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Effects of menopause, hormone replacement therapy and aging on the health in Asian women

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Abstract

The cross-sectional study examined whether menopause and hormone replacement therapy (HRT) can and how they modify the aging process in Asian women.

Methods: All women answered a questionnaire on their medical history, exercise regime, sexual functions, sleep hygiene, general well-being and menopausal and HRT status. Serum biochemical and hormones, blood pressures, handgrip strength and forced expiratory capacity were measured. Cognitive functions were monitored, and bone and body composition were evaluated using the dual energy absorptiometry (DXA).

Results: The results showed that aging affected many health compartments starting mainly in the 6th decade. Aging affects the cognitive functions, body form, physical and general well-being, metabolic and cardiovascular risk, bone health and the incidence of both general and abdominal obesity. The onset of menopause further aggravated the poor bone health, strength and higher body fat due to age alone. These ill effects in postmenopausal women not having HRT were negated by either estrogen alone or estrogen/progestin HRT. However, estrogen alone HRT was associated with significantly lower IGF1 and BP3 and higher incidence of abdominal obesity than by age alone. The combined estrogen/progestin HRT, on the other hand was associated with lower levels of HDL.

Conclusion: Aging affects most health compartments by the 5th and 6th decades. The onset of menopause further aggravated the ill effects of aging on bone health. While HRT could negate the ill effects of menopause, HRT may have other adverse effects on some aspects of women health.

Keywords: *Asian women, aging, menopause, hormone replacement therapy.*

Introduction

In 2014 in the USA, the CDC reported that there was about a five-year difference in life expectancy between men (76.5y) and women (81.3y) [1]. However, the primary concern today is the concept of health expectancy; that is a measure of how long a person remains healthy in his/her life cycle. Therefore, health expectancy is tied intimately to how a person ages, rather than merely a measure of the chronological aging. It is known that aging affects individuals at different rates. There are individuals who look beyond their age and conversely, others look much younger than their age. The rate of aging is dependent on many factors including the biological make up; an individual who is genetically predisposed to have some diseases such as premature aging will age much faster than his/her chronological age. The environment has a definite bearing on how a person ages – living in an environment with poor sanitation, lack of clean water and polluted air will greatly stress the body leading to a higher rate of aging. Countries have very different socioeconomic and geopolitical situations. In some countries, people who live in abject poverty will have higher rates of aging. In addition, the lifestyle that a person adopts - whether he/she gets involved in drug, alcohol abuse, or engages in excessive eating can lead to poor health and thus accelerate the aging process. Unlike men, apart from all the factors affecting aging mentioned above, the onset of menopause is a major biological event that can further impact the aging process in women.

The menopause happens around the age of 50 years when a woman stops menstruating and the ovaries stop producing, cyclically, estrogen and progesterone. Following the onset of menopause, women may experience varying degrees of biological, psychological and somatic changes ranging from hot flushes, night sweats, aches and pains, crawling or itching sensations under the skin, forgetfulness, headaches, irritability, lack of self-esteem, reduced sex drive (libido), tiredness, difficulty sleeping – wakefulness or waking hot and sweaty, urinary frequency, vaginal dryness and discomfort with sexual intercourse [2]. The Long-term health risks with menopause as a result of a decrease in female hormones may lead to thinning of the bones (osteoporosis) and an increased risk of fractures, an increase in the risk of heart attack and heart diseases, high blood pressure and stroke [3].

Since the publication of the Women's Health Initiative [4] and the Million Women Study [5], and the reported links between combination (estrogen and progestin) HRT and cardiovascular disease and breast cancer, The National Institute for Health and Care Excellence (NICE) suggests that many women are suffering in silence because of fears about such adverse outcomes. In November 12, 2015, NICE gave

guideline that tries to assuage fears about HRT and together with other studies offer a new perspective that could help women to make a more informed treatment decision based on a balanced review of the evidence [6].

While the impact of menopause and HRT on the major illnesses including cancer, coronary heart diseases and osteoporosis has been well researched, relative less is known about its impact on sexual functions, homeostasis and other lifestyle factors [7, 8]. The present study examined how menopause and HRT affect or modify the aging process in a large cohort of healthy and community living Asian women.

Subjects, materials and methods

Subjects

The Institutional Review Board of the National University Hospital of Singapore approved this study and each volunteer gave her written informed consent. The method was previously reported [9, 10]. A large cohort of 1326 women, aged between 29y and 72y, were included in the analyses.

General questionnaire

Each subject answered a self-administered and investigator-guided questionnaire. Questions asked included their medical, social, sex, exercise regime, and family history. As the primary objective of the study was to evaluate the determinants of the natural aging process, only women without a history of medical illnesses such as cancer, hypertension, thyroid dysfunction, diabetes, osteoporotic fracture, cardiovascular events, major sleep disorders, and major joint surgery were included in the study. Subjects were not paid for their participation. The cohort of women represented the diverse spectrum of people in Singapore, ranging from those with low to high levels of education, working and non-working women (retirees), and those in various types of vocation [10]. Their profiles were typical of Singapore, which is a highly urbanized city-state with no rural population.

Age groups (AgeGps)

All women were classified into four age groups: AgeGp1 – women below age 40 y, AgeGp2 – women between ages of 41 to 50 y, AgeGp3 – women between ages 51 to 60 y and AgeGp4 – women above 60 y old.

Menopause groups (MenoGps)

In order to evaluate whether the onset of menopause and the presence of hormone replacement therapy (HRT) have a modifying effect on the aging process, all women aged between 50 – 60 y were classified into four menopause groups: MenoGp1 – all premenopausal women within this age group; MenoGp2 – postmenopausal women not on any HRT; MenoGp3 – postmenopausal women on estrogen only replacement therapy (ERT) for at least the past year (mainly on 0.625 mg Premarin (Pfizer, NY) or progynova (2 mg estradiol valerate, Schering AG, Berlin); and MenoGp4: postmenopausal women on estrogen/progestin hormone replacement therapy (E/PRT) for at least the past year (mainly Prempak C (0.625mg Conjugated estrogen and 0.15mg norgestrel, Pfizer Ltd, NY).

