THE ROLE OF REPRODUCTIVE HEALTH IN MUSCULOSKELETAL AGING: A LIFE-COURSE APPROACH

by

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ABSTRACT

In the United States, older individuals (≥65 years), account for about 34% of healthcare expenditures with women accounting for 22% greater expenditure than men. Musculoskeletal disease and disability alone costs nearly $950 billion/year. Over 40% of older women (≥70 years) live with disability and/or functional limitations. These gender differences suggest the role of gender specific factors. In addition to greater lifetime risk of chronic diseases like arthritis, depression and osteoporosis, women are more likely to accumulate greater allostatic load from physiological insults and dysregulation across the reproductive life course. Together, these factors could increase the risk of functional limitations and disability in older women. However, our current understanding of the effect of women's reproductive health (menarche, parity, breastfeeding, menopause, hysterectomy and oophorectomy) on age related structural and functional changes is limited. Understanding these associations could have significant public health implications on disability prevention in later life.

Through this dissertation, we assessed the associations of reproductive factors across the life course, with physical function decline, risk of hip osteoarthritis (OA) and changes in hip geometry in later life. We found that women with early life reproductive factors like later age at menarche, greater parity and breastfeeding were more likely to maintain their grip strength in

later life. These findings are likely due to lifestyle factors associated with child rearing. In contrast, same cohort of women demonstrated associations between greater parity and breastfeeding with lower risk of radiographic hip OA. These findings maybe attributable to pregnancy related changes at the hip joint. In a cohort of midlife women, early life reproductive factors including older age at first birth, and breastfeeding with associated with unfavorable levels and accelerated change in hip geometry measure during the menopausal transition (MT). Changes in Follicle Stimulating Hormone (FSH) and Sex Hormone Binding Globulin (SHBG) were associated with poorer hip geometry levels and accelerated its change during the MT. Put together, the 3 studies demonstrated associations between early life reproductive health and musculoskeletal structure and function in later life. Future understanding of underlying mechanisms could help design targeted interventions to prevent disability in later life.

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PREFACE

I would like to thank Dr. Jane Cauley and the committee for their trust in me and immense support and guidance. I would also like to thank my family for the unchallenged love and immense support during my doctoral journey.

1.0 SPECIFIC AIMS

In the United States, individuals 65 and older, account for about 34% of healthcare expenditures with nearly 6% projected average growth in Medicare utilization for 2018-19. On average, women spent 22% more than men[1]. Musculoskeletal disease and disability alone cost nearly $950 billion/year[2]. More than 40% of women aged 70 or older, suffer from some form of disability and poor physical function[3]. Women live longer with disability, thus a compromised quality of life[4]. The gender gap in disability suggests the role of gender specific factors. Women are subject to greater risk of chronic diseases like arthritis, osteoporosis, and depression[5]. In addition, greater predisposition to disability and functional decline may be related to socio-behavioral factors like education, smoking, and physical activity[6,7]. However, these factors only account for part of the gender gap in disability. Interestingly, our current understanding of the effect of women's reproductive life [from menarche to menopause] on age related changes in the bone and muscle is limited. With the rapidly aging population[8] and the increasing disability rates, it is of utmost importance to improve the quality of life ensure successful aging of older women.

The ***overall objective*** is to improve our understanding of the relationships of reproductive and hormonal factors with changes in musculoskeletal structure and functioning in later life. Our ***central hypothesis*** is that reproductive history and hormonal changes in women affects musculoskeletal health with increasing age. Our hypothesis is based on results from studies exploring the associations between reproductive factors and other age-related diseases. A large

Norwegian study showed that both early and later age at menarche were associated with an increased risk of mortality[9]. Similarly, extremes of parity were associated with an increased risk of cardiovascular disease[10] and mortality[11]. Fewer years of menstruation was associated with increased risk of fractures[12]. While the effects of reproductive health on some chronic diseases and mortality are well known, the relationship between reproductive health and musculoskeletal aging remains to be understood. The proposed research attempts to enhance our understanding of the role of reproductive health on changes in muscle function and bone geometry with age. The rationale for the proposed research is to identify modifiable and non-modifiable reproductive factors that impact the age-related bone and muscle changes. This is important to designing appropriate interventions and prevention of functional limitation and disability in women. We believe our findings shall help to identify "poor" reproductive factors [characterized by early age at menarche, nulliparity, non-breastfeeding, oral contraceptive use, early age at menopause, hysterectomy or oophorectomy and shorter length of reproductive life] that prevent functional decline and disability later in life.

To test our central hypothesis and achieve our overall objective, our specific aims were:

Aim 1: Evaluate association between reproductive factors and physical function in later life

We hypothesize that poor reproductive factors will be associated with lower physical function levels and faster decline in physical function in older women.

Aim 2: Determine the association between reproductive factors and risk of hip osteoarthritis

We hypothesize that poor reproductive factors will be associated with greater odds of prevalent and incident hip osteoarthritis in older women.

Aim 3: Assess the association between reproductive factors and hip geometry in midlife women

We hypothesize that at risk reproductive health and sex steroid hormone levels will be associated with worse hip geometry in later life and greater changes in hip geometry across the menopausal transition.

As an *outcome* of this dissertation, we expect to identify the specific reproductive factors [Figure 1] and quantify independently, their effect on musculoskeletal aging characterized by physical function decline (Aim 1), risk of osteoarthritis (Aim 2) and change in hip geometry (Aim 3). The dissertation uses data from the Study of Osteoporotic Fractures (SOF) cohort and Study of Women's health Across the Nation(SWAN). Through this dissertation, we hope to improve current understanding of the overall aging process by identifying the reproductive factors contributing to successful aging.

