It should be noted that the relationship between the onset age of late perimenopause and stroke was almost statistically significant ($p = 0.0793$) (**Table 2**).

Finally, the third ANOVA test examined the relationships between the age of post-menopausal onset with race and health conditions. Three relationships resulted in statistical significance: the onset age of post-menopause and race ($p = 4.38x10^{-10}$), stroke ($p = 0.0423$), and the combination of heart attacks and stroke ($p = 0.0198$). It should be noted that the relationship between the onset age of post-menopause and race, osteoporosis, and stroke was close to being statistically significant ($p = 0.0591$) (**Table 2**).

Discussion

Ethnic variation in onset age of early and late perimenopause

None of the ethnic populations in SWAN were found to differ significantly in their onset age of early perimenopause. However, significant differences were noted between many ethnicities in their onset age of late perimenopause. Chinese and Japanese women both had a significantly higher mean onset age than African American women (i.e., Chinese and Japanese women reached late perimenopause later, on average). Additionally, Hispanic women had a significantly lower mean average onset age of late perimenopause than Chinese, Japanese, and Caucasian women.

Currently, the only SWAN-related publication that has properly investigated ethnic variation in the onset age of perimenopause is the study by Chan et al. [16], although it makes no distinction between early

perimenopause and late perimenopause. The study found a significantly lower perimenopausal onset age in Hispanic women when compared to the remaining ethnicities [16]. The late perimenopausal onset results from this study support the findings from Chan et al., except for the lack of a significant difference between Hispanic and African American women, although these ethnicities were close to differing significantly. Following Chan et al., the results from this study indicate that reproductive changes may still be evolving in women, even if incrementally in each ethnic population [16]. However, it should be noted that the subpopulation of Hispanic women was much smaller than the other ethnic subpopulations, which may have biased the results.

Additional literature regarding ethnic variation in the onset age of perimenopause, whether early or late, is limited. In a study by Hardy and Kuh, the onset age of perimenopause was found to be 48 years in a cohort of exclusively British women [18]. Race and/or ethnicity was not mentioned in the study, even in the capacity of an adjusted analysis [18]. Another study found the onset age of perimenopause to be 47.5 years, but similarly race and/or ethnicity was not specified [19]. In a study by Sammel et al., Caucasian and African American women were recruited [20]. It was found that African American women entered pre-menopause earlier than Caucasian women, but not perimenopause [20]. The latter observation supports the absence of a meaningful difference found between the two ethnicities in this analysis. Given the limited literature, it proves to be difficult to make comparisons between the study's findings and additional results regarding age of perimenopausal onset and race.

Ethnic variation in onset age of post-menopause

Various ethnicities differed significantly in their onset age of post-menopause. Japanese women had a significantly higher mean age of onset than African American women (i.e., Japanese women reached post-menopause later, on average), and Hispanic women had a significantly higher mean age of onset than African American, Chinese, Japanese, and Caucasian women (i.e., Hispanic women reached post-menopause later, on average).

Interestingly, the latter result is inconsistent with those found in the study by Chan et al. [16], where Hispanic women reached menopause significantly earlier than all other ethnicities. Again, the relatively small population size of Hispanic women should be taken into consideration, in addition to the sole inclusion of data from visit 9 in this study versus the inclusion of all 10 visits in Chan et al. [16]. Given that a statistically significant difference was still observed, these results may still be indicative of a difference in the timing of menopausal onset in Hispanic women, following the conclusions of Chan et al. [16].

A study by Palacios et al. found that the onset age of menopause for women in Latin America was lower than the onset age for European and North American women [21], differing from the results found in this study. A similar study found that Latina women reached natural menopause significantly earlier than Caucasian women, while Japanese women reached it later than Caucasian women [22]. Both observations differ from the results in this analysis. With the use of SWAN data, one study found that the median age at menopause was relatively similar across all ethnicities, with the corresponding value for

Hispanic women being only slightly lower [23]. While this slight variation works in favour of the Chan et al. findings [16], median and mean calculations provide distinct insight into the distribution of a population.

The study by Palacios et al. also found that Asian women reached post-menopause earlier than any other ethnicity, supporting this study's finding that Chinese and Japanese women reached post-menopause significantly earlier than Hispanic women [21]. One study found that Japanese women reached post-menopause later than Caucasian, African American, Hispanic, and Chinese women [23]. Similar results were seen in a SWAN-related study that found that Japanese women experienced premature ovarian failure (i.e., premature menopause) less than African American, Chinese, Caucasian, and Hispanic populations, indicating that the Japanese population reached menopause later [24]. Both studies support the finding that Japanese women reached post-menopause significantly later than African American women, but they don't align with the finding that Hispanic women reached post-menopause significantly later than Japanese women from this analysis.

Another SWAN-related study found that African American women tended to reach menopause earlier than all other ethnicities, although this was not a significant finding [25]. Still, this tendency supports the earlier onset age seen in African American women in comparison to Japanese and Hispanic women in this study. It should also be noted that the study's sole focus is on the menopausal transition (i.e., the onset of the menopausal transition defined as the persistent difference of at least 7 days in the length of consecutive menstrual cycles) [25] instead of distinct menopausal stages. A similar study found that African American women experience menopause earlier than their peers of other racial backgrounds [26], consistent with the relationships between African American and Japanese and Hispanic women. Various studies have found that African American women have reached menopause earlier than Caucasian women [27–29], and others have found that there was no significant difference between the two races [20, 22, 23]. Our analysis found no significant difference between African American and Caucasian women at the onset age of menopause, supporting the latter findings [20, 22, 23].

Interestingly, a study analyzing datasets regarding women from India found that their average age of menopause was significantly lower than their Western counterparts [30]. This observation calls into question the effect of location, culture, and genetics on the evolution of menopause. Future studies should consider international populations in their analyses to investigate this potential effect.

Health conditions associated with onset age of menopause

Various significant associations were found in the study's analysis of menopause and women's health. It was found that the diagnosis of osteoporosis was associated with the onset of both early and late perimenopause, diagnosis of heart attacks was associated with the onset of late perimenopause, and diagnosis of stroke was associated with the onset of post-menopause. In addition, race, osteoporosis, and stroke were, in combination, associated with the onset of late perimenopause, while the combination of heart attack and stroke diagnoses was associated with the onset of post-menopause. Therefore, in the SWAN population, only a diagnosis of stroke was found to be associated with the onset of both

perimenopause and post-menopause, either on its own or in combination with another variable. No significant associations were found across all three stages of menopause, which may imply that the distinct hormone fluctuations at each point in the menopausal transition may have a different effect.

Given the increased risk of osteoporosis due to the fluctuations of estrogen in menopause, various studies have investigated whether this risk is reflected in actual populations. The findings of the relevant literature are summarized in Table 1. One study measured bone density at various skeletal sites in a cohort of pre-menopausal and perimenopausal women [31]. It was found that while pre-menopausal women showed no significant bone loss over a 3-year period, perimenopausal women lost a significant amount of bone density at various sites [31], supporting this study's observation of an association between the onset of perimenopause and osteoporosis. A study solely focused on women from India found that post-menopausal women had an increased risk of osteoporosis [30], although this significant relationship was not observed in this analysis. Another study investigated the effect of different age intervals at menopause on the prevalence of osteoporosis [32]. Age at menopause was found to be negatively correlated with osteoporosis (i.e., as the age of menopausal onset increased, the prevalence of osteoporosis decreased in the population) [32], which calls into question the presence of other factors that may contribute to this finding.

Many studies have additionally investigated the relationship between earlier menopause and cardiovascular disease (Table 1). Post-menopausal women from India were found to have an increased risk of heart attacks [30], supporting the association found between post-menopause and heart attack and stroke diagnoses in this study. Studies have found an association between an earlier onset of menopause and a higher risk of cardiovascular disease and stroke [33], as well as with actual diagnoses of cardiovascular disease [34], supporting this study's findings. Similarly, another study found that while pre-menopausal women had a low incidence of cardiovascular disease, the incidence drastically increased once the women entered perimenopause [35]. A study focused solely on French women found that menopause was associated with a higher prevalence of hypertension and hypercholesterolemia, a finding that remained when the age of the women investigated was restricted [36]. This indicates that the higher prevalence of these conditions, which can lead to cardiovascular disease, is a result of menopause itself rather than age [36]. This contradicts the studies which found a relationship between the age at menopause and heart disease [33, 34]. The study also found that their perimenopausal population of women had significantly lower risk factors for heart disease than the post-menopausal women [36]. One study found a relationship between the onset of hypertension in perimenopausal and early post-menopausal women [37], again supporting the findings of this analysis. This onset was attributed to an increase in body weight [37], which aligns with the fluctuations of weight commonly seen during the menopausal transition.

Literature on the relationship between the onset of menopause and stroke diagnoses draws inconsistent conclusions. These various findings are summarized in Table 1. One study found no significant linear relationship between age at menopause and stroke mortality, and, as such, age at menopause was found to be weakly, if at all, associated with stroke risk [38]. The association between age at menopause and

stroke mortality was not influenced by women who reached menopause earlier (i.e., < 40 years) or later (i.e., > 55 years) [38]. Another study investigated the risk of stroke in a large sample of women and found that age at menopausal onset was not significantly associated with stroke [39], again differing from the results of this analysis. However, it was found that a later age of menopause tended to have a higher risk of hemorrhagic stroke [39]. Multiple studies did note a positive correlation between early menopause and stroke diagnoses in a multiethnic cohort [33, 34, 40, 41], although other studies have found no relation between the two [38, 39, 42]. Therefore, our study's significant association between stroke and the onset of post-menopause is supported by some studies but not consistently by all in the greater literature.

Table 1
Summary of the relevant health condition literature.

Health Condition	Author	Similarities with this analysis	Differences from this analysis	Reference
Osteoporosis	Chapurlat, R.D., et al.	Bone density loss increased for perimenopausal women	-	[31]
	Ahuja, M.[a]	-	Increased risk of osteoporosis observed in post-menopausal women	[30]
	Demir, B., et al.	-	Later age at menopausal onset negatively associated with osteoporosis	[32]
Heart Attack	Ahuja, M.[a]	Increased risk of heart attacks observed in post-menopausal women	-	[30]
	El Khoudary, S.R.	Early menopausal onset associated with higher risk of cardiovascular disease	-	[33]
	Wellons, M., et al.[a]	Early menopausal onset associated with increased cardiovascular disease	-	[34]
	Stevenson, J.C., S. Tsiligiannis, and N. Panay	Incidence of cardiovascular disease increased in perimenopausal women	-	[35]
	Trémollières, F.A., et al.	Menopause associated with higher prevalence of cardiovascular conditions	Perimenopausal women at lower risk of cardiovascular disease than post-menopausal women	[36]
	Juntunen, M., et al.	Association found between onset of hypertension in perimenopausal and early post-menopausal women	-	[37]
Stroke	Jacobsen, B.K., I. Heuch, and G. KvåLe	-	Age at menopause weakly associated with stroke risk	[38]

[a] Study reports on various applicable health conditions.

Health Condition	Author	Similarities with this analysis	Differences from this analysis	Reference
	Choi, S.H., et al.	Later age at menopause onset associated with higher risk of hemorrhagic stroke	Age at menopause onset not significantly associated with stroke risk	[39]
	El Khoudary, S.R.	Earlier onset of menopause associated with increased risk of stroke	-	[33]
	Wellons, M., et al.[a]	Positive correlation between early menopause and stroke diagnoses	-	[34]
	Lisabeth, L.D., et al.	Positive correlation between early menopause and stroke diagnoses	-	[40]
	Baba, Y., et al.	Positive correlation between early menopause and stroke diagnoses	-	[41]
	Hu, F.B., et al.	-	Lack of a significant relationship between early menopause and stroke diagnoses	[42]

[a] Study reports on various applicable health conditions.

While menopause has reached fixation in all human populations, the health effects of menopause may continue to evolve through life. More variation may be seen due to the interactions of both biological (menopause) and non-biological factors that modulate health. Such factors could include smoking, socioeconomic status, body mass index, use of oral contraceptives, and use of hormone therapy. Menopause may be making women more susceptible to such non-biological factors, unfortunately resulting in the increased risk of serious health conditions. Future studies should focus on this interaction and its effect on women's health.

Conclusions

Population genetics–based mate choice theory [6] provides the simplest mechanism for the evolution of menopause, and the theory predicts continued origination of variation and evolution in ethnic populations. This study found significant variation in the onset of late perimenopause and post-menopause between the five ethnic populations included in SWAN, providing support for the prediction of the mate choice theory [6]. Future analyses should consider additional ethnicities, international populations, and genetics to increase the scope of menopause-related literature. Other menopausal characteristics should be considered as well, such as the duration of each menopausal phase or the severity of symptoms, across and within ethnicities.

The study also found various significant associations between the onset of menopause and serious health conditions, such as stroke, heart attacks, and osteoporosis. These findings provide evidence that in real populations, the hormonal changes occurring in menopause influence the diagnoses of serious health conditions. This analysis considers the effect of menopause on women's health, but future studies should consider the interaction between biological factors (e.g., menopause) and non-biological factors (e.g., socioeconomic status, smoking, body mass index) as well. Finally, this study's results on women's health and menopause call into question how preventative care and individualized medicine can be adapted to better support middle-aged women as they transition through menopause. Adaptations may include yearly screening for health conditions past a prespecified age, proper education, and an understanding of the variables that can be controlled to reduce the risk of conditions such as heart attacks, stroke, and osteoporosis.

Abbreviations

ANOVA: Analysis of Variance; HSD: Honestly significant difference; ICPSR: Inter-University Consortium for Political and Social Studies; SWAN: Study of Women's Health Across the Nation.

Declarations

Ethics approval and consent to participate

Data were accessed through the publicly available datasets on ICPSR (Inter-University Consortium for Political and Social Studies) by agreeing to their terms of reference for data use. No additional permissions were required to access and use the data/records described in this study.

Consent for Publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is available in the SWAN Study Repository, https://www.icpsr.umich.edu/web/ICPSR/series/00253.

Competing Interests

The authors declare that they have no competing interest.

Author's Contributions

S.B. collected and analyzed the data and wrote the manuscript; M.B. provided expertise and help in the analysis of data; and R.S.S. gave the idea for the study and provided guidance and support. All authors edited the manuscript.

Acknowledgements

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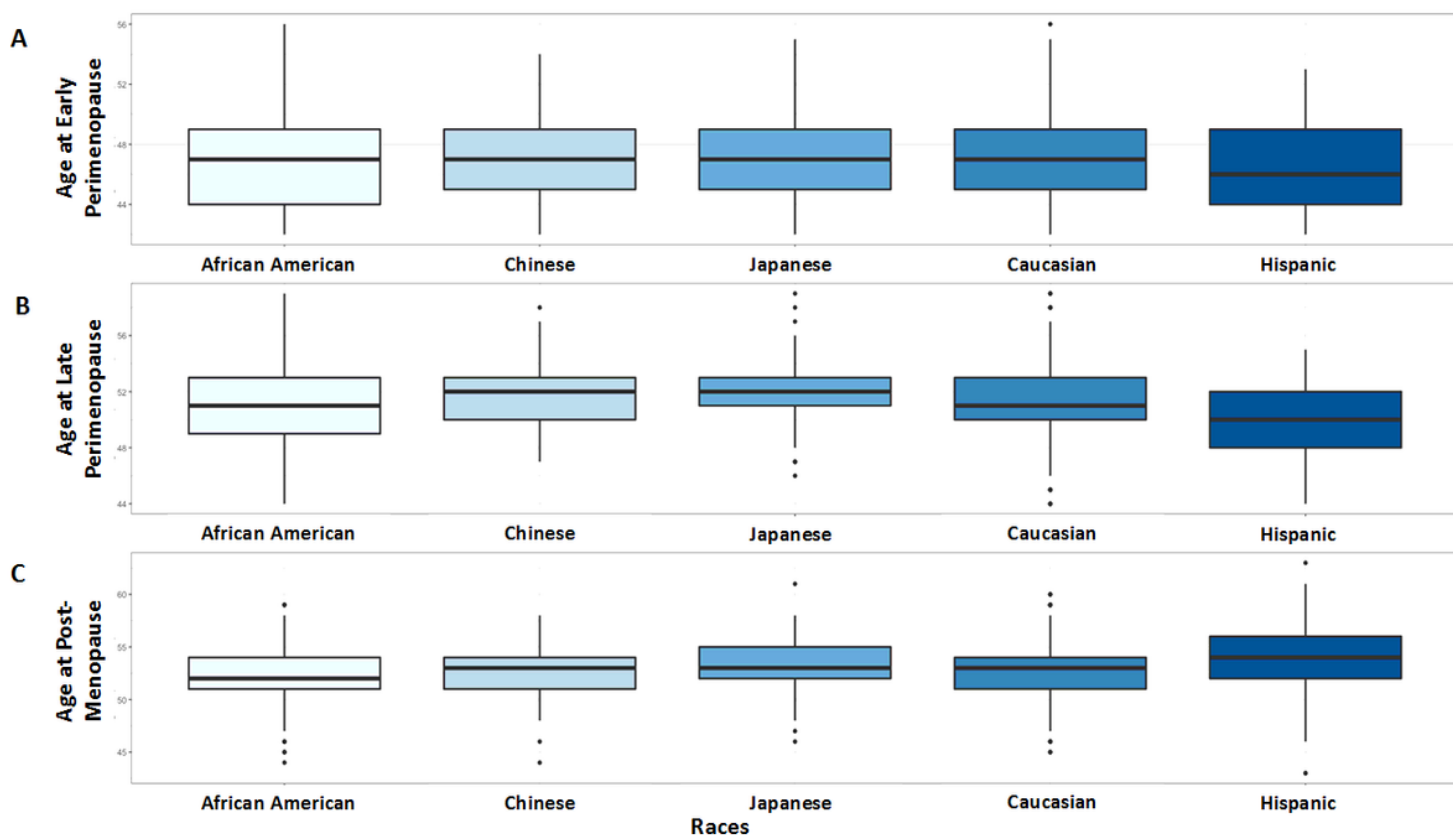
Figures

Figure 1

Ethnic distributions for (A) onset age of early perimenopause, (B) late perimenopause, and (C) post-menopause.

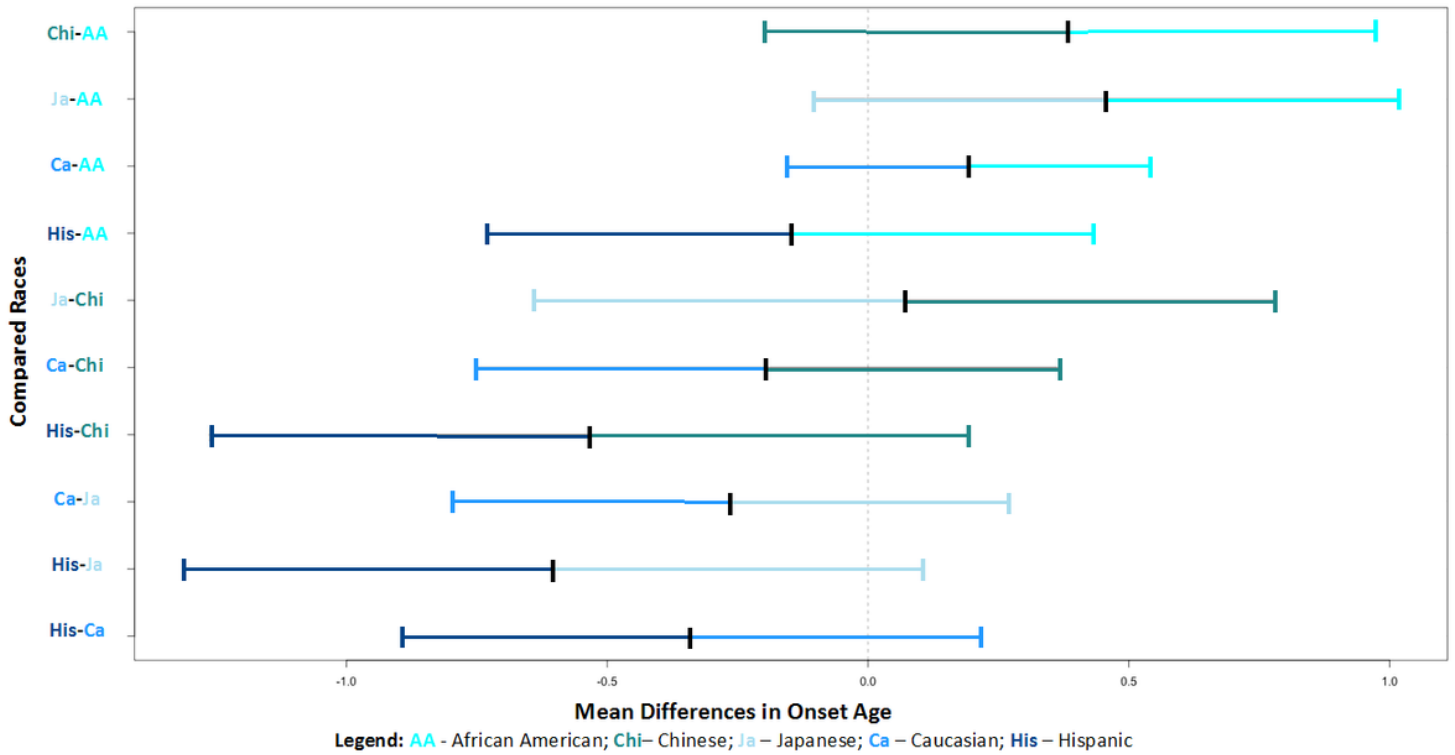**Mean Ages of Early Perimenopause**
Tukey Test 95% Confidence Intervals

Legend: AA - African American; Chi– Chinese; Ja – Japanese; Ca – Caucasian; His – Hispanic

Figure 2

Tukey's HSD test examining differences in the mean onset age of early perimenopause across SWAN ethnicities.
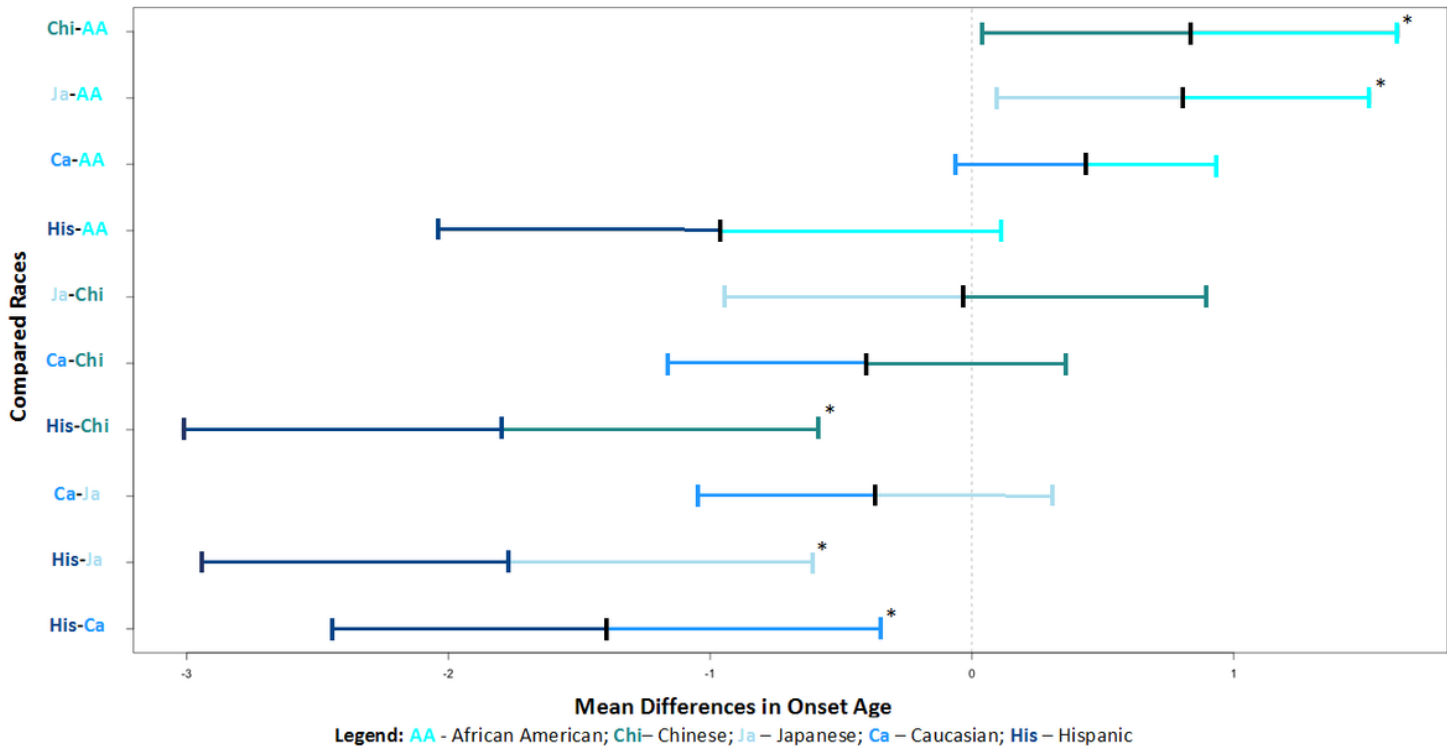
Figure 3

Tukey's HSD test examining differences in the mean onset age of late perimenopause across SWAN ethnicities (* represents statistical significance (p < 0.05)).
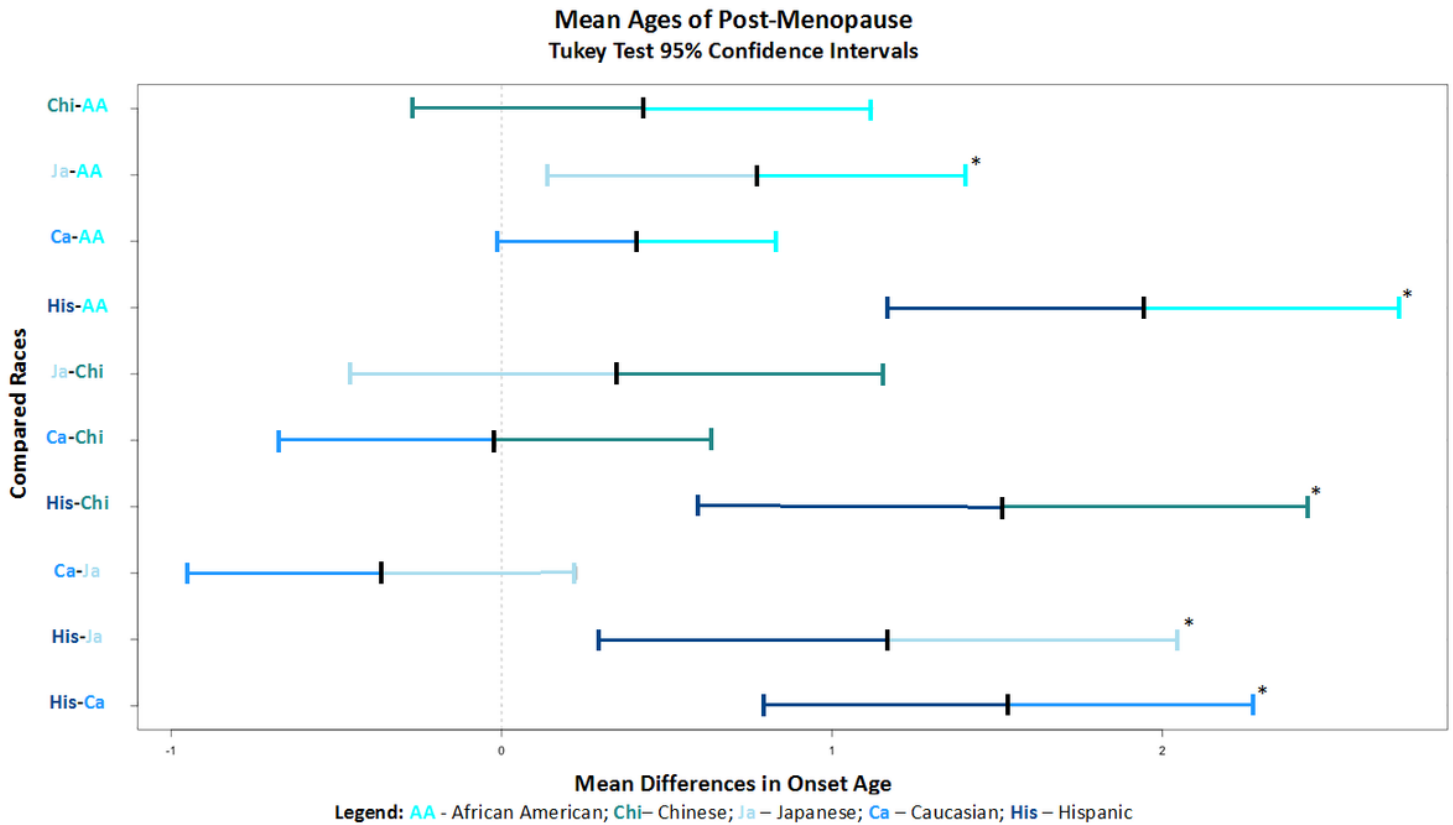
Mean Ages of Post-Menopause
Tukey Test 95% Confidence Intervals

Legend: AA - African American; Chi– Chinese; Ja – Japanese; Ca – Caucasian; His – Hispanic

Figure 4

Tukey's HSD test examining differences in the mean onset age of post-menopause across SWAN ethnicities (* represents statistical significance ($p < 0.05$)).

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