Biochemical and hormone measurements

An overnight 12h fasting blood sample was collected in the morning between 9.00am and 11.00am for all postmenopausal women. For premenopausal women, a blood sample was collected between Day 3 to Day 5 of their menstrual cycle. The sera were stored at -80^{o}C until analyses. Serum levels of total cholesterol (TC) and triglycerides (TG), high-density lipoprotein-cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and fasting glucose level (Glu) were measured by methods reported earlier [11]. Serum testosterone (T), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG) and cortisol (Cor) were measured by established radioimmunoassay methods reported earlier [9]. Serum concentrations of insulin-like growth factor-1 (IGF1) and insulin like growth factor binding protein-3 (BP3) was measured using immunoradiometric assay kits (Diagnostic Systems Laboratories, Inc., Webster, TX) as reported earlier [12, 13]. Serum concentrations of insulin (INS) were measured in-house using the Axsym platform from Abbott. Bioavailable testosterone (BioT) was calculated using the computer formula of Vermeulen, which is available on the ISSAM website. [www.issam.ch]

Whole body DXA and bone scans

Each subject had a whole body scan using the DXA Hologic, Bedford, MA, and USA. The DXA scanner calculated the percent total body fat (PBF) automatically using the Siri formula. Total body and regional distribution in the trunk (Tk), abdomen (Abd), arms (Arm) and legs (Leg) of lean (L) and fat (F) mass, expressed in mass (g) and per cent were computed from the whole body scan. Total bone mineral content (Tbmc) and per cent mineral content (Pbmc) were also derived from the whole body scan.

Spine and hip osteoporosis and osteopenia

Each subject underwent a lumber spinal scan at the L2-L4, and a scan of the hip (representing the femoral neck, shaft, and trochanter) using DXA. The DXA scanner computed the spine bone mineral density (Sbmd, the average bone mineral density of L2-L4) and femoral neck bone mineral density (Hbmd). The T-scores for the spine and femoral neck were computed with reference to the bone mineral density (bmd) for young women established for the local population. According to the WHO guidelines, a T-score >-1.00 is normal, while T-scores <-1.00 to -2.50 denote osteopenia and T-scores of <-2.50 denote osteoporosis [14]. Hence, the following groups were identified: Spine osteopenia (SOsteopn) and spine osteoporosis (SOsteop) and hip osteopenia (HOsteopn) and hip osteoporosis (HOsteop) and were used in the analyses for incidence.

Handgrip strength (Grip)

A handgrip dynamometer (Takei Scientific Instruments, Japan) was used to test the handgrip strength as reported earlier [15]. The purpose of this test was to measure the maximum isometric strength of the hand and forearm muscles. Also, as a general rule, people with strong hands tend to be strong also elsewhere, so this test is often used as a general test of strength [16, 17]. Each subject performed the handgrip test three times and the maximum score (Grip) of the

three was used for the analysis. The handgrip strength was expressed as kilogram force (Kgf).

Well-being score (WBSc), well-being symptoms (WBsym)

The well-being questionnaire contains 31 items regarding a wide variety of symptoms, such as vegetative symptoms, concentration deficit, fatigue, tiredness, dizziness, and symptoms of peripheral neuropathy. The subjects were asked to rate the frequency of occurrence of each symptom during the last 24 hours on a four-point scale with 0, denoting none and 3, frequent. This test was taken from the SPES package [18]. The individuals' sense of well-being is dependent on many factors including sleep; levels of stress at work and at home, any circadian rhythm disruption and the presence of emotional distress. A higher score, therefore, would reflect a greater sense of being unwell. A higher number of symptoms (WBSym) add up to a higher sense of being unwell.

Forced expiration capacity test (FEC)

Subjects were asked to blow into an instrument (from Takei, Japan) to measure the forced expiratory capacity. The measurement was adjusted for gender and age of the subjects. The score was then set as a percent of the mean at the individual's age and gender group. It is a measure of tiredness and an indication of the lung capacity at the time of testing. A lower percentage (FEC) indicates a more tired or weaker physical state.

Blood Pressures

Brachial systolic (Sys) and diastolic (Dia) blood pressures were measured by trained clinical researchers using a standardized manual sphygnomanometric method and after the participants had rested for at least 5 min. Both blood pressures were recorded as millimeter of mercury (mmHg).

Cognitive function tests

The Swedish Performance Evaluation System (SPES) was developed more than 40 years ago [18]. Two prospective tests from the SPES, the Symbol Digit for perceptual capacity and Digit Span for short-term memory were used in the study. The digit symbol and digit span tests were computer-based tests. All participants underwent a familiarization trial test before the actual scorings were recorded.

Symbol Digit – The Symbol Digit is a test of perceptual capacity, which includes matching, memory and the speed of processing. In one row, a key to this coding task is given by the pairing of symbols with randomly arranged digits, 1 to 9. The task is to key in as fast as possible the digits corresponding to the symbols presented in random order in a second row. Each set consists of nine pairs of randomly arranged symbols and digits, and a total of 10 sets are presented. Performance is evaluated as the mean reaction time in milliseconds (RT) and the number of errors (Err) for the last 54 pairs of the test. Symbol digit tests the individual's ability to interpret and correctly match what he sees as well as the speed of his mental perception. It also involves hand-eye coordination. The two components of this test are reaction time (RT) and the number of errors (Err) [18].

Digit Span – The Digit Span is a test of the short-term visual memory capacity. In this test, a series of digits is presented on the computer screen. The digits are presented one at a time with a 1-second presentation time, and the task is to reproduce the series on the keyboard. Depending on the answer, the length of the following series is either increased or decreased. The test starts with a series of three digits and it is terminated after six incorrect answers. Performance is evaluated as the maximum string of numbers (DSpan) that the subject could remember successfully. A longer DSpan indicates a better short-term visual memory [18].

Obesity

Definitions of general (GOb) and abdominal (AbO)

Per cent total body fat (PBF) computed from the DXA-whole body scan was used to define general obesity. General obesity (GOb) was defined when the PBF is >35% for women [19]. Abdominal obesity (AbO) was defined when the per cent abdominal fat is >21.8% in women [19].

Metabolic Syndrome (MetS) Groupings

The most commonly used NCEP ATPIII definition of metabolic syndrome (MetS) was used for the purpose of the present study [20]. According to the recommendations of the NCEP ATP III [23], the 5 risk factors of MetS are:

- High density lipoprotein cholesterol (HDL) <1.03mmol/l
- Fasting glucose level (Glu) >5.6mmol/l
- Systolic blood pressure/diastolic blood pressure - B/P >130/>85 mmHg
- Triglyceride level (TG) > 1.7mmol/l
- For the present study, the risk factor of waist circumference was replaced by a PBF of >35% for women to defined obesity.

An individual was considered to have metabolic syndrome (MetS) when she has 3 or more of the above 5 metabolic syndrome risk factors.

Indices of Insulin resistance

Besides high levels of insulin as indicative of possible insulin resistance, the Homeostasis Model Assessment (HOMA) score was established as a measure of insulin resistance. As suggested by Matthews et al, HOMA is computed by multiplying fasting insulin with fasting glucose levels and then dividing it by 22.5 [24]. A HOMA value of >2.8 computed from a single fasting blood sample correlated well with other measures of insulin resistance [21].

Surveys sleep and sexual activities

In the general questionnaire, subjects were asked to rate their duration of sleep, ease of falling asleep and their sexual functions. The scores were based on the following questions:

Sleep duration per night (SlpD)	Score
• <4h	1
• 4 - 6h	2
• 6 – 8h	3
• >8h	4

Do you have problem falling asleep? (Fallslp)	Score
• No	1
• Yes	2

Sexual activities

Subjects were asked, on an average,

1. How many times they had coitus with their partner per month (CoitalF)
2. Whether they self-masturbate (Masturbate)

Score	
• No	1
• Yes	2

3. If they do, how many times per month (No.Times)
4. What is your response to your coital frequency?
    1. Want more
    2. Happy with frequency
    3. Want less
5. How is your libido?
    1. Normal
    2. Reduced
6. Do you have pain during sex?
    1. No
    2. Yes

Statistical analyses

Statistical analyses were performed using SPSS for windows version 21.0. Basic descriptive statistics as well as comparison of means using the Multivariate analyses of the General Linear Model coupled with the Bonferroni as the Post-Hoc test for multiple means were used on continuous measurements. Comparisons were carried out among the four age and four menopausal groups and significance differences were denoted when the p value is <0.05. For non-parametric measures such as the incidence of osteopenia and osteoporosis, ease of falling asleep, number who were engaged in masturbation, the numbers who were obese, cross-tab analyses with the four age and menopausal groups were computed and the Fisher's exact test was used for statistical analyses.

Results

The results showed that aging affected many of the major health compartments evaluated in the present study. In the cognitive perceptual capacity domain, errors (Err) in matching was significantly degraded after the 6th decade, while noticeable and significant increase in reaction time (RT) occurred after the 5th decade and was worst after the 6th decade (Table 1). Similar to RT of the perceptual capacity, short-term memory (Dspan) was significantly shorter after the 5th decade and was further and progressively poorer after the 6th decade (Table 1).

Handgrip strength was significantly lower in women in the 6th and 7th decades when compared to women in the 4th and 5th decade, and the handgrip strength in women in the 7th decade was significantly lower when compared to women in the 6th decade (Table 1). As far as the forced expiratory capacity (FEC) was concerned, women in the 7th decade had significantly lower FEC when compared to all other groups of younger women (Table 1). Likewise, women in the 7th decade experienced significantly more unwell symptoms when compared to all other groups of younger women (Table 1). In addition, the sense of well-being was significantly lower in women in the 7th decade when compared only to women in the 4th decade (Table 1).

Systolic blood pressure was significantly and progressively higher in women after the 4th decade, while diastolic blood pressure was significantly and progressively higher in women after 5th decade (Table 1).

Significantly more women in the 6th decade age groups slept less than 6 hour per night when compared to women in the 4th decade age group (Table 1). Women in the 6th and 7th decade had progressively less sex than women in the 4th and 5th decade (Table 1). On the other hand, younger women, in the 4th decade wanted to have more sex than all the older women in the 5th to 7th decade (Table 1). Significantly more women in their 4th decade were engaged in masturbation than older women in their 6th decade (Table 1). Significantly more women, in their 6th and 7th decade experienced pain in sex than younger women in their 4th and 5th decade (Table 1).

Aging related changes in body composition were reflected in changes in the three major elements of bone, lean and fat masses. Per cent bone mineral content (Pbmc) was significantly lower in women in the 6th and 7th decade when compared to women in the 4th and 5th decade. Furthermore, Pbmc was significantly lower in women in the 7th decade when compared to women in the 6th decade (Table 2). Per cent lean mass (PLM) and Per cent body fat (PBF) on the other hand, were significantly and progressively lower and higher, respectively, from the 4th decade onwards (Table 2). Interestingly, on an average, per cent lean mass decrease by about 4.0% over a span of 30 years, while per cent fat mass increase by about 5.4% over a span of 30 years which is close to the combine loss of 4.62% of lean and bone mass (Table 2). Regional body composition changed as a person aged. Both spine bone mineral density (Sbmd) and hip bone mineral density (Hbmd) were significantly lower, starting in women in the 6th decade and continued to be even lower in 7th decade when compared to women in the 4th and 5th decade (Table 2). Over the span of 30 years, Sbmd and Hbmd were lower by 16.2% and 13.9%, respectively, when compared to corresponding levels in women in the 4th decade (Table 2).

The incidence of spinal osteopenia and osteoporosis among Singaporean women increased progressively with age. For spinal osteopenia, the increase was from 10.5% in the 4th to 37.6% in the 6th and a high of 53.4% in the 7th decade (Table 3). For spinal osteoporosis, the increase was from 0.6% in the 4th decade to 3.8% in the 6th and to

10.5% in the 7th decade (Table 3). On the other hand, the incidence of hip osteopenia was already high (50.8%) in the 4th decade and did not increase significantly through to the 7th decade (Table 3). The incidence of osteoporosis of the hip, on the other hand, was significantly higher in the older age groups. It increased significantly from 6.1% in the 4th decade to 15.7% in the 6th and to 36.8% in the 7th decade (Table 3).

Table 1. Comparisons of various parameters among the four age groups

	AGp1 n = 181	**AGp2 n = 533**	**AGp3 n = 479**	**AGp4 n = 133**
Age (y)	36.8 ± 0.20	48.0 ± 0.12	54.5 ± 0.12	64.4 ± 0.22
AGp1vAGp2,3,4 (<0.001, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (<0.001)				
Err	1.72 ± 0.18	1.95 ± 0.12	2.07 ± 0.13	2.59 ± 0.29
AGp1vAGp4 (0.046)				
RT (msec)	2319 ± 38	2404 ± 22	2483 ± 22	2786 ± 52
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp4 (<0.001), AGp3vAGp4 (<0.001)				
Dspan	6.91 ± 0.13	6.89 ± 0.05	6.61 ± 0.05	6.22 ± 0.10
AGp1vAGp3, 4(0.022, <0.001), AGp2vAGp3, 4(0.001, <0.001), AGp3vAGp4 (0.003)				
Grip (Kgf)	25.4 ± 0.23	24.1 ± 0.37	22.5 ± 0.19	20.4 ± 0.36
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (0.004)				
FEC (%)	70.4 ± 1.6	66.7 ± 0.94	65.9 ± 0.95	59.5 ± 1.9
AGp1,2,3vAGp4 (<0.001,0.003, 0.010)				
Sys (mmHg)	113 ± 1.0	119 ± 0.7	125 ± 0.8	131 ± 1.8
AGp1vAGp2,3,4 (<0.001, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (0.001)				
Dia (mmHg)	74.0 ± 0.7	76.2 ± 0.4	78.7 ± 0.4	79.4 ± 1.0
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp3,4 (<0.001,0.005)				
WBSc	21.1 ± 0.7	19.9 ± 0.4	20.0 ± 0.5	17.4 ± 1.0
AGp1vAGp4 (0.013)				
WBsym	17.3 ± 0.5	16.4 ± 0.3	16.2 ± 0.3	14.2 ± 0.7
AGp1,2,3vAGp4 (0.001,0.008,0.023)				
CoitalF	4.74 ± 0.28	4.45 ± 0.16	3.77 ± 0.17	2.02 ± 0.26
AGp1vAgp3,4 (0.14, <0.001), AGp2vAGp3,4 (0.022, <0.001), AGp3vAGp4 (0.003)				
Masturb	23/156 (9.1%)	50/448 (11.2%)	31/375 (8.3%)	6/79 (7.6%)
AGp1vAGp3 (0.030)				
SlpD <6h	19/170 (11.1%)	71/511 (13.9%)	98/466 (21.0%)	23/130 (17.7%)
AGp1vAGp3 (0.015)				
Want more sex	24/129 (18.6%)	36/395 (9.1%)	12/273 (4.4%)	2/48 (4.2%)
AGp1vAGp2,3,4 (0.10,0.001,0.02)				
Painful sex	16/132 (12.1%)	70/393 (17.8%)	79/269 (29.4%)	13/45 (28.9%)
AGp1vAGp3,4 (0.001,0.030), AGp2vAGp3 (0.004)				

Err = number of errors; RT = reaction time; Dspan = digit span; Grip = handgrip strength; FEC = forced expiratory capacity; Sys = systolic blood pressure; Dia = diastolic blood pressure; WBSc = well being score; WBsym = number of unwell symptoms; Coitalf = number of coitus per month; masturb = number/per cent of women engaged in masturbation; SlpD = number/per cent of women who slept less than 6h per night; want more sex = number/per cent of women who want more sex than currently engaged in; Painful sex = number/per cent of women who experienced pain during sex.

Table 2. Comparisons of body compositions among the four age groups

	AGp1 N = 181	AGp2 N = 533	AGp3 N = 479	AGp4 N = 133
Pbmc (%)	4.49 ± 0.034	4.40 ± 0.021	4.17 ± 0.022	3.87 ± 0.040
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp3, 4 (<0.001, <0.001), AGp3vAGp4 (<0.001)				
PLM (%)	60.7 ± 0.37	59.2 ± 0.21	58.1 ± 0.22	56.7 ± 0.26
AGp1vAGp2,3,4 (0.002, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vsAGp4 (0.026)				
PBF (%)	26.3 ± 0.38	27.8 ± 0.21	29.6 ± 0.22	31.7 ± 0.39
AGp1vAGp2,3,4 (0.002, <0.001, <0.001), AGp2vAGp3,4 (<0.001,0.001), AGp3vGp4 (<0.001)				
Sbmd (g/cm^2)	1.076 ± 0.010	1.070 ± 0.006	0.986 ± 0.007	0.902 ± 0.014
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (<0.001)				
Hbmd (g/cm^2)	0.837 ± 0.008	0.829 ± 0.005	0.787 ± 0.005	0.721 ± 0.009
AGp1vAGp3,4 (<0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (<0.001)				
PTkL (%)	37.2 ± 0.09	37.4 ± 0.05	37.5 ± 0.06	37.7 ± 0.11
AGp1vAGp3,4 (0.033, 0.004)				
PAbdL (%)	18.0 ± 0.08	18.3 ± 0.05	18.6 ± 0.06	18.8 ± 0.10
AGp1vAGp2,3,4 (0.002, <0.001, <0.001), AGp2vAGp3,4 (0.019, <0.001)				
PLegL (%)	28.7 ± 0.12	28.3 ± 0.07	27.9 ± 0.07	27.4 ± 0.17
AGp1vAGp2,3,4 (0.008, <0.001, <0.001), AGp2vAGp3,4 (0.003, <0.001), AGp3vAGp4 (0.007)				
PAbdF (%)	17.8 ± 0.13	18.5 ± 0.08	19.0 ± 0.09	19.2 ± 0.16
AGp1vAGp2,3,4 (<0.001, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001)				
PTkF (%)	37.7 ± 0.15	38.6 ± 0.11	39.3 ± 0.28	39.5 ± 0.19
AGp1vAGp2,3,4 (<0.001, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001)				
PLegF (%)	29.8 ± 0.25	28.8 ± 0.16	27.9 ± 0.15	27.7 ± 0.28
AGp1vAGp2,3,4 (0.003, <0.001, <0.001), AGp2vAGp3,4 (0.001, 0.008)				

Pbmc = per cent bone mineral content; PLM = per cent total lean mass; PBF = per cent body fat; Sbmd = average bone mineral density of L2-L4; Hbmd = bone mineral density of the femoral neck of the hip; PTkL = per cent trunk lean mass; PAbdL = per cent abdominal lean mass; PLegL = per cent leg lean mass; PAbdF = per cent abdominal fat mass; PTkF = per cent trunk fat mass; PlegF = per cent leg fat mass.

Per cent trunk lean (PTkL) showed significant increases in older women in the 7th decade when compared to younger women in the 4th decade (Table 2). Per cent abdominal lean mass (PAbdL), on the other hand, was significantly lower in younger women in the 4th decade when compared to women in all the older groups (Table 2). In addition, women in the 5th decade had significantly lower PAbdL than women in both the 6th and 7 decades (Table 2). Contrary to the per cent trunk and abdominal lean mass, the per cent leg lean mass (PLegL) was significantly lower in women in all the older age groups when compared to the younger women in the 4th decade and was progressively and significantly lower from the 4th decade through the 7th decade (Table 2). Per cent trunk and abdominal fat mass (PTkF) was significantly and progressive higher starting from the 4th decade through the 7th decade and was significantly higher in the 6th and 7th decade as compared to the 5th decade (Table 2). A similar trend was noted for per cent leg fat (PLegF), except that it was progressively lower in women in the older age groups (Table 2).

Bioavailable testosterone (BioT) tended to be lower in women in the older age groups, but only reached significantly level when comparing women in the 5th and 6th decade (Table 3). Insulin growth factor-1 (IGF1) was significantly and progressive lower from the 4th decade onwards and reaching the lowest level in women in the 7th decade, decreasing, on an average, 1% per year from the 4th decade onwards (Table 3). On the other hand, the insulin growth factor binding protein-3 (BP3) was significantly higher in women in the 6th decade when compared to women in both the 4th and 5th decade (Table 3). Insulin (INS) levels in women in the 7th decade were significantly higher than in women in the 4th decade (Table 3). The HOMA level of women in the 7th decade was significantly higher than corresponding levels in women in the 4th and 5th decade (Table 3). There were no significant changes with age noted for cortisol, testosterone and DHEAS levels.

Table 3. Comparisons of biochemical and hormone factors and incidences among the four age groups

	AgeGp1 n = 181	**AgeGp2 n = 533**	**AgeGp3 n = 479**	**AgeGp4 n = 133**
BioT (ng/dl)	17.6 ± 0.67	18.2 ± 0.40	16.3 ± 0.40	16.1 ± 0.69
AGp2vAGp3 (0.004)				
IGF1	211 ± 5.7	185 ± 3.1	172 ± 3.8	146 ± 6.2
AGp1vAGp2,3,4 (0.001, <0.001, <0.001), AGp2vAGp3,4 (0.040, <0.001), AGp3vAGp4 (0.003)				
BP3	3814 ± 71	3827 ± 44	4109 ± 54	4047 ± 110
AGp1,2v3 (0.012, <0.001)				
INS (mIU/l)	6.10 ± 0.24	6.58 ± 0.19	6.52 ± 0.17	7.37 ± 0.32
AGp1vAGp4 (0.024)				
TC (mmol/l)	5.14 ± 0.060	5.54 ± 0.036	5.85 ± 0.044	6.11 ± 0.08
AGp1vAGp2,3,4 (<0.001, <0.001, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (0.017)				
HDL (mmol/l)	1.59 ± 0.022	1.64 ± 0.016	1.71 ± 0.019	1.66 ± 0.032
AGp1,2vAGp3 (0.001, 0.007)				
LDL (mmol/l)	3.16 ± 0.58	3.43 ± 0.032	3.62 ± 0.04	3.84 ± 0.071
AGp1vAGp2,3,4 (0.001, <0.001, <0.001), AGp2vAGp3,4 (0.001, <0.001), AGp3vAGp4 (0.029)				
TC/HDL	3.34 ± 0.060	3.55 ± 0.040	3.59 ± 0.045	3.89 ± 0.093
AGp1vAGp3,4 (0.014, <0.001), AGp2,3vAGp4 (0.001, 0.009)				
Glu (mmol/l)	3.57 ± 0.034	4.71 ± 0.023	3.84 ± 0.024	4.91 ± 0.051
AGp1vAGp2,3,4 (0.010, <0.001, <0.001), AGp2vAGp3,4(0.001, 0.001)				
HOMA	1.26 ± 0.055	1.41 ± 0.049	1.43 ± 0.040	1.67 ± 0.09
AGp1,2vAGp4 (0.002, 0.040)				
GOb	10/181 (5.5%)	49/533 (9.2%)	68/479 (14.2%)	32/133 (24.1%)
AGp1vAGp3,4 (0.008, <0.001), AGp2vAGp3,4 (0.030, <0.001), AGp3vAGp4 (0.030)				
AbO	1/181 (0.6%)	16/533 (3.0%)	36/479 (7.5%)	5/133 (3.8%)
AGp1,2 vAGp3 (<0.001, 0.003)				
MetS	1/181 (0.6%)	11/533 (2.1%)	23/479 (4.8%)	11/133 (8.3%)
AGp1vAgp3,4 (0.008, <0.001), AGp2vAGp3,4 (0.023, 0.002)				
SpOsteopn	19/181 (10.5%)	90/533 (16.9%)	180/479 (37.6%)	71/133 (53.4%)
AGp1vAGp3,4 (<0.00, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (0.047)				
SpOsteop	1/181 (0.6%)	0/533 (0%)	18/479 (3.8%)	14/133 (10.5%)
AGp1vAGp3,4 (0.033, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (0.008)				
HOsteop	11/181 (6.1%)	31/533 (5.8%)	75/479 (15.7%)	49/133 (36.8%)
AGp1vAGp3,4 (0.003, <0.001), AGp2vAGp3,4 (<0.001, <0.001), AGp3vAGp4 (<0.001)				

BioT = bioavailable testosterone; IGF1 = insulin growth factor-1; BP3 = insulin growth factor binding protein-3; INS = insulin; TC = total cholesterol; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; TC/HDL = total cholesterol/high density lipoprotein cholesterol ratio; Glu = glucose level; HOMA = homeostasis model assessment score; GOb = number/per cent of women with general obesity; AbO = number/per cent of women with abdominal obesity; MetS = number/per cent of women with metabolic syndrome; SOsteopn = number/per cent of women with osteopenia of the spine; SOsteop = number/per cent of women with osteoporosis of the spine; HOsteop = number/per cent of women with osteoporosis of the hip

Both total cholesterol (TC) and low density lipoprotein cholesterol (LDL) were significantly and progressively higher from the 4th to the 7th decade. High density lipoprotein cholesterol (HDL), on the other hand tended to be higher in older women, but only reached significantly levels when comparing levels in women in the 6th decade with those in women in the 4th and 5th decade (Table 3). The ratio of TC/HDL increased with age and levels in women in the 6th and 7th decade were significantly higher than corresponding levels in women in the 4th and 5th decade (Table 3). Glucose (Glu) levels were significantly higher in all other older age groups when compared to those in women in the 4th decade; and levels in women in the 6th and 7th decade, were significantly higher than levels in women in the 5th decade (Table 3). No significant change with age was noted for TG levels.

The incidence of general obesity (GOb) increased with age and was significantly higher in women in the 6th and 7th decade when compared to women in the 4th and 5th decade; likewise the incidence was significantly higher in women in the 7th decade when compared to that in women in the 6th decade (Table 3). As with general obesity, the incidence of abdominal obesity (AbO) tended to be higher in older women, reaching significantly levels in women in the 6th decade when compared to corresponding levels in women in the 4th and 5th decade (Table 3).

Significantly more women in the 6th and 7th decade had metabolic syndrome (MetS) when compared to women in the 4th and 5th decade (Table 3).

Taking all women in the age range of 50 to 60 y old and categorized them into four groups of premenopausal, postmenopausal without HRT, postmenopausal with estrogen replacement therapy and postmenopausal women with combined estrogen/progestin therapy, has enabled the evaluation of whether the onset of menopause and how different HRT can influent the aging effects on various health compartments. Comparing between the premenopausal and the postmenopausal women without HRT in this age group revealed that the onset of the menopause had additional effects on top of those due to aging alone. Handgrip strength in postmenopausal women without HRT (MenoGp2) was significantly lower than corresponding levels in premenopausal women (MenoGp1) (Table 4).

The onset of menopause (MenoGp2) was associated with significant reduction of Sbmd, bone mineral content (Tbmc, Pbmc) when compared to premenopausal women in the same age group (Table 4). In addition the number of women who had spinal osteopenia in postmenopausal women without HRT was significantly higher than premenopausal women in the same age group (Table 4).

The per cent body fat (PBF) in postmenopausal women without HRT was significantly higher when compared to corresponding values in premenopausal women in the same age group (MenoGp1) (Table 4).

The systolic blood pressure (Sys) and testosterone of postmenopausal women on the estrogen/progestin (E/P) combined HRT was significantly higher than premenopausal women in the same age group (Table 4). The levels of BP3 and HDL in postmenopausal women on the E/P HRT were significantly lower than postmenopausal women who were not on any HRT (Table 4).

On the other hand, postmenopausal women in the estrogen only HRT group (MenoGp3) had significantly lower IGF1 and BP3 levels than postmenopausal women not on HRT in the same age group (Table 4). More postmenopausal women on estrogen only HRT had abdominal obesity than premenopausal women in the same age group (Table 4).

Discussion

Results of the present cross-sectional study, involving a large cohort of healthy community living Asian women, showed that aging affects most health compartments and each to varying extent. The deleterious effects of aging occurred mostly after the age of 50 y old, with some occurring earlier, after 40 y. In addition, in some compartments, the magnitude of the ill effects that occurred after 40 y or 50 y did not deteriorate any further with age, while in others; the ill effects became progressively worse through to the 7th decade.

An obvious age-related effect was the change in body form, noticeably, the accumulation of body fat in the trunk, abdomen and hip that occurred as earlier as after 40 y of age. Interestingly, unlike in the trunk, hip and abdomen, lean and fat mass in the legs decreased with age, perhaps explaining the flabby looks noted in the legs many older women.

Associated with the changes in body form were biochemical changes that are indicative of increase risks of metabolic syndrome and cardiovascular diseases. The increased risks were reflected by increases in total cholesterol, LDL, TC/HDL and glucose level as well as systolic and diastolic blood pressure that started occurring in the 5th and 6th decade. Further evidence of the increase risk of metabolic syndrome was the observed increase in insulin levels and the index for insulin resistance (HOMA) that occurred in the 7th decade. These metabolic changes were associated with the increases in the incidence of metabolic syndrome in women in the 6th and 7th decade of life. In addition, there was an increase in the incidence of general obesity and abdominal obesity. The results give further credence to an earlier report that it is abdominal and not general obesity that was associated with increased risk of metabolic syndrome and cardiovascular diseases [19].

Osteoporosis is frequently referred to as the silent killer or the silent epidemic and has become a major public health problem, especially in older men and women [22]. There is abundant evidence that the incidence of osteoporosis increases with age [23], and the results of the present study supported this observation. In conjunction with the significant loss of the Sbmd and Hbmd as well total bone mineral content, the incidence of osteoporosis and osteopenia of the hip and spine showed significant increases in the 6th and 7th decade. The increased incidence of osteopenia and osteoporosis in women in the 6th and 7th decade coincided with the onset of the menopause. The depletion of the female hormone in postmenopausal women is considered a major risk factor for osteoporosis [24].

An interesting feature of the bone health among the Singaporean women was that the incidence of hip osteopenia was already very high in women in the 4th decade. Unfortunately the cohort of the present study did not include participants younger than 30 y old. Therefore,

it is not known when the increase in incidence of osteopenia of the hip had occurred in this population. It is also not clear whether this is a peculiar feature of the Singapore cohort as no comparison with other populations was available. It is however not surprising that the incidence of osteopenia in Singaporean women even as young as those in their 4th decade was very high, given the rather sedentary lifestyle prevalent in Singapore, a highly urbanized City State.

Table 4. Comparisons of various parameters among the four menopausal groups

	MenoGp1 N = 89	**MenoGp2 N = 296**	**MenoGp3 N = 31**	**MenoGp4 N = 63**
Age (y)	52.4 ± 0.19	54.8 ± 0.15	55.4 ± 0.50	55.4 ± 0.34
MenoGp1vsMenoGp2,3,4 (<0.001, <0.001, <0.001)				
Grip (Kgf)	23.6 ± 0.45	22.1 ± 0.25	23.1 ± 0.67	23.1 ± 0.50
MenoGp1vMenoGp2 (0.013)				
Sys (mmHg)	122 ± 1.6	124 ± 1.0	130 ± 3.5	131 ± 2.3
MenoGp1,2vMenoGp4 (0.006, 0.10)				
Sbmd (g/cm^2)	1.053 ± 0.017	0.960 ± 0.009	1.025 ± 0.027	0.997 ± 0.018
MenoGp1vMenoGp2 (<0.001)				
Tbmc (g)	2369 ± 30	2247 ± 15	2347 ± 41	2298 ± 27
MenoGp1vMenoGp2 (<0.001)				
PBF (%)	28.2 ± 0.54	29.9 ± 0.27	29.8 ± 1.00	29.6 ± 0.57
MenoGp1vMenoGp2 (0.026)				
Pbmc (%)	4.30 ± 0.05	4.13 ± 0.29	4.23 ± 0.09	4.14 ± 0.05
MenoGp1vMenoGp2 (0.016)				
T (ng/ml)	0.63 ± 0.09	0.66 ± 0.05	0.71 ± 0.19	1.14 ± 0.22
MenoGp1,2vMenoGp4 (0.019, 0.006)				
IGF1 (ng/ml)	173 ± 7.5	177 ± 4.8	129 ± 12	169 ± 13
MenoGp2vMenoGp3 (0.013)				
BP3 (ng/ml)	3996 ± 129	4285 ± 68	3540 ± 215	3719 ± 120
MenoGp2vMenoGp3,4 (0.004, 0.003)				
HDL (mmol/l)	1.66 ± 0.04	1.75 ± 0.02	1.88 ± 0.07	1.57 ± 0.04
MenoGp2,3vMenoGp4 (0.012, 0.021)				
AbO	3/89 (3.4%)	21/296 (7.1%)	5/31 (16.1%)	7/63 (11.1%)
MenoGp1vMenoGp3 (0.039)				
SOsteopn	7/89 (7.9%)	129/296 (43.6%)	11/31 (35.5%)	23/63 (36.5%)
MenoGp1vMenoGp2 (0.0033)				

MenoGp1 = premenopausal women in the age group of 50–60y; MenoGp2 = postmenopausal women without HRT; MenoGp3 = postmenopausal women on estrogen only HRT; MenoGp4 = postmenopausal women on estrogen/progestin HRT; Grip = handgrip strength; Sys = systolic blood pressure; Sbmd = bone mineral density of spine; Tbmc = total bone mineral content; Pbmc = per cent bone mineral content; PBF = per cent body fat; T = testosterone level; IGF1 = insulin growth factor-1; BP3 = insulin growth factor binding protein-3; HDL = high density lipoprotein cholesterol; AbO = number/percent of women with abdominal obesity; SOsteopn = number/per cent of women with osteopenia of the spine.

Physical strength as measured by handgrip strength showed decline with age, reaching significant levels by the 6th decade and continued into the 7th decade. Expiratory capacity, a measure of the lung capacity showed significant decline only in the 7th decade.

The study also showed that sexual functions declined with age. Coital frequency showed significant decline only after the 5th decade, while the number of women who were engaged in self-masturbation decline in the 6th decade when compared to women in the 4th decade.

On the other hand, the number of women who wanted to have more sex declined significantly in women in the 5th, 6th and 7th decade when compared to women in the 4th decade. Likewise, more women experienced painful sex in the 6th and 7th decade. These data support the notion that sexual functions in women decreased with age. In Singapore, decrease in sexual function may be attributed to the highly stressful lifestyle – and the present author coined the term "lifestyle impotency" to denote this form of impotency for the Singapore's population [25].

Older women tended to sleep less when compared to younger women. Interestingly, contrary to other parameters evaluated, the sense of well-being increased and the number of unwell symptoms declined with age. In the Singapore's context, this could possibly due to the much more stressful lifestyle that is common among younger than in older women. Singapore is known to be a highly competitive society and younger women face the challenges of establishing their career and raising young families. In contrast, older women have more established career and mature family or have already retired, hence have a less stressful lifestyle and less subjected to being unwell.

Decline in bioavailable testosterone with age was not dramatic. The decline of insulin growth factor-1 was quite dramatic, decreasing progressively from the 4th decade to 30.8% less by the 7th decade. Concurrent to the decline in IGF-1 was an increase in the insulin growth factor binding protein 3. However, the increase was noted in 6th decade. The biological significance of these changes is not known.

Despite methodological difficulties in the research in normal brain aging, cognitive change in normal aging has been well documented [26]. The present study showed that the perceptual capacity and processing speed significantly declined in the 6th and 7th decade in agreement with earlier studies [27]. On the other hand, short-term memory declined progressively from the 6th to the 7th decade, a finding in line with other forms of memory declines [28].

The present study showed that aging has ill effects on most major health compartments. Most ill effects began in the 6th decade with a few occurring in the 5th decade. Hence any modality to prevent or slow down the ill effects should be instituted earlier, preferably in the second or third decade of life. The author, in a paper on the same cohort of women and published earlier showed that having a regular physical exercise/sport as a lifestyle habit can effectively mitigate, to some extent, the ill effects of aging [29]. In this study, it was clearly shown that different physical exercise as a lifestyle habit and when engaged in sufficiently high intensity can impart beneficial effects on cognitive, bone, cardiovascular, metabolic, sexual, and general health, and muscular and hormonal functions, and thus could reverse or tamper some of the ill effects of the aging process [29]. In the light of very high incidence of osteopenia of the hip, even in women in the 4th decade, it is important to promote engagement in regular exercise in women early in life. High intensity of physical exercise was also associated with higher amount of total lean mass and lean mass in the legs of women. Physical exercise would be beneficial to mitigate the risk of sarcopenia in women as they age [30].

Comparisons between postmenopausal women and premenopausal women in the same age group have provided a means of knowing whether the onset of menopause has additional effects on the age-related impact on the various health compartments. Interestingly, only bone health was worst in postmenopausal women who were not on any HRT when compared to premenopausal women within the same age group. Spinal bmd and bone mineral content were significantly lower, and the incidence of spine osteopenia was significantly higher in this group when compared to premenopausal women within the same age group. On the other hand, the bone health of postmenopausal women either on estrogen only or the combination of estrogen/progestin was similar to that of the premenopausal women within the same age group suggesting that HRT was able to reverse the deterioration of bone health caused by the onset of the menopause. The results showed, as has been widely reported, that bone health in women deteriorate with increasing age and the loss of estrogen with the onset of menopause [30, 31]. The losses of bone mass and increase in incidence of osteopenia seen in postmenopausal women without HRT were partially attenuated in women on either estrogen alone or estrogen/progestin HRT. This observation gives further credence to the importance of estrogen in bone health in women. Although hormone therapy is beneficial for the bone health of postmenopausal women, in the light of the Women's Health Initiative, WHI, hormone therapy was not recommended even to women with high fracture risk [4]. However, with the lapse of time, there are more recent studies that support the introduction of newer forms of hormone therapy for postmenopausal women to mitigate the high fracture risk due to osteoporosis [24, 32]. As mentioned earlier, a non-drug treatment modality is encouraging postmenopausal women to take part in physical exercise of sufficient intensity as a lifestyle habit.

Handgrip strength was significantly lower and total body fat was higher in postmenopausal women than those due to age alone. If left unchecked, the long-term prognosis may be the increased risk of metabolic syndrome and sarcopenic frailty. In addition the decline in handgrip strength and the increase in total body fat in postmenopausal women without HRT were reversed in postmenopausal women on HRT, and thus would reduce the risks associated with reduced strength and increase fat.

While the positive impact of HRT for bone health, strength and fat was evident, the different types of HRT have varying effects on other health parameters. Postmenopausal women on the estrogen/progestin HRT had significantly higher systolic blood pressure and lower levels of HDL, implying perhaps, that the combination of estrogen/progestin HRT may be associated with increased risk of cardiovascular diseases. The clinical significance of higher levels of testosterone and lower levels of BP3 in postmenopausal women on the combination HRT is unclear. Postmenopausal women on the estrogen alone HRT, on the other hand, had significantly higher incidence of abdominal obesity with its attendant increase risk of metabolic syndrome as reported earlier [19]. Another negative effect of estrogen only HRT was the significant reduction of IGF1 and BP3, the clinical significance is unclear from the present study.

In summary, aging in women has significant and deleterious effects on most of the major health compartments including the bone, metabolic, cardiovascular, cognitive, and muscular compartments, strength, physical tone and general well-being, with most of the

ill effects occurring in the 5th and 6th decade of life. The onset of menopause is associated with further deterioration of bone health, strength, and body fat. Hormone replacement therapy, whether it was estrogen only or the combination of estrogen/progestin, was able to reverse or attenuate the ill effects due to the onset of the menopause. On the other hand, estrogen only and the combination of estrogen/progestin therapy may increase the risk of metabolic syndrome and cardiovascular disease. The one non-drug modality that can attenuate or slow down the effect of aging is the engagement of regular physical exercise at a sufficiently high intensity as a lifestyle habit.

Authors' contributions

This study was designed, conducted and data collected while Professor Victor H H Goh was at the Department of Obstetrics and Gynaecology, National University of Singapore. Professor Goh was involved in the interpretation, drafting of the manuscript and critical revision of the paper for submission.

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Declaration of interest

The author reports no declaration of interest.

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