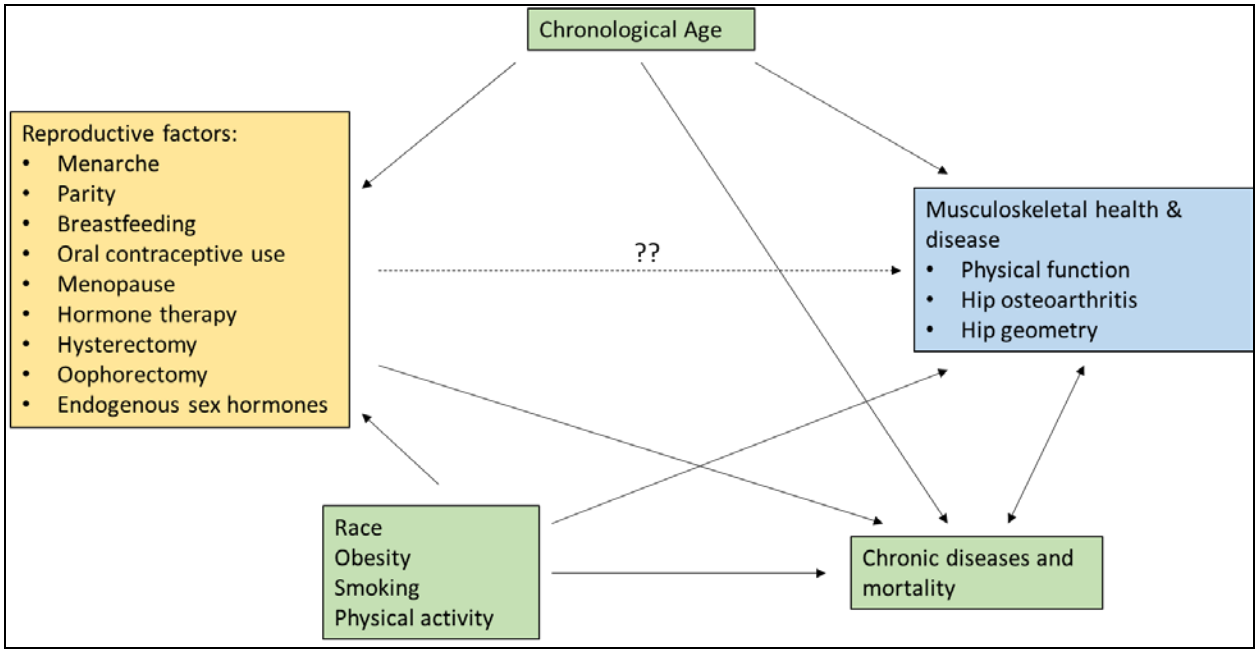

Figure 1-1: Conceptual model for the study

2.0 BACKGROUND AND SIGNIFICANCE

2.1 AGING POPULATION OF WOMEN

Aging has been defined as the time dependent decline in function[13]. In 2012, 8% (562 million) of the world's population were aged 65 or older[14]. In United States, the population of individuals aged 65 and over was estimated to be 46 million in 2014. That is, 1 in 7 individuals were 65 or older, forming 14.5% of the population. With the aging of the baby boomers, the older (≥ 65 years) population is rising and is projected to double to over 98 million by the year 2060 (accounting for 25% of the population)[15]. With the increase in life expectancy, the gender gap has widened. As of 2014, average life expectancy at age 65 was 20.5 years for females and 18 years for males[15]. This is reflected in the sex ratio of 127 women for every 100 men 65 or older. At age 85 or older, this ratio increases to 192 women per 100 men.

However, the Center for Disease Control (CDC) estimates that nearly 22% of the elderly individuals (≥65 years) have fair to poor health, and about 7% of them require help with personal care[16]. With the increasing economical and healthcare burden of this population, it becomes important to understand the many factors contributing to successful aging. While prior research and healthcare had been largely focused on increasing the lifespan of an individual, in the recent years the view has become more robust, with focus on preventing decline in health[17], maintenance of function and social well-being and therefore, "successful aging".

2.2 SUCCESSFUL AGING

Many definitions for “successful aging” have been put-forth. However, the components of what constitutes “successful aging” is yet to be completely understood. In 1961, Havighurst defined “successful aging” as not only increasing the life span but also the satisfaction from life[18]. Rowe and Kahn revised this to distinguish between “successful aging” and “normal aging”, defining “successful aging” and high social, physical and cognitive functioning as well as being free from disability[19]. They further explained “successful aging” to consist of 3 components - low probability of disability and disease, high physical and cognitive function and an active engagement with life [figure 2][20]. While this model is largely accepted, being disease free in older age is not realistic[18]. Therefore, this definition has been modified to include those with minimal disease and disability, i.e., individuals with high levels of physical function[21-23].

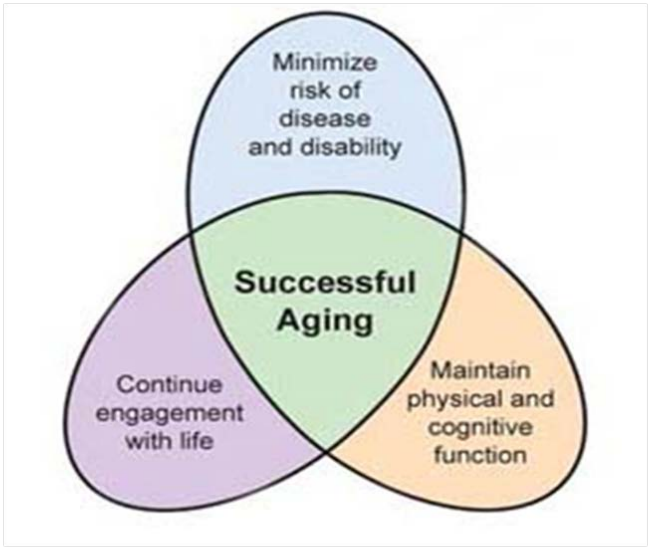

Figure 2 : Successful aging model (Rowe and Kahn)[19]

Figure 2-1: Successful aging model (Rowe and Kahn)

Despite the many definitions, the concept of "successful aging" aims to maximize the functional status of an individual, making them more self-reliant, and resilient. "Successful aging" may be achieved through a subtle balance of lowering the risk factors to adverse events and increasing resilience in its presence[19]. With an increasing population of older adults in the community, it has become increasingly important to understand the various factors which could promote "successful aging".

2.3 DISABILITY IN WOMEN

One of the important components of successful aging is living free of disability. Functional limitations and disability produce a highly vulnerable population. In 2008, the US Department of commerce reported that approximately 19% of the population was living with some form of disability with 12% reporting severe disability[24]. The health expenditure associated with disability alone was estimated to be nearly $398 billion[25]. These levels are increasing with the aging population[26]. Women (24.4%) have higher prevalence of disability compared to men (19.8%)[27]. Studies have shown that 10-15% of women may be disabled as early as midlife (45 years)[28]. Higher disability levels are associated with lower health related quality of life[29]. Individuals with disability are predisposed to greater risk of obesity[30], physical inactivity[31] and smoking[32], all of which are associated with poor health and chronic diseases. Disability also increases the risk of death from heart diseases, cancers, stroke and suicides[33]. Conversely, chronic diseases also increase the risk of disability. However, at any level of comorbidity, women have greater disability[34]. Disability is also associated with socio-economic disparities. The prevalence of disability was greatest in American Indians (31%) and lowest in the Asian

(10.1%) population[35]. Thus, disability contributes greatly to the social, economic and healthcare burdens of the country. Women have greater life expectancy than men but spend greater proportion of life in disability[36]. With the increasing population of older women, there is an important need to understand and prevent the risk factors for disability. Although reproductive life is a major part of women's life, very little is understood about its influence on later life health and the aging process. Through this dissertation, we expect to understand the effect of reproductive health on musculoskeletal aging in women.

The Nagi model[37] (1976), with modifications from Verbrugge & Jette[38] (1994) still serves as the most well accepted models of the disability process. This model has been accepted by sociology and medical disciplines[39], and preferred by the Institute of Medicine[40]. The model suggests an accumulation of pathology resulting in impairment and limitations. These processes culminate in an individual's ability to perform socially expected activities[39], like adequate physical functioning. Therefore, understanding the pathological processes and risk factors leading to functional impairment, limitations or disability, shall help design appropriate disability prevention strategies. Through the course of this dissertation we aim to understand the risk of poor reproductive health on 3 musculoskeletal factors associated with current or future disability – decline in physical function, prevalence and incidence of hip osteoarthritis and change in hip geometry. Using a life course approach, we shall be able to assess and quantify individually the effect of these reproductive factors on musculoskeletal aging.

3.0 A LIFE COURSE APPROACH REPRODUCTIVE HEALTH AND DISEASE

The concept of health and aging is multi-dimensional and dynamic[41]. In 1965, Dubos suggested that an important predictor of health is the ability of an organism to adapt to the immediate environment and its demands[42]. These demands change over the course of life, producing varied changes in the biology and physiology of an individual. In addition, these experiences prepare an individual for impending environmental needs. Therefore, the assessment of health and aging at a given point in life may not adequately reflect the true relationship between the two[43]. Many studies have demonstrated that the influences during early developmental periods i.e., intrauterine and post-natal periods bear a strong influence on the age-related declines in later life[44] for the mother and the child. A life-course approach is thus required. The life-course approach aims at understanding the associations between the social and biological exposures during fetal life, childhood and adult-life to the age-related changes in health and disease in later life[45].

Martin and Finch, described 6 stages in the life of an individual – developing (from fetal life to childhood), maturing, reproducing, sageing (intermediate between mature, reproducing adult to senescing adult stage, constantly adapting to the changing demands of the environment), senescing (phase of cognitive and functional decline) and dying[44]. The demands and exposures of each of these stages vary greatly, resulting in changes aimed at adaptation. Interestingly, each of these stages are inter-related and bear a significance in the overall well-being in later life.

Thus, understanding the components and effects of each of these stages on aging is important to the development of interventions for successful aging.

The basis for life course epidemiology was set by David Barker in 1992[45]. Barker proposed the Fetal Origins of Disease hypothesis - postulating that the diseases in adult life are outcomes of in-utero insults to the fetus, particularly nutrition[45]. As an extension, in 2002, the developmental origins of adult health and disease were proposed. Gluckman et al, hypothesized that early life events and environments, influenced the susceptibility to chronic diseases in later life[46]. The life course approach aims to understand the relationship between growth, plateau and degeneration phases of life[47].

3.1.1 Epidemiology of reproductive events

While the changes in the reproductive system begin with the fetal life[48], the period of active reproductive life does not begin till adolescence. The first menstrual period or menarche, marks the beginning of this reproductive period, which ends with the cessation of menstruation or menopause. The reproductive health of a woman is closely related to the overall physical and mental health. It is further characterized by events such as menstrual regularity, pregnancy, child-birth, lactation, successive pregnancies and other gynecological conditions, that have been known to yield valuable information regarding many subclinical diseases[49]. Besides genetic influences[50], many social, behavioral and lifestyle factors influence the timing of these events.

Across the world, the average age at menarche is between 12 - 13.5 years[48,51]. An early age at menarche is associated with low birth weight and faster growth during infancy[52,53], paternal absence[54], childhood sexual or physical abuse[55], and childhood obesity[56]. Compared to breast fed children, girls who received formula feeds had an earlier age at menarche[57]. Study

from NHANES (from 1988-1994 and 1999-2002) reported a decline in age at menarche in both Non-Hispanic Whites (12.8 to 12.52 years) and Non-Hispanic Blacks (12.9 to 12.08). This decline was associated with higher BMI across ethnicities[58].

While the mean age at menopause is 51 years, it can range from 40-60 years[59]. Low socioeconomic status is associated with early age at menopause[60]. Menarche $\leq$ 11 years[60], nulliparity[60], and smoke exposure (prenatal or premenopausal)[61], are associated with early menopause. It has been suggested that greater body fat may act as a source of estrone, thus delaying the age at menopause[62]. However, studies testing this hypothesis have shown inconsistent results. Some studies reporting later menopause in heavier women[62,63], others have shown no association[64]. Interestingly, a longitudinal evaluation of BMI over the life course, showed no influence on age at menopause[65]. The Black women's health study reported that BMI was inversely related to age at menopause in African American women[66,67]. However, a multi-ethnic comparison showed no difference in age at natural menopause between Caucasian and African American women[64]. Similar inconsistencies have been noted with diabetes status as well. While some studies have reported Type 1[68] and Type 2 diabetes[69] as independent predictors of early menopause, others have shown no association[64,70]. In addition to age at menarche and parity, younger age at first birth and older age at last birth, and longer duration of breastfeeding have been associated with later age at menopause[71]. Reports from the United States[72] (from 49.1 years in 1915 to 50.5 years in 1969), Finland[73], Sweden[74], and across Europe[75] have reported an increase in the age at menopause over the years. However, establishing a trend in age at menopause is limited by inconsistent definitions of menopause ranging from self-report to final menstrual period to biomarkers and 12 months of amenorrhea[76]. Thus, it is evident that the timing of these reproductive events serves as a marker of underlying social, behavioral and

overall well-being of an individual. While many of the reproductive factors are genetically determined, some factors like use of oral contraceptives, hormone therapy and breast feeding may be modifiable.

3.1.2 Hormonal regulation of reproductive system

Reproductive life in a woman is regulated by age and event specific hormonal changes regulated by the hypothalamo-pituitary ovarian axis [Figure. 4].

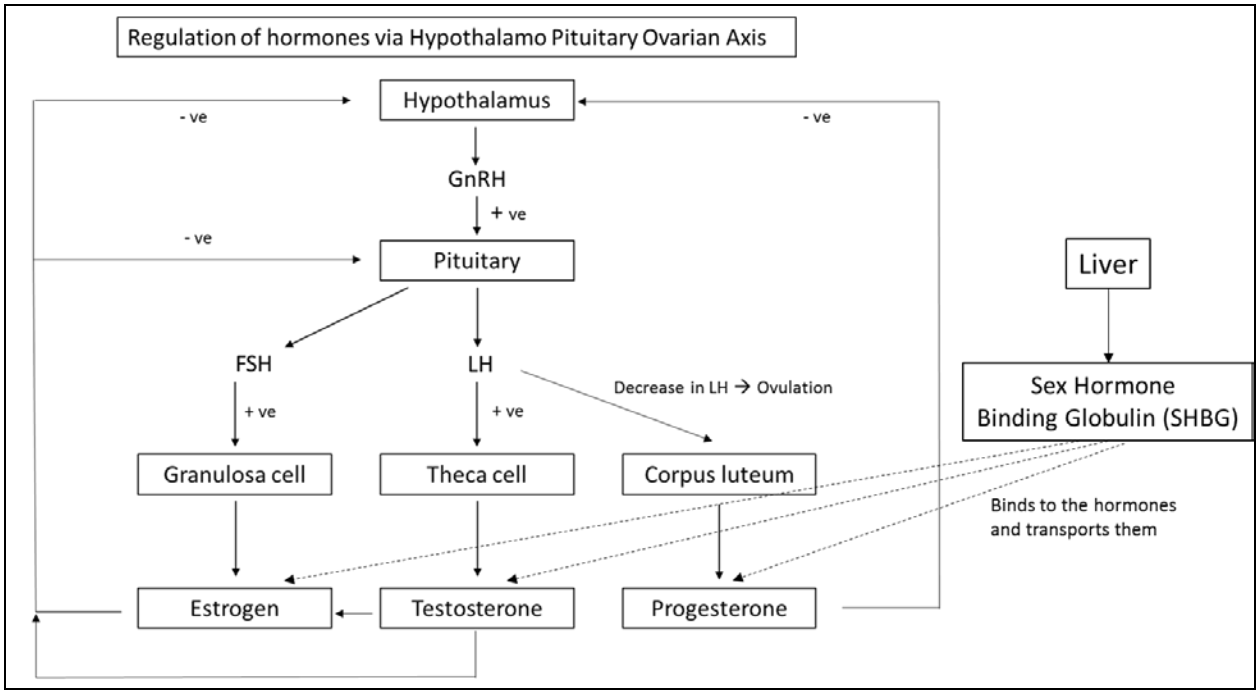

Figure 3-1: Regulation of hormones via Hypothalamo-Pituitary Ovarian (HPA) axis

Gonadotropin Releasing Hormone (GnRH), secreted from the hypothalamus, stimulates the secretion of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH). Both LH and FSH are dynamically regulated across the menstrual cycle[77]. FSH stimulates ovarian follicles and increases release of estradiol from the ovaries[78]. LH acts on the theca cells to aid in the

synthesis of androgens from cholesterol. In addition, LH is essential to ovulation. and corpus luteum formation. After ovulation, the corpus luteum (temporary endocrine organ from the luteinized granulosa cells], supported by LH, secretes progesterone to prepare endometrium for implantation of the ovum[79]. In the absence of fertilization, the corpus luteum function decreases leading to fall of progesterone levels and menstruation. Simultaneously, the estradiol levels rise and fall twice during the menstrual cycle. The first rise occurs in the mid-follicular level decreasing after ovulation subsequently rising again in the mid-luteal phase (parallel to rise in progesterone). Both estradiol and progesterone, with the hormone inhibin, regulate secretion and release of GnRH. Through negative feedback mechanism, estradiol lowers GnRH secretion while progesterone, along with estradiol reduces the frequency of GnRH pulses[77].

Menarche – GnRH secretion is temporarily active in early fetal life but remains dormant till the onset of puberty[48]. GnRH release and subsequent activation of the HPA axis play a crucial role in gonadal development and function. Serum leptin (a hormone produced from the fat tissue) levels may play a modulatory role on GnRH, to initiate puberty[48].

Pregnancy and lactation: Pregnancy and lactation are periods of suppressed ovulation[78]. Pregnancy is maintained by elevated levels of progesterone. First from the corpus luteum and subsequently from the placenta[78,79]. Concurrently, estradiol is produced from the placenta and fetal adrenal glands[80,81]. The levels of these hormones continue to rise throughout pregnancy[82] with estradiol levels decline rapidly following delivery[82]. The decline in estrogen and progesterone levels at delivery allows for action of prolactin on breast tissue, resulting in milk production[83]. Despite high FSH levels, inadequate LH stimulation during lactation leads to low levels of estrogen and subsequent amenorrhea[84]. During pregnancy, the body undergoes dramatic changes to accommodate for the increased metabolic demand[85]. This is characterized by increase

in visceral adipose tissue, insulin resistance and circulating lipids[86]. It is hypothesized that lactation helps mobilize this fat and thus re-setting the maternal metabolism and lowering risk of metabolic diseases[87].

Menopause: Although most of the ovarian follicles are lost in fetal life[88], there is progressive loss during reproductive life[89]. This loss is exponentiated during menopausal transition[90]. Inhibin B is an early marker of ovarian aging. It regulates the steep increase in FSH compared to LH[78]. The increase in the levels of FSH is hallmark of the transition[90]. FSH levels increase drastically leading up to the menopausal transition and thereafter plateau[91]. Menopausal transition is characterized by onset of irregular and unpredictable cycles. Early menopausal transition may be associated with elevated estradiol[92]. This elevation may reflect augmented folliculogenesis and shorter follicular phase during the early menopausal transition[89]. Rapid decline in estradiol levels were noted starting 2 years before the final menstrual period and stabilizing around 2 years after[91,93]. More recent studies have demonstrated that such a pattern is not consistent in all women. Studies in the same cohort of women has demonstrated distinct trajectories of hormone change in E2 and FSH[94]. The E2 trajectory groups showed 4 distinct patterns of slow decline, flat, rise and steep decline or rise and slow decline. While FSH increase was more consistent, women showed 3 distinct trajectory patterns of low, medium or high rise across the MT[94]. With menopause, the ovarian production of testosterone also decreases. However, the concurrent drop in Serum Hormone Binding Globulin(SHBG) – the carrier protein (synthesized in the liver) for both estradiol and testosterone, offsets this decrease[95]. The decline in SHBG complements the decline in estradiol and increase in insulin resistance[89]. The mechanism that relates lower SHBG to lower insulin resistance is not clearly understood. Although independent of BMI[96], higher liver fat could decrease SHBG production and impair

insulin sensitivity[97]. Decrease in SHBG and/or greater bioavailable T levels are associated with greater visceral fat[98]. However, adipose tissue could also facilitate activation of androstenedione[99] leading to hyperandrogenesis[98]. Excess androgen [testosterone to estradiol ratio] has been shown to be associated with increased risk of metabolic syndrome over time[100].

It is thus evident that the reproductive events are characterized by a subtle balance of the many hormones in the body. Thus, reproductive events and factors serve as underlying markers of health at a given time of life. It is plausible that reproductive events and sex hormones are early life marker for musculoskeletal health in later life. Complex hormonal, biomechanical, inflammatory and socio-behavioral factors may mediate the associations between reproductive events, sex hormones and musculoskeletal aging.

4.0 POTENTIAL MECHANISMS RELATING REPRODUCTIVE HEALTH TO MUSCULO-SKELETAL HEALTH

4.1 HORMONAL PATHWAY

4.1.1 Muscle and physical function

The timing and type of reproductive factors may produce different impact to adapt to the concurrent needs of the body functioning and environment[101]. Across reproductive health, the exposure to levels of hormones particularly estrogen, progesterone and testosterone vary. Studies have shown that these hormones may act independently[102-105] or along with other hormones[106] to affect physical functioning. A meta-analysis of 23 studies demonstrated that post-menopausal women receiving Hormone Therapy (HT) had nearly 5% greater muscle strength compared to women not receiving HT[107]. The authors indicated that HT improved the functioning of the muscle by improving the muscle quality[108]. These findings are supported by molecular studies in rats. Compared to rats with intact ovary, ovariectomized rats produced 20% lower specific force from the permeabilized fibers of the soleus muscles. Conversely, supplementation of estradiol to ovariectomized rodents restored muscle protein (myosin) function to control levels[109]. The authors hypothesized that the lack of sex-steroid hormones potentially resulted in a decrease in force generating protein crossbridges[109]. Together with the variation in hormones across life, it is

possible to hypothesize a cumulative role of hormone affecting muscle strength in later life. Pregnancy is associated with increased levels of both estrogen and progesterone. High levels of progesterone can alter the effect of estrogen in the body[110] by blocking estrogen receptors[111]. Therefore, the effect of higher cumulative exposure to estrogen with greater parity, may be altered through high levels of progesterone. In addition, breast feeding reduces the synthesis of estrogen[112] and progesterone[113] while increasing the levels of follicle stimulating hormone[111]. These changes in hormones could have lasting effects on muscle structure and function. The rapid decline in estrogen may have negative effects on muscle health[114]. Decrease in the estrogen levels during menopause may be associated with Vitamin D deficiency[115]. Vitamin D deficiency subsequently leads to muscle weakness[116]. Decrease in estrogen is also related to an increase in oxidative stress, and decrease in insulin sensitivity, growth hormone, Insulin like Growth Factor-1 (IGF-1), all of which have been related to low muscle mass in women[117]. Variation in hormones over time could thus lead to significant changes in muscle mass and strength. Accumulation of these insults and changes across the life course could result in disability and functional limitations in later life.

4.1.2 Joint and osteoarthritis

Both weight bearing and non-weight bearing joints in the body are affected by OA, suggesting the role of systemic factors[118]. In addition to its effect on muscle mass and function, estrogen could have direct impact on the joints[118]. This is supported by postmenopausal increased risk of OA[119] and presence of estrogen receptors in the joint tissue[120]. Both mice and rabbit models have shown an increased cartilage and bone turnover after completion of sexual maturation[121]. In rabbits' removal of ovaries was associated with increased osteoarthritic

damage, further supporting the role of female hormones in the structure and functioning of the musculoskeletal system[122]. Such a post-maturational increase in risk of OA was also noted in humans. Nearly 65% of women with knee OA had osteoarthritic symptoms starting from perimenopause to 5 years after menopause (natural or hysterectomy)[123]. Post-menopausal women with radiologically confirmed OA had low levels of estradiol and hydroxyestrone (a metabolite of estradiol)[124]. Together, it is possible that the changes in estradiol over the life course many bear significant impact on the joint tissue, manifesting as OA in later life.

4.1.3 Bone

The effect of hormones on bone metabolism is well established. Estrogen plays an important role in the development and remodeling of the bones[125]. Estrogen increases osteoblast cell numbers and promote bone formation. A decline in estrogen is associated with greater bone resorption with increased osteoclastic activity, thus increasing the risk of osteoporosis[126] and subsequent fractures. Bone loss begins around the 3rd decade of life[127], but is accelerated during the menopausal transition.

In the SWAN population, accelerated loss of BMD at the lumbar spine and femoral neck was noted between 1 year before FMP to 2 years after. The loss continued in the post-menopausal era, at a slower rate[128]. In the same population, lower E2 and greater FSH were associated with faster LS BMD loss across menopause. However, these associations varied by phase of MT[129]. In older women (≥ 65 years), E2 <5 pg/ml had 2.5 times greater risk of subsequent hip fracture, compared to women with detectable levels[130]. In the Women's Health Initiative (WHI), women with E2 ≥8 pg/ml had 50% lower risk of hip fractures[131]. In models with SHBG, T and E2 together, high SHBG was an independent risk factor while high

bioavailable T was protective. However, the association with E2 was no longer significant. In the WHI hormone trial, women on equine estrogen with or without progestin had 30% - 40% significantly lower fractures. Despite a slight attenuation in the risk reduction post-intervention, a significant hip fracture benefit persisted during the follow up[132]. Overall there exists strong support for the effect of sex hormones on skeletal health.

4.2 OBESITY

4.2.1 Muscle and physical function

In healthy individuals, muscle and bone strength are correlated with body weight. Gravity and inertia may increase the production of growth factors through stimulation of mechanoreceptors during movement[133]. Studies have demonstrated that obese individuals have low muscle strength and increased risk of disability[134]. With the slow but continuous increase in fat deposition in the muscle, the anti-gravity adaptations may be compromised. Additionally, with aging and lack of physical activity, the levels of lipo-protein lipase (LPL) is decreased. This could result in increase in intramuscular fat[135].

Reproductive factors are closely related to obesity and body composition. For example, early age at menarche (8-11 years) was associated with a 77% greater risk of obesity [OR(95% CI) = 1.77(1.30-2.41)][136]. Parity was shown to be associated with greater mean BMI [β(95% CI) = 0.34(0.29, 0.39)] and 72% higher obesity risk[137]. The menopausal transition is associated with weight gain and greater obesity risk[138]. Both animal and human studies have shown that early bilateral oophorectomy was associated with an increased body fat percentage[139]. Put together,

reproductive factors may affect physical functioning in later life through obesity. It is also important to note that the association between low physical functioning and obesity is bi-directional. It is thus difficult to differentiate the effect and the cause.

4.2.2 Joint and Osteoarthritis

Obesity is a major risk factor for the development and progression of OA[140]. A meta-analysis of 14 studies reported that for every 5-unit increase in BMI, the risk of hip OA increases by 11%[140]. Holliday et al, reported that life course BMI was associated with 46% greater risk of hip OA. In addition, overweight (BMI≥25kg/m^2) early in adult life increased the risk of OA, independent of age, gender, occupation, social class, smoking, physical activity and metabolic diseases[141]. The increase in the load on the joint, decreased muscle strength and other metabolic factors could contribute to an increased risk of OA[142]. Leptin levels (produced from the adipose tissue) parallel that of degenerative enzymes like metalloproteases and nitric oxide[143,144], which is harmful to the cartilage cells – chondrocytes. Leptin has shown differential effects on chrondrocytes between normal and overweight individuals with OA. Lipid (hypercholesterolemia) and metabolic (hypertension, metabolic syndrome, low insulin sensitivity) factors could also contribute to initiation and progression of OA[145].

Reproductive events may be associated with an increase in body weight and obesity[136-139]. Increase in body weight over the life course could contribute to an increased risk of OA in later life (i.e., mediation effect).

4.2.3 Bone

Contrary to the effect on joint and muscle, greater weight is protective of bone loss with age[146]. Increased mechanical loading stimulates differentiation of osteoblasts to increase bone formation[147]. In a meta-analysis (mean age = 63 years), higher BMI was associated with lower Bone Mineral Density (BMD) and increased risk of fracture[148]. Since adipocytes and osteoblasts are derived from the same stem cell[149], obesity may increase adipogenesis and decrease in bone formation[150]. Adipokines like leptin and adiponectin from fat tissue may play an important role in the association between obesity and bone health. In mouse models, greater leptin levels in obese individuals also may be detrimental to bone health[151]. In humans, some studies have shown an inverse relationship between adiponectin and BMD[152]. However, after accounting for adiposity, higher adiponectin and not leptin were associated with greater BMD loss[153] and fracture risk[154]. Reproductive factors influence body composition and obesity in later life[136-139]. Thus, it is plausible that the association between reproductive factors and bone health is mediated by obesity.

4.3 INFLAMMATION

4.3.1 Muscle and Physical function

Greater levels of inflammatory markers like Insulin like Growth Factor -1 (IGF-1), Interleukin 6 (IL-6), cystatin-C, and adiponectin have been associated with functional decline in older women, independent of age, race and education[155]. These factors have also been associated with

increased risk of disability and mortality in older women[156]. The association between inflammation and functional limitations maybe related to increased protein breakdown in the muscle[157] and decrease in protein chain synthesis[158]. This could result in muscle atrophy, and lower muscle strength[159].

Reproductive health has been linked to inflammation[160-164]. Low ovarian function and low estrogen levels were associated with greater inflammation[160]. In a small study (n=25) of young Polish women, age at menarche and estradiol were strongly associated with C-Reactive Protein (CRP), a non-specific inflammatory marker[160]. An early age at menarche was also associated with a greater cumulative allostatic load over the course of life[161]. Multiparity maybe a precursor to inflammation and obesity[162]. Breastfeeding has anti-inflammatory benefits in both mother and child[163]. With the menopausal transition, there is an increase in the levels of pro-inflammatory cytokines like interleukins and Tumor Necrosis Factor-α (TNF-α)[164], further supporting the protective role of estrogen. Put together, these suggests a possible inflammatory pathway between reproductive factors and physical function decline in later life.

4.3.2 Joint and Osteoarthritis

Like physical function, an inflammatory pathway to development of OA has been suggested. In a subset of patients with OA, the presence of chronic low-grade inflammation serves as a precursor for chronic joint disease[165]. Inflammation of the synovium precedes structural changes. In the presence of mechanical stress, proinflammatory markers may be produced by the chondrocytes, synovium or by the surrounding tissues. Increase in the inflammatory markers and cartilage degrading proteinases could induce death of

chondrocytes[166]. Together with the evidence of reproductive health on inflammation[160-164], it is plausible that the association between reproductive health and OA is mediated by inflammation.

4.3.3 Bone

Skeletal and immune systems are closely related due to shared microenvironment and lineages[167]. IL-6 promotes osteoclast activation and differentiation[168]. TNF-α has been linked to increased bone resorption and osteopenia[169]. In addition, activation of NO synthesis pathway by cytokines, stimulates osteoblast apoptosis[170]. In addition to the direct protective effect of estrogen and androgens on the bone, sex hormones could also down regulate IL-6 expression[171]. Decline in ovarian functioning is also associated with an increase in pro-inflammatory and pro-osteoclastic cytokines like IL-6, TNF-α and IL-1[172]. Together with the associations between reproductive factors and inflammation[160-164], inflammation could mediate the association between reproductive factors and poor bone health.

5.0 PHYSICAL FUNCTION AND REPRODUCTIVE HEALTH

Compared to men, women have poorer self-reported health[173,174] and perform more poorly on physical performance tests than men[175,176]. Both men and women experience decline in physical function over time with accelerated loss with increasing age. Oksuzyan et al, reported that while men started with greater grip strength, they experienced a linear decline with age as opposed to a non-linear decline (accelerated) in women[177]. Forrest et al, reported that women lost about 2.4% grip strength annually[178]. Studies have demonstrated a potential hormonal pathway leading to accelerated decline in physical function in the post-menopausal era. Samson et al, reported that women showed accelerated loss of hand grip strength and knee extensor strength after 55 years[179]. Phillips et al, showed that women in the peri- or post-menopausal state were more likely to experience muscle weakness, compared to pre-menopausal women or men[180]. These differences suggest the role of gender specific factors. Both biological and social factors have been suggested to explain this difference. Over the life course, women undergo various physiological changes to adapt to increasing demands of life. These repeated physiological insults could accumulate together and manifest in later life[181]. Women are also at a greater risk for diseases like depression, arthritis and osteoporosis, which could limit physical functioning[5]. In addition, socio-behavioral factors like education, smoking, physical activity could contribute to the gender difference in functional decline and disability[182]. However, the gap persists even after accounting for all these factors.

Few studies have assessed the effect of reproductive health on functional decline in women. The International Mobility in Aging study (aged 65-74 years) reported that early age at first birth (≤ 18 years) was associated with 1.75 odds of poorer physical performance (from the Short Physical Performance Battery) compared to older mothers. This association was independent of age, education, childhood economic adversities and parity[183]. Similar results were reported in midlife Brazilian women (N=473) where women with age at first birth ≤ 18 years took 0.5s longer to complete the chair stand test compared to older mothers[184]. This association was independent of age, physical activity, education, menopausal status and hysterectomy. No association was noted with grip strength and gait speed. Interestingly, Pirkle et al, did not account for the effect of BMI in their study, citing a potential mediatory role of BMI in the association between parity and physical function. Despite the potential mediatory role of BMI and its change over time, concurrent body weight could significantly influence physical function. On the other hand, Camara et al, reported a significant mediation effect of BMI for the associations of physical function (chair stand, grip strength and gait speed) with parity and age at first birth. Additionally, it is important to note that these results were reported from low education and low-income countries. Both factors have been independently associated with poor physical function[185,186].

In a study of older Mexican women (≥ 65 years), women with 6 or more pregnancies (irrespective of the pregnancy outcomes) performed poorer on the chair rise and walk time tests, compared to women with 4 or fewer pregnancies. This association was independent of age, nativity, education, severity of incontinency, hysterectomy, and chronic diseases like diabetes, arthritis, osteoporosis, stroke and heart failure[187]. The authors alluded to a potential interplay between socioeconomic and biological risk factors that put Mexican Americans at an increased

risk of poor physical function in later life. The incomplete uterine involution and cumulative stress to the musculature of the pelvic floor could result in subclinical neural damage. With age related functional decline, these limitations may become more apparent. Interestingly, like prior studies, Aiken et al, failed to account for the effect of body weight on the association between pregnancy and physical function in later life. While it could be argued that the change in BMI over time, could be in the causal pathway of such an association, it is important to account for the effect of current body weight on physical function.

Tseng et al, reported that, compared to premenopausal women, women with natural or surgical menopause were at a 3 folds' greater risk of substantial functional limitations (defined as score of <50 on physical function subscale of Short Form -36 questionnaire), independent of age, ethnicity, education, BMI, smoking, diabetes, hypertension, arthritis, depression, and hormone use[188]. This was attributed to a cascade of events (like the Nagi model), including changes in the body composition and loss of bone mass which eventually resulted in functional limitation and disability. An NHANES (National Health and Nutrition Examination Survey) of older women (≥ 60 years) reported that age and type of menopause significantly affected physical functioning in later life. Women with surgical menopause had 4.4% slower chair rise compared to women with natural menopause. Women with later age at menopause (≥ 55 years) had faster walk speed compared to early age at menopause (<45 years)[189]. Sowers et al, reported similar associations between surgical menopause and low physical functioning[190]. Interestingly, the British Birth Cohort reported that women with hysterectomy before 40 had significantly lower grip strength (5.21 kg lower) compared to hysterectomy after 50 years[191]. However, the association between other reproductive events/factors and level and change in physical function in older women is not

clearly understood. Most of these studies were limited by their cross-sectional design and relatively small sample sizes.

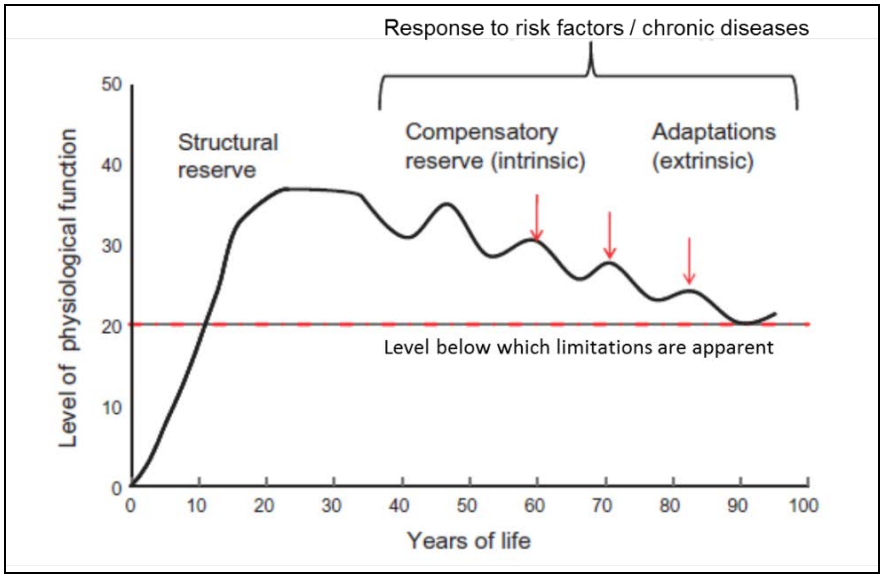

Figure 5-1: Influence of structural and compensatory reserve on life course trajectory

It was previously believed that over the life course, the functional ability of an individual changed over 3 phases – growth, plateau (structural reserve) and then decline[42]. However, it is now believed that there exists an interaction between chronic diseases/risk factors and these phases. For example, following exposure to a risk factor or illness, the functioning of a system would depend not only on the structural reserve innate to a person, but also on their ability to recover from it. This ability has been termed as compensatory reserve[48]. The compensatory reserve changes with age and thus altering the decline in function over time [Figure 3]. In addition, these compensatory/adaptive responses may bear an influence on functioning in later life. To the best of our knowledge, no studies have assessed the association between reproductive factors and changes in physical function over time in older women. Thus, we aim to assess these associations cross-sectionally and over time in older women. We hypothesize that reproductive

factors and timing of reproductive events shall influence the level of physical functioning in later life as well as rate of change of physical function over time.

6.0 REPRODUCTIVE HEALTH AND OSTEOARTHRITIS

Osteoarthritis (OA) is the most common joint disorder accounting for about 3.1 million hospitalizations[192] and 21.7 million ambulatory physician visits in the country[193]. In 2003, 9.6% men and 18% of women over 60 years had symptomatic OA[194] across the world. In the United States, 33.6% of those 65 or older suffered from OA[195], with nearly 80% reporting functional limitations[196]. Women have 45% greater risk of incident knee and 36% greater risk of hip OA[197] compared to men.

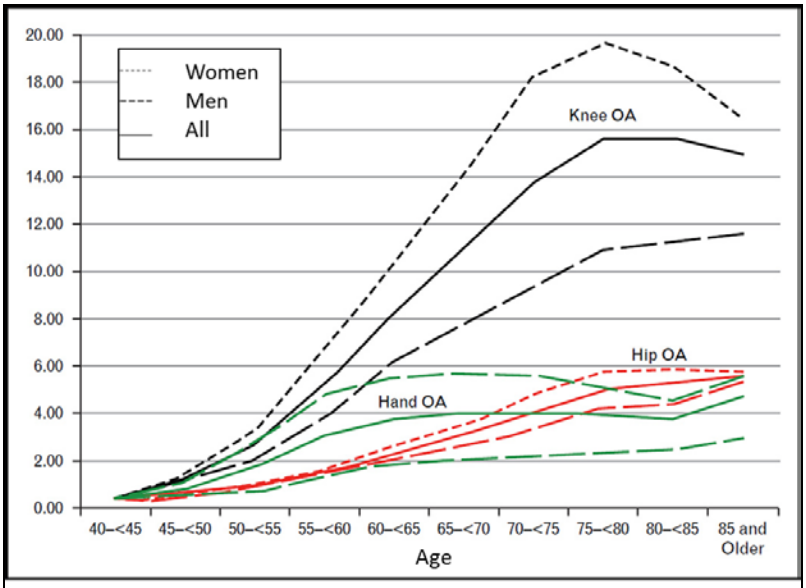

Figure 4: Age, sex and site specific incidence rates of OA
Adapted from Prieto-Alhambra D et al, Ann Rheum Dis, 2014.

Figure 6-1: Age, sex and site-specific incidence rates of OA

Age is one of the most important risk factors for OA. The risk of OA increases greatly after 50 years[197] (around the time of menopausal transition). The risk of hip OA increases

continuously with age, reaching peak incidence around 70-79 years[198]. This increase in risk after menopause suggests a potential role of hormones in the development of OA. However, this association is unclear. While some observational studies have reported lower odds of OA with hormone replacement[199], randomized control trials have shown no significant association[200].

The effect of reproductive history on OA risk is poorly understood. Few studies have assessed the association between reproductive factors and OA in later life. Lui et al, from the Million Women Study assessed the association between age at menarche, parity, and age at menopause and the risk of hip or knee replacement. Women who attained menarche ≤ 11years had a greater risk of hip (9%) and knee (15%) replacement compared to menarche at age 12. Interestingly, the linear trend for inverse association between hip and knee replacements were significant. However, later age at menarche (>12 years) showed no significant association. Compared to nulliparous women, women with 4 or more children had a greater risk of both hip (10%) and knee replacement (46%), with significant linear trends. Current or past use, longer duration of HT use and type of hormone (estrogen only or estrogen and progestagen) were significantly associated with 13% to 72% increased risk of joint replacement[201]. These associations were independent of age, BMI, alcohol, socioeconomic status(SES), smoking, use of oral contraceptive or hormone therapy, parity and age at menarche appropriately[201]. The authors suggested that estrogen exposure may promote osteoarthritic changes resulting in joint replacement. No associations or trends were noted with age at menopause. However, it is important to note that joint replacement is largely an elective surgery. Socioeconomic status, education, diet and physical activity and access to healthcare could be important determinants of this association. While OA is the most common cause of joint replacement, the study had limited information on knee injury and occupation, which are important risk factors for joint

replacement. Additionally, women of low SES in the United States, are less likely to undergo joint replacement, possibly due to disparity in access to care[202]. With the centralized healthcare system in the United Kingdom, these results might be less generalizable[203].

Wise et al, demonstrated a direct association between parity and knee OA or replacement. Compared to women with 1 child, having 2, 3, or ≥5 children were associated with greater risk of knee OA, independent of age, race, education, occupation, or knee injury[204]. The authors attributed these findings to redistribution of weight during pregnancy overloading the knee joint and retention of weight following pregnancy may lead to obesity in later life[205]. It is important to note that the study included women with risk factors for knee OA including obesity, knee injury, and knee pain or stiffness in the last 30 days. Thus, it is likely that the sample was not representative of the general population[204]. The effect of physical activity was also not accounted for.

Jorgensen et al, reported that greater number of live births were associated with a greater risk for OA hospitalization in both men and women. Compared to nulliparous women, women with one or more children had a 14% increased risk of hospital diagnosed knee OA, but not hip OA. This association was independent of age, marital status, birth cohort, family education, and household income[206]. The authors suggested that the association was possibly due to pregnancy related weight gain and retention. However, they could not account for effect of obesity due to lack of anthropometric measures from the Danish Population Registers. In addition, use of International Classification of Diseases (ICD) