# Hormone Replacement Therapy (HRT): Utilisation Rates, Determinants and Impact on Health-Related Quality of Life in a Multi-Ethnic Asian Population

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## ABSTRACT

**Introduction:** Hormone Replacement Therapy (HRT) is widely prescribed to provide relief from unpleasant climacteric symptoms, however for several decades, the benefits and risks of HRT have been debated. Most of the current HRT literature is focused on western population, with very less available information on Asians.

**Aim:** To examine the HRT utilisation rate, determinants and impact on Health-Related Quality Of Life (HRQOL) in a multi-ethnic Asian population in Singapore.

**Materials and Methods:** A total of 3408 women from the Singapore Epidemiology of Eye Diseases study, comprising Chinese (n=1215), Malay (n=1091) and Indian (n=1102) were included in the analyses. HRT utilisation was self-reported and HRQOL was assessed using the EuroQoL-5 Dimensions questionnaire. Multivariable logistic and linear regression models were used to elucidate the determinants of HRT utilisation and its association with HRQOL, respectively.

**Results:** The age-standardised HRT utilisation rate was 8.80%, with majority being Chinese. Aged between 50-69 years, have reading literacy, of Christian religion and history of oophorectomy were independent determinants of HRT utilisation. Ethnicity-stratified analyses found that monthly income (≥SG$1,000) in Indians, and older age of menstruation cessation in Chinese, were independently associated with HRT utilisation. Malay, Indian and Chinese women using HRT had worse mobility, pain/discomfort, and anxiety/depression, respectively, compared to non-users.

**Conclusion:** HRT utilisation rates in this Asian sample were relatively low compared to most Western countries, and with the Chinese being the highest users. The factors associated with HRT utilisation appeared to be multifactorial and usage is associated with poorer HRQOL in some aspects, varied by ethnicity.

## INTRODUCTION

HRT is widely prescribed to peri and post-menopausal women and those who have undergone oophorectomy (removal of one or both ovaries) to provide relief from unpleasant climacteric symptoms such as hot flushes, headache and vaginal dryness [1]. Only a few studies have reported prevalence rates of HRT usage since 2002, mostly in Western populations, and these have ranged between 12 and 50% [2-6]. Rates of HRT use in Singapore was reported to be 12.60%, but this figure was not representative of Singapore multi-ethnic population as the study sample comprised only of Chinese [7].

Women using HRT have been reported to have different socio-demographic characteristics compared to those who were not on HRT [3,6,8]. Higher socioeconomic status and education, history of alcohol consumption, and not being overweight or a current smoker have commonly been reported as determinants of HRT use, although this is not consistent across all studies [3,8-11]. However, the determinants of HRT usage in Asians remain poorly understood as most of the previous findings were derived from western populations. Determinants of HRT utilisation amongst Singaporean women remain unknown as they have never been investigated.

Studies exploring the impact of HRT use on HRQOL have produced conflicting findings. For example, the Pan-Asia Menopause (PAM) study [12], the largest current study examining the relationship between HRT and HRQOL, found that women who used HRT had significantly better HRQOL {measured using the Menopause-specific Quality Of Life (MENQOL)} compared to non-HRT users. In contrast, others have reported no perceived change or even a worsening in HRQOL with the use of HRT; however, the wide range of HRQOL questionnaires used makes comparisons across studies difficult [12-16]. Nonetheless, data on the impact of HRT use on HRQOL in Singapore is not available.

Given that Singapore is an urban cityscape with equal access to education, information and healthcare for three major Asian ethnicities (Chinese, Malay and Indian), there exists a unique opportunity to obtain ethnic-specific population-based data on the rates, determinants and impact of HRT usage on HRQOL. In this study, the prevalence and determinants of HRT use and its impact on HRQOL in a well-defined multi-ethnic population of postmenopausal women in Singapore were examined. Based on the sparse Asian data available [6], it is hypothesised that the national usage of HRT in Singapore will be low but will vary across ethnic groups. It is speculated that several factors will be independently associated with the use of HRT in this cohort including socioeconomic factors and education level, and that HRT usage will have a positive HRQOL impact in women from Singapore.

## MATERIALS AND METHODS

### Study Design and Population

Participants were recruited from the Singapore Epidemiology of Eye Diseases (SEED) study, which comprised of three population-based cohorts of Malay, Indian and Chinese individuals aged 40-80 years. Only data from the baseline studies were included {Singapore Malay Eye Study (SiMES), 2004-2006, N=3,280; Singapore Indian Eye Study (SINDI), 2007-2009, N=3,400; and Singapore Chinese Eye Study (SCES), 2009-2011, N=3,353}. All studies utilised the same protocol and were conducted in the same clinical research facility

{Singapore Eye Research Institute (SERI)}. Details of the SEED study have been reported previously [17].

All studies adhered to the declaration of Helsinki, with ethics approval obtained from the SERI Institutional Review Board (SiMES: R341/34/2003; SINDI and SCES: R498/47/2006). Written informed consent was obtained from all participants. Males (N=4,943) and individuals with missing data (N=1,682) were excluded, leaving data from 3,408 individuals for this analysis. The large number of data that were missing (N=1,682) were from questions that asked about age of menstruation cessation, HRT usage, and history of oophorectomy.

## Outcome Measures

### HRT

HRT was defined in this study as any form of hormone therapy that consisted of oestrogen and/or progestins. HRT utilisation was based on the participant's response to an in-house questionnaire administered by trained interviewers in English, Mandarin, Malay or Tamil based on participant's preference. Specifically, an individual was considered to be a HRT user if she answered *yes* to the question "Did you take hormone replacement therapy after menopause or for menopausal symptoms?".

### HRQOL

HRQOL was assessed using the raw scores from the five dimensions of the 3-level EuroQoL-5 Dimensions (EQ-5D) multi-attribute utility instrument. The EQ-5D asks individuals to rate their level of difficulty with mobility, self-care, usual activity, pain/discomfort and anxiety/depression on a 3-point scale, where higher and lower scores represent worse and better outcomes, respectively [18].

### Co-variables

Data on socio-demographic and lifestyle factors were collected via a standardised questionnaire. Key variables included age (years), ethnicity (Malay/Indian/Chinese), current marital status (single or divorced/widowed/presently married), highest education level attained {≤Primary school (6 years)/> primary school (6 years)}, housing type (living in a <5-room flat/≥5-room flat), gross monthly income (<SGD$1,000/≥SGD$1,000), literacy in reading (yes/no) and writing (yes/no), religion (Buddhism/Christianity/Hindu/Islam/Others), current smoking (yes/no), alcohol consumption (yes/no), menstruation cessation age (years), history of oophorectomy (yes/no), and presence of systemic diseases (includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease). Definition of each ethnicity followed the criteria set by the Singaporean Census and was collected from participants' National Registration Identity Card. Clinical parameters were collected following a standardised clinical protocol, with height assessed using a wall-mounted measuring tape, and weight using a digital scale (SECA, model 782 2321009; Vogel & Halke, Germany) [17]. BMI was calculated using the formula weight in kilograms divided by height in meters squared.

## STATISTICAL ANALYSIS

All analyses were performed using Stata 15 for Windows (StataCorp LC, College Station, TX). The overall and ethnicity-stratified prevalence of HRT utilisation, both unadjusted and directly standardised by 10-year age bands to the 2010 Singapore Census were reported [19]. The differences in socio-demographic, lifestyle and clinical characteristics between HRT users and non-users were assessed using t and chi-squared statistics for continuous and categorical variables, respectively. Logistic regression was used to estimate the Odds Ratios (OR) relating each characteristic to HRT usage, adjusting for co-variables that were significantly different in univariable comparisons, as well as variables (smoking and

alcohol consumption) previously reported to be associated with HRT usage [3,8,20,21]. Multivariable linear regression was used to determine associations between HRT usage and the five EQ-5D items. Whether these associations depend on age was assessed by testing the significance of a multiplicative interaction parameter between HRT usage and age category (≤65/> 65 years) in each regression model. Finally, the analyses were stratified by ethnicity, to examine whether there were differences in the associations of HRT usage with EQ-5D between the ethnic groups. All estimates were reported with 95% confidence intervals and a p-value <0.05 was considered statistically significant.

## RESULTS

### Sociodemographic and Clinical Characteristics of Participants

A total of 3,408 females with a mean age (Standard Deviation; SD) of 62.50 (8.60) were included in the analyses. The overall prevalence of HRT usage was 8.7% {n=296; Age-standardised (AS)=8.8% (CI: 7.12-10.90)} comprising 4% Chinese {AS=10.6% (CI: 7.84-14.50)}, 1.9% Malays {AS=8.3% (CI: 4.58-14.60)}, and 2.8% Indians {AS=8.1% (CI: 5.31-12.40) (p<0.05). Stratified by ethnicity, the prevalence of HRT usage was 11.3%, 8.6% and 5.9% amongst Chinese, Indian and Malay women, respectively (p<0.05).

The mean (SD) overall age of HRT users was 60.59 (7.06), with the Chinese, Malay and Indian groups aged 62.07 (7.17), 58.25 (6.66) and 60.03 (6.70), respectively (p<0.05). The mean (SD) starting HRT age was 47.79 (6.39) years for the overall group, and 48.02 (6.20), 47.71 (7.34) and 47.50 (6.01) for Chinese, Malay and Indian women, respectively (p>0.05). Compared to non-users, HRT users were younger, single, Chinese, staying in ≥5-room flats, of Christian religion, lower BMI, more highly educated {>primary school (6 years)}, had higher income (≥SGD$1000), reading and writing literacy, had a lower age of menopause and a history of oophorectomy ([Table/Fig-1], all p<0.05).

| Characteristics | Non-HRT user (n=3112) | HRT Users (n=296) | p-value |
|---|---|---|---|
| **Mean age (years)** | 62.63 | 60.59 | **<0.001** |
| **Age (years) (%)** | | | |
| 40-49 | 5.01 | 5.07 | |
| 50-59 | 37.31 | 43.58 | **<0.001** |
| 60-69 | 34.16 | 40.88 | |
| ≥70 | 23.52 | 10.47 | |
| **Ethnicity (%)** | | | |
| Chinese | 34.64 | 46.28 | |
| Malay | 33 | 21.62 | **<0.001** |
| Indian | 32.36 | 32.09 | |
| **Mean BMI (kg/m²)** | 26.04 | 25.12 | **<0.01** |
| **BMI (%)** | | | |
| Underweight (<18.5) | 4.18 | 4.05 | |
| Normal (18.5-24.9) | 42.38 | 51.69 | |
| Overweight (25.0-29.9) | 33.8 | 30.07 | **<0.05** |
| Obese (≥30) | 19.63 | 14.19 | |
| **Current marital status (%)** | | | |
| Single (never married before) | 4.98 | 8.45 | |
| Divorced/widowed/presently married (ever been married) | 95.02 | 91.55 | **<0.05** |
| **Education (%)** | | | |
| ≤Primary school (6 years) | 74.52 | 57.43 | **<0.001** |

| >Primary School (6 years) | 25.48 | 42.57 | |
|---|---|---|---|
| **Housing categories** | | | |
| <5-room HDB | 73.39 | 60.47 | **<0.001** |
| ≥5-room HDB | 26.61 | 39.53 | |
| **Income (%)** | | | |
| <SGD$1000 | 77.19 | 64.19 | **<0.001** |
| ≥SGD$1000 | 22.81 | 35.81 | |
| **Reading literacy (%)** | | | |
| Yes | 77.67 | 91.89 | **<0.001** |
| **Writing literacy (%)** | | | |
| Yes | 74.23 | 88.51 | **<0.001** |
| **Religion (%)** | | | |
| Buddhism | 18.93 | 19.93 | |
| Christianity* | 9.13 | 18.24 | |
| Hindu | 52.19 | 40.54 | **<0.001** |
| Islam | 6.52 | 4.73 | |
| Others | 13.24 | 16.55 | |
| **Smoking (%)** | | | |
| Yes | 3.86 | 2.7 | 0.32 |
| **Alcohol consumption (%)** | | | |
| Yes | 1.54 | 2.7 | 0.13 |
| **Menstruation cessation age (years)** | 49.33 | 47.29 | **<0.001** |
| **History of oophorectomy (%)** | 10.86 | 42.23 | **<0.001** |
| **Presence of systemic disease# (%)** | | | |
| Yes | 86.70 | 82.43 | **<0.05** |
| **EQ-5D (mobility)** | | | |
| Overall | 1.21 | 1.19 | 0.41 |
| Chinese | 1.10 | 1.12 | 0.44 |
| Malay | 1.28 | 1.39 | 0.07 |
| Indian | 1.27 | 1.17 | **<0.05** |
| **EQ-5D (self-care)** | | | |
| Overall | 1.03 | 1.01 | **<0.05** |
| Chinese | 1.01 | 1.01 | 0.67 |
| Malay | 1.03 | 1.00 | 0.20 |
| Indian | 1.06 | 1.01 | 0.07 |
| **EQ-5D (usual activities)** | | | |
| Overall | 1.10 | 1.09 | 0.68 |
| Chinese | 1.04 | 1.05 | 0.42 |
| Malay | 1.15 | 1.16 | 0.82 |
| Indian | 1.12 | 1.11 | 0.72 |
| **EQ-5D (pain/discomfort)** | | | |
| Overall | 1.48 | 1.52 | 0.26 |
| Chinese | 1.28 | 1.34 | 0.16 |
| Malay | 1.55 | 1.59 | 0.55 |
| Indian | 1.61 | 1.72 | 0.11 |
| **EQ-5D (anxiety/depression)** | | | |
| Overall | 1.35 | 1.40 | 0.15 |
| Chinese | 1.17 | 1.28 | **<0.05** |
| Malay | 1.45 | 1.56 | 0.12 |
| Indian | 1.45 | 1.46 | 0.87 |

**[Table/Fig-1]:** Comparison of clinical and demographic characteristics of 3408 participants, stratified by usage of HRT.
HRT: Hormone replacement therapy; BMI: Body mass index; HDB: Housing and development board; SGD: Singapore dollar; Bolded values indicate statistical significance
*Pairwise comparisons showed that HRT users are more likely to be Christian
#Includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease

## Determinants of HRT Usage

In age-adjusted models, younger age, lower BMI, >6 years education, living in ≥5-room flats, monthly income ≥SGD$1,000, reading and writing literacy, of Christian religion, younger age of menstruation cessation and history of oophorectomy were all associated with higher likelihood of using HRT. Malays (OR: 0.50, 95% CI: 0.36-0.68) and Indians (OR: 0.72, 95% CI: 0.54-0.94) were less likely to be using HRT compared to Chinese. After multivariable adjustments, participants who were older (aged 50 to 69-year-old), more literate in reading, Christian and had previous oophorectomy; remained independently associated with higher likelihood of using HRT [Table/Fig-2].

In ethnicity-stratified multivariable models, having a history of oophorectomy was a common determinant of HRT use across the three groups. Ethnic-specific determinants of HRT use included being aged between 60-69, and higher menstruation cessation age in the Chinese group; being aged between 50-59 in the Malay group; and being aged between 60-69, and having a higher income in the Indian group [Table/Fig-2].

## Association of HRT Usage and HRQOL

Scores were similar between those who used HRT and those who didn't, both overall and across the three ethnic groups, except for overall in self-care, Indian in mobility and Chinese women in anxiety/depression ([Table/Fig-1]; p<0.05).

After multivariable adjustment for co-variables that demonstrated significant differences in the univariate comparison [Table/Fig-3], pain/discomfort (β: 0.10, 95% CI: 0.04 to 0.16) and anxiety/depression (β: 0.10, 95% CI: 0.04 to 0.17) scores were significantly higher (worse) in HRT users compared to non-users. This relationship appeared to be mostly driven by the Indian (β: 0.15, 95% CI: 0.03 to 0.28) and Chinese (β: 0.13, 95% CI: 0.05 to 0.20; [Table/Fig-4]) groups, respectively. Malay women who used HRT had significantly worse mobility scores compared to non-users (β: 0.16, 95% CI: 0.04 to 0.27). The relationships between HRT usage and EQ-5D dimensions did not differ by age group (p-values for interaction >0.05).

### Comparison of baseline characteristics by participation status

Significant differences were demonstrated for co-variables including age, race, age group, reading and writing literacy, income ≥$1000, religion, >primary school, married before, ≥5-room HDB and presence of systemic disease [Table/Fig-5].

## DISCUSSION

In this large, population-based study of 3,408 multi-ethnic Asian women, an overall HRT utilisation rate of almost 9% was demonstrated, with Chinese women (4%) having significantly higher rates compared to Indians (2.8%) and Malays (1.9%). Women who used HRT had a medical history of oophorectomy, were aged between 50-69 years old, were able to read and were Christian. In terms of ethnic-specific determinants, Indians with a monthly income of ≥SG$1,000 and Chinese with older age of menstruation cessation had a higher likelihood of using HRT. Those who used HRT had approximately 9-11% higher levels of pain/discomfort and anxiety/depression compared to non-users, although this finding was only significant in Indian and Chinese women, respectively. Overall findings from this study suggest a conservative use of HRT in Singapore, particularly those of Malay and Indian ethnicity, although independent determinants appear to be multifactorial. A small but significant loss in HRQOL for women using HRT was noted, suggesting that more research is needed to understand the underpinning reasons using more condition-specific HRQOL instruments and qualitative interviews.

Overall HRT utilisation rate in the multi-ethnic Asian population of this work was low (8.7%). This finding could be due to concerns

| Parameters | | | Overall | | | Chinese | | | Malay | | | Indian | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Age-adjusted† | Multivariate‡ | | | Multivariateα | | | Multivariateα | | | Multivariateα |
| | (N) | HRT users (%) | OR (95% CI) | OR (95% CI) | (N) | HRT users (%) | OR (95% CI) | (N) | HRT users (%) | OR (95% CI) | (N) | HRT users (%) | OR (95% CI) |
| **Age (year)** | | | | | | | | | | | | | |
| 40-49 | 171 | 8.77 | Reference | Reference | 63 | 9.52 | Reference | 40 | 10 | Reference | 68 | 7.35 | Reference |
| 50-59 | 1290 | 10 | 1.16 (0.66-2.02) | **2.71 (1.49-4.96)** | 461 | 10.63 | 2.48 (0.96-6.38) | 396 | 9.85 | **4.37 (1.18-16.21)** | 433 | 9.47 | 2.55 (0.92-7.09) |
| 60-69 | 1184 | 10.22 | 1.18 (0.67-2.08) | **3.55 (1.91-6.59)** | 411 | 15.82 | **5.48 (2.10-14.27)** | 367 | 4.63 | 1.77 (0.44-7.23) | 406 | 9.61 | **3.53 (1.24-10.05)** |
| ≥70 | 763 | 4.06 | **0.44 (0.23-0.84)** | 1.46 (0.72-2.95) | 280 | 6.07 | 2.31 (0.80-6.71) | 288 | 1.39 | 0.45 (0.08-2.35) | 195 | 5.13 | 1.97 (0.60-6.47) |
| | | | **P-trend <0.001** | P-trend=0.70 | | | **P-trend=0.036** | | | **P-trend=0.003** | | | P-trend=0.280 |
| Age (per year decrease) | 3,408 | - | **1.03 (1.01-1.04)** | 1.00 (0.98-1.01) | 1,215 | 11.28 | **1.03 (1.01-1.05)** | 1,091 | 5.87 | **0.94 (0.90-0.98)** | 1,102 | 8.62 | 1.01 (0.98-1.04) |
| **Ethnicity** | | | | | | | | | | | | | |
| Chinese | 1215 | 11.28 | Reference | Reference | - | - | - | - | - | - | - | - | - |
| Malay | 1091 | 5.87 | **0.50 (0.36-0.68)** | 0.76 (0.39-1.47) | - | - | - | - | - | - | - | - | - |
| Indian | 1102 | 8.62 | **0.72 (0.54-0.94)** | 0.65 (0.38-1.10) | - | - | - | - | - | - | - | - | - |
| **BMI** | | | | | | | | | | | | | |
| BMI (per unit decrease) | 3,408 | - | **1.04 (1.01-1.06)** | 1.02 (0.99-1.05) | 1,215 | 11.28 | 0.98 (0.93-1.03) | 1091 | 5.87 | 1.02 (0.97-1.08) | 1102 | 8.62 | 0.95 (0.91-1.00) |
| **BMI (WHO category)** | | | | | | | | | | | | | |
| Underweight (<18.5) | 142 | 8.45 | Reference | Reference | 76 | 10.53 | Reference | 40 | 0 | Reference | 26 | 15.38 | Reference |
| Normal (18.5-24.9) | 1472 | 10.39 | 1.20 (0.65-2.22) | 1.14 (0.59-2.19) | 768 | 12.11 | 1.28 (0.57-2.90) | 334 | 6.59 | 1.19 (0.60-2.36) | 370 | 10.27 | 0.56 (0.17-1.88) |
| Overweight (25.0-29.9) | 1141 | 7.8 | 0.85 (0.45-1.61) | 0.89 (0.45-1.76) | 301 | 10.3 | 1.17 (0.49-2.84) | 396 | 5.3 | 0.73 (0.37-1.46) | 444 | 8.33 | 0.39 (0.11-1.32) |
| Obese (≥30) | 653 | 6.43 | 0.70 (0.36-1.36) | 0.86 (0.42-1.78) | 70 | 7.14 | 1.01 (0.30-3.41) | 321 | 6.54 | 1β | 262 | 6.11 | 0.33 (0.09-1.19) |
| | | | **P-trend <0.001** | P-trend=0.19 | | | P-trend=0.74 | | | P-trend=0.613 | | | **P-trend=0.048** |
| **Married before (%)** | | | | | | | | | | | | | |
| No | 180 | 13.89 | Reference | Reference | 104 | 16.35 | Reference | 27 | 0.00 | Reference | 49 | 16.33 | Reference |
| Yes | 3228 | 8.4 | 0.64 (0.41-1.00) | 0.79 (0.48-1.29) | 1,111 | 10.80 | 0.78 (0.42-1.44) | 1,064 | 6.02 | β | 1,053 | 8 | 0.49 (0.21-1.15) |
| **Education (%)** | | | | | | | | | | | | | |
| ≤Primary School (6 years) | 2489 | 6.83 | Reference | Reference | 773 | 9.06 | Reference | 950 | 5.16 | Reference | 766 | 6.66 | Reference |
| >Primary School (6 years) | 919 | 13.71 | **1.97 (1.52-2.55)** | 1.24 (0.90-1.71) | 442 | 15.16 | 1.40 (0.89-2.22) | 141 | 10.64 | 1.25 (0.57-2.71) | 336 | 13.1 | 1.23 (0.73-2.09) |
| **Housing categories (%)** | | | | | | | | | | | | | |
| <5-room HDB | 2463 | 7.27 | Reference | Reference | 779 | 9.5 | Reference | 936 | 5.24 | Reference | 748 | 7.49 | Reference |
| ≥5-room HDB | 945 | 12.38 | **1.73 (1.35-2.22)** | 1.28 (0.96-1.70) | 436 | 14.45 | 1.27 (0.84-1.91) | 155 | 9.68 | 1.35 (0.67-2.72) | 354 | 11.02 | 1.24 (0.77-2.00) |
| **Income (%)** | | | | | | | | | | | | | |
| <SGD$1000 | 2592 | 7.33 | Reference | Reference | 771 | 10.12 | Reference | 991 | 5.65 | Reference | 830 | 6.75 | Reference |
| ≥SGD$1000 | 816 | 12.99 | **1.67 (1.28-2.19)** | 1.08 (0.79-1.48) | 444 | 13.29 | 1.04 (0.67-1.62) | 100 | 8 | 0.52 (0.20-1.31) | 272 | 14.34 | **1.86 (1.10-3.15)** |
| **Reading literacy (%)** | | | | | | | | | | | | | |
| No | 719 | 3.34 | Reference | Reference | 167 | 2.99 | Reference | 364 | 3.57 | Reference | 188 | 3.19 | Reference |
| Yes | 2689 | 10.12 | **2.90 (1.87-4.51)** | **2.37 (1.14-4.90)** | 1,048 | 12.60 | 3.00 (0.50-18.07) | 727 | 7.02 | 1.30 (0.46-3.66) | 914 | 9.74 | 3.58 (0.90-14.32) |
| **Writing literacy (%)** | | | | | | | | | | | | | |
| No | 836 | 4.07 | Reference | Reference | 182 | 3.3 | Reference | 451 | 4.21 | Reference | 203 | 4.43 | Reference |
| Yes | 2572 | 10.19 | **2.38 (1.62-3.49)** | 0.92 (0.48-1.77) | 1,033 | 12.68 | 1.71 (0.33-8.82) | 640 | 7.03 | 0.68 (0.26-1.76) | 899 | 9.57 | 0.56 (0.17-1.86) |
| **Religion (%)** | | | | | | | | | | | | | |
| Non-Christianity | 3070 | 7.88 | Reference | Reference | - | - | - | - | - | - | - | - | - |
| Christianity | 338 | 15.98 | **2.24 (1.62-3.08)** | **1.67 (1.17-2.9)** | - | - | - | - | - | - | - | - | - |
| **Smoking (%)** | | | | | | | | | | | | | |

| | N | % | β (95% CI) | (95% CI) | N | % | (95% CI) | N | % | (95% CI) | N | % | (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | 3,280 | 8.78 | Reference | Reference | 1,160 | 11.38 | Reference | 1,034 | 6.09 | Reference | 1,086 | 8.56 | Reference |
| Yes | 128 | 6.25 | 0.72 (0.35-1.50) | 0.68 (0.31-1.47) | 55 | 9.09 | 0.83 (0.31-2.23) | 57 | 1.75 | 0.25 (0.03-2.00) | 16 | 12.5 | 1.22 (0.22-6.75) |
| **Alcohol consumption (%)** | | | | | | | | | | | | | |
| No | 3,352 | 8.59 | Reference | Reference | 1,179 | 11.37 | Reference | 1,089 | 5.88 | Reference | 1,084 | 8.3 | Reference |
| Yes | 56 | 14.29 | 1.69 (0.79-3.63) | 1.68 (0.75-3.76) | 36 | 8.33 | 1.02 (0.30-3.48) | 2 | 0 | 1.00$^\beta$ | 18 | 27.78 | 2.46 (0.77-7.89) |
| Menstruation cessation age (per year decrease) | 3,408 | - | **1.06 (1.04-1.09)** | 1.02 (1.00-1.05) | 1,215 | 11.28 | **0.95 (0.91-0.99)** | 1,091 | 5.87 | 0.99 (0.94-1.05) | 1,102 | 8.62 | 1.00 (0.96-1.04) |
| **History of oophorectomy (%)** | | | | | | | | | | | | | |
| No | 2945 | 5.81 | Reference | Reference | 1,034 | 7.93 | Reference | 1,008 | 3.77 | Reference | 903 | 5.65 | Reference |
| Yes | 463 | 27 | **5.74 (4.42-7.44)** | **4.96 (3.70-6.65)** | 181 | 30.39 | **4.13 (2.66-6.40)** | 83 | 31.33 | **9.12 (4.67-17.82)** | 199 | 22.11 | **4.68 (2.85-7.67)** |
| **Presence of systemic disease# (%)** | | | | | | | | | | | | | |
| No | 466 | 11.16 | Reference | Reference | 235 | 10.64 | Reference | 73 | 6.85 | Reference | 158 | 13.92 | Reference |
| Yes | 2942 | 8.29 | 0.86 (0.62-1.19) | 0.81 (0.57-1.17) | 980 | 11.43 | 1.18 (0.70-2.00) | 1,018 | 5.80 | 0.87 (0.31-2.45) | 944 | 7.73 | 0.45 (0.25-0.81) |

**[Table/Fig-2]:** Factors associated with utilisation of HRT (N=3408) for the overall population and stratified by ethnic groups (Chinese, Malay and Indian).
†Includes age
‡Additionally, includes all other variables in the model (ethnicity; BMI; married before; education; housing categories; income; reading literacy; writing literacy; religion; smoking; alcohol consumption; menstruation cessation age; and history of oophorectomy).
$^\beta$Dropped due to insufficient numbers
#Includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease
HRT: Hormone Replacement Therapy; BMI: Body Mass Index; WHO: World Health Organisation; HDB: Housing and Development Board; SGD: Singapore Dollar
Bolded values indicate statistical significance

| | Overall | | | |
|---|---|---|---|---|
| Parameters | Adjusted mean (SE) | β (95% CI) | p-value | % different |
| Age (year) | - | -0.004 (-0.005 to -0.003) | **<0.001** | |
| **Ethnicity** | | | | |
| Chinese | 0.90 (0.01) | Reference | | |
| Malay | | -0.12 (-0.13 to -0.10) | **<0.001** | 13.33% |
| Indian | | -0.15 (-0.16 to -0.13) | **<0.001** | 16.67% |
| **BMI** | | | | |
| BMI (kg/m$^2$) | - | -0.008 (-0.01 to -0.007) | **<0.001** | |
| **BMI (WHO category)** | | | | |
| Underweight (<18.5) | 0.84 (0.02) | Reference | | |
| Normal (18.5-24.9) | | 0.01 (-0.02 to 0.05) | 0.46 | 1.19% |
| Overweight (25.0-29.9) | | -0.03 (-0.07 to 0.01) | 0.10 | 3.57% |
| Obese (≥30) | | -0.09 (-0.13 to -0.06) | **<0.001** | 10.71% |
| **Married before (%)** | | | | |
| No | 0.87 (0.02) | Reference | | |
| Yes | | -0.05 (-0.09 to -0.02) | **<0.05** | 8.05% |
| **Education (%)** | | | | |
| ≤Primary school (6 years) | 0.80 (0.004) | Reference | | |
| >Primary school (6 years) | | 0.07 (0.05 to 0.08) | **<0.001** | 8.75% |
| **Housing categories (%)** | | | | |
| <5-room HDB | 0.81 (0.004) | Reference | | |
| ≥5-room HDB | | 0.04 (0.03 to 0.06) | **<0.001** | 4.94% |
| **Income (%)** | | | | |
| <SGD$1000 | 0.80 (0.004) | Reference | | |
| ≥SGD$1000 | | 0.09 (0.07 to 0.11) | **<0.001** | 11.11% |
| **Reading literacy (%)** | | | | |
| No | 0.77 (0.01) | Reference | | |
| Yes | | 0.06 (0.05 to 0.08) | **<0.001** | 7.79% |
| **Writing literacy (%)** | | | | |
| No | 0.76 (0.01) | Reference | | |
| Yes | | 0.07 (0.06 to 0.09) | **<0.001** | 9.21% |
| **Religion (%)** | | | | |
| Non christianity | 0.82 (0.004) | Reference | | |
| Christianity | | 0.02 (-0.004 to 0.04) | 0.11 | 2.44% |
| **Smoking (%)** | | | | |
| No | 0.82 (0.003) | Reference | | |
| Yes | | -0.03 (-0.07 to 0.01) | 0.14 | 3.66% |
| **Alcohol consumption (%)** | | | | |
| No | 0.82 (0.004) | Reference | | |
| Yes | | 0.05 (-0.01 to 0.10) | 0.10 | 6.10% |
| Menstruation cessation age (years) | - | 0.001 (-0.0002 to 0.003) | 0.09 | 0.12% |
| **History of oophorectomy (%)** | | | | |
| No | 0.82 (0.004) | Reference | | |
| Yes | | 0.01 (-0.02 to 0.03) | 0.60 | 1.22% |
| **Presence of systemic disease#(%)** | | | | |
| No | 0.86 (0.01) | Reference | | |
| Yes | | -0.05 (-0.72 to -0.03) | **<0.001** | 5.81% |
| **Use HRT** | | | | |
| No | 0.82 (0.004) | Reference | | |
| Yes | | -0.01 (-0.04 to 0.01) | 0.35 | 1.22% |

**[Table/Fig-3]:** Factors associated with HRQOL in unadjusted linear regression models (n=3408).
#Includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease; HRT: Hormone replacement therapy; BMI: Body mass index; WHO: World health organisation; HDB: Housing and development board; SGD: Singapore dollar; SE: Standard error
Bolded values indicate statistical significance

of negative health consequences related to HRT usage, such as increased risk of cardiovascular diseases and breast cancers that were reported by the Women's Health Initiative in their 2002 study [3,22]. Although this misinterpretation of increased risk was later rectified in a report published in 2007 in the Wall Street Journal titled "How NIH misread the Hormone Study in 2002" [2], HRT usage

| EQ-5D dimensions | No HRT (n=3112) Adjusted mean (SE) | With HRT (n=296) Adjusted mean (SE) | β (95% CI) | p-value | % difference |
|---|---|---|---|---|---|
| **Mobility** | | | | | |
| Overall | 1.21 (0.007) | 1.24 (0.02) | 0.04 (-0.01 to 0.08) | 0.13 | 3.31% |
| Chinese | 1.09 (0.009) | 1.13 (0.02) | 0.04 (-0.01 to 0.09) | 0.12 | 3.67% |
| Malay | 1.28 (0.01) | 1.43 (0.06) | 0.16 (0.04 to 0.27) | **<0.05** | 12.50% |
| Indian | 1.26 (0.01) | 1.21 (0.04) | -0.05 (-0.14 to 0.04) | 0.30 | 3.97% |
| **Self-care** | | | | | |
| Overall | 1.03 (0.003) | 1.02 (0.01) | -0.01 (-0.03 to 0.006) | 0.17 | 0.97% |
| Chinese | 1.01 (0.004) | 1.01 (0.01) | -0.00004 (-0.02 to 0.02) | 0.10 | 0.004% |
| Malay | 1.02 (0.005) | 1.01 (0.02) | -0.01 (-0.05 to 0.03) | 0.50 | 0.98% |
| Indian | 1.05 (0.007) | 1.02 (0.02) | -0.03 (-0.08 to 0.02) | 0.18 | 2.86% |
| **Usual activities** | | | | | |
| Overall | 1.10 (0.006) | 1.12 (0.02) | 0.02 (-0.01 to 0.06) | 0.20 | 1.82% |
| Chinese | 1.04 (0.006) | 1.06 (0.02) | 0.02 (-0.01 to 0.06) | 0.16 | 1.92% |
| Malay | 1.14 (0.01) | 1.20 (0.05) | 0.05 (-0.04 to 0.15) | 0.26 | 4.39% |
| Indian | 1.12 (0.01) | 1.12 (0.04) | 0.005 (-0.07 to 0.08) | 0.89 | 0.45% |
| **Pain/Discomfort** | | | | | |
| Overall | 1.47 (0.01) | 1.57 (0.03) | 0.10 (0.04 to 0.16) | **<0.05** | 6.80% |
| Chinese | 1.28 (0.01) | 1.35 (0.04) | 0.07 (-0.01 to 0.15) | 0.09 | 5.47% |
| Malay | 1.55 (0.02) | 1.61 (0.07) | 0.06 (-0.07 to 0.20) | 0.36 | 3.87% |
| Indian | 1.61 (0.02) | 1.76 (0.06) | 0.15 (0.03 to 0.28) | **<0.05** | 9.32% |
| **Anxiety/Depression** | | | | | |
| Overall | 1.35 (0.01) | 1.45 (0.03) | 0.10 (0.04 to 0.17) | **<0.05** | 7.41% |
| Chinese | 1.17 (0.01) | 1.30 (0.04) | 0.13 (0.05 to 0.20) | **<0.05** | 11.11% |
| Malay | 1.45 (0.02) | 1.56 (0.07) | 0.11 (-0.04 to 0.26) | 0.15 | 7.59% |
| Indian | 1.45 (0.02) | 1.51 (0.06) | 0.07 (-0.07 to 0.20) | 0.33 | 4.83% |

**[Table/Fig-4]:** Multivariable-adjusted* associations between HRT usage and EQ-5D dimensions, overall and stratified by ethnicity.
*Adjusted for age, ethnicity, BMI, married before, education, housing categories, income, reading and writing literacy, smoking, alcohol consumption and presence of systemic diseases (includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease)
HRT: Hormone replacement therapy; SE: Standard error
Bolded values indicate statistical significance

| Variable | Mean (SD) or n (%) Excluded N=1682 | Included N=3408 | p-value |
|---|---|---|---|
| Age (years) | 50.3 (8.2) | 62.5 (8.6) | **<0.001** |
| BMI (kg/m²) | 26.2 (5.4) | 26.0 (5.1) | 0.150 |
| Menstruation cessation age (years) | 48.5 (6.4) | 49.2 (5.3) | 0.236 |
| **Race** | | | |
| Chinese | 614 (36.5) | 1091 (32.0) | **<0.001** |
| Malay | 592 (35.2) | 1102 (32.3) | |
| Indian | 476 (28.3) | 1215 (35.7) | |
| **Age group** | | | |
| 40-49 | 1117 (66.4) | 171 (5.0) | **<0.001** |
| 50-59 | 396 (23.5) | 1290 (37.9) | |
| 60-69 | 68 (4.0) | 1184 (34.7) | |
| 70+ | 101 (6.0) | 763 (22.4) | |
| Reading literacy | 153 (9.1) | 719 (21.1) | **<0.001** |
| Writing literacy | 178 (10.6) | 836 (24.5) | **<0.001** |
| Income ≥$1000 | 729 (46.1) | 816 (23.9) | **<0.001** |
| **BMI category** | | | |
| Underweight | 71 (4.3) | 142 (4.2) | 0.072 |
| Normal | 713 (43.3) | 1472 (43.2) | |
| Overweight | 502 (30.5) | 1141 (33.5) | |
| Obese | 359 (21.8) | 653 (19.2) | |
| **Religion** | | | |
| Buddhism | 937 (56.3) | 1744 (51.2) | **<0.001** |
| Hinduism | 140 (8.4) | 217 (6.4) | |
| Islam | 166 (10.0) | 338 (9.9) | |
| Christianity | 246 (14.8) | 648 (19.0) | |
| Others | 176 (10.6) | 461 (13.5) | |
| >Primary school (6 years) | 825 (49.2) | 919 (27.0) | **<0.001** |
| **Married before** | 132 (7.9) | 180 (5.3) | **<0.001** |
| **≥5-room HDB** | 585 (35.0) | 945 (27.7) | **<0.001** |
| **Use HRT** | 12 (7.2) | 296 (8.7) | 0.500 |
| **History of oophorectomy** | 26 (15.0) | 463 (13.6) | 0.590 |
| **Presence of systemic disease#** | 1017 (60.5) | 2942 (86.3) | **<0.001** |

**[Table/Fig-5]:** Comparison of baseline characteristics by participation status.
#includes hypertension, hyperlipidemia, diabetes, cardiovascular disease and chronic kidney disease

dropped worldwide for several years. On the other hand, utilisation rate in this work is lower compared to Western populations which range between 12 and 50% (reported after 2002) [2-5]. These differences may be attributed to cultural differences, for example the lower self-reported prevalence and severity of climacteric symptoms in Asian women as their culture normalises menopausal symptoms and accepts it as part of the normal aging process [23]. With regard to Asian data, HRT usage rate from this work is similar to that reported in Japan (8.80%) [6] in 1996, but approximately four-fold higher than that observed in China {Shanghai (2.10%)} [24] in 2015 and almost five times higher than HRT utilisation rates in Indonesia (1.8%) [5] reported in 2008. The large disparity in utilisation rates between Indonesia and Singapore may be attributed to differences in culture, religious beliefs, health literacy and accessibility to healthcare since almost half of Indonesia's population resides in rural regions [25].

When HRT usage was stratified by ethnicity in this study, the utilisation rate amongst Singaporean Chinese was 11.30%, which was five times higher than that reported in China (2.10%). This difference may be explained by very low HRT awareness amongst women in China due to language barriers and restrictions in obtaining updated health-related information from international media [24]. A previous study on the HRT usage between 1993 and 1998 in Singaporean Chinese women (n=34,022; age between 45-74 years) found a utilisation rate of 12.60% which, although slightly higher than results from this work, could potentially be due to difference in sample size and representativeness since this work consisted of 3,408 women and only those living in the southwestern part of Singapore as well as a difference in timeline since a decade has past [7].

Those aged between 50 and 69 years, literate, being of Christian religion and having a history of oophorectomy were found to be associated with higher likelihood of using HRT. Results from this work contrast markedly with factors reported in Western populations. A study in Portugal found that higher education level was associated with higher HRT utilisation [3]. Similarly while not being overweight (not found in this work) is a commonly reported factor associated with HRT utilisation in the West [26,27]. It is difficult to compare the findings from this work with studies conducted in Asian populations with similar socio-economic status as data are limited. In a community survey in Japan, Nagata and associates found a significant relationship between HRT utilisation and history of oophorectomy, which corresponds to this study likely due to the similar socio-economic status (SES; Japan: SES=89.42; Singapore: SES=89.23) [6,28]. Differences in determinants of HRT usage between Western and Asian populations may be explained by cultural differences in healthcare usage. For example, cultural beliefs around physical space, health temporal orientation and internal control were found to affect uptake of mammogram screening in a population of African American and Caucasian women [29]. Indeed, certain determinants of HRT utilisation in this study were ethnic-specific, such as monthly income (≥SG$1,000) in Indians, suggesting that cost of HRT may impact the decision to use the drug, and older age of menstruation cessation in Chinese which

suggests that women with a later menstruation cessation age may be more likely to take HRT, potentially due to the additional benefits such as protection against neurocognitive and osteoporosis [30], although further research is needed to explore these speculations in more detail.

### Limitation(s) and Strength(s)

In the present study, HRT use was associated with negative impact on HRQOL, which is surprising since many studies have reported a positive impact of HRT usage on HRQOL [12-14]. As menopausal age and duration of HRT usage were not recorded in this study, no association regarding cause and effect can be drawn. The discrepancy between this and other studies could also be the different type of HRQOL instruments used across studies such as MENQOL, 36-item Short Form Health Survey (SF-36), Women's Health Questionnaire [12-16], making comparisons difficult. Similarly, the five individual dimensions of EQ-5D were used which may have lacked sensitivity to detect the HRQOL impact associated specifically with HRT issues. Nonetheless, the findings from this study will contribute to the currently limited literature on HRT and HRQOL amongst Asians, especially for minor ethnic groups such as Malay and Indian. Longitudinal data on HRT usage in Singapore using appropriate HRQOL instruments such as the MENQOL and qualitative research methods are warranted to confirm these cross-sectional observations and also to investigate underpinning mechanisms causing poor HRQOL amongst HRT users.

Strengths of this study include a large multi-ethnic and population-based sample, which allowed for a parallel comparison of women across three Asian ethnic groups. Comprehensive questionnaire and clinical examinations were also used which allowed for adjustment of confounders during data analyses. However, several limitations should also be acknowledged. Firstly, the cross-sectional nature of this study means that no firm conclusions on causality can be drawn from the findings of this work. Secondly, there was a potential for recall and information bias since HRT usage, age of menstruation cessation and history of oophorectomy were based on self-report. Third, since this study documented lifetime usage of HRT which could potentially be years before QOL was measured, it cannot be ascertain if the negative impact of QOL observed in this study was directly related to HRT usage. Lastly, as large number of data was missing for menstruation cessation age, HRT usage, and history of oophorectomy, there may be potential for selection bias [Table/Fig-5] and hence precaution is needed when interpreting findings. Future population-based longitudinal studies, designed to measure HRQOL just before HRT prescription and at different time points during the usage of the drug, are needed to determine the true impact of HRT on HRQOL, as well as the mechanism underlying the HRT-HRQOL relationship amongst the three ethnic groups in Singapore.

## CONCLUSION(S)

The overall HRT utilisation rate in the multi-ethnic Asian population of this study was low and most of the independent determinants (such as reading literacy and being Christian) of HRT utilisation were different from those reported in Western populations. Higher monthly income and older age of menstruation cessation were independently associated with HRT utilisation for Indians and Chinese respectively. Finally, HRT utilisation was found to be associated with worse mobility, pain/discomfort and anxiety/depression in Malay, Indian and Chinese women, respectively. The age- and ethnicity-adjusted prevalence rates of HRT usage from this study, along with the information on determinants and patient-centered impact, provide useful information for clinicians, researchers and policy planners working in women's health in Singapore.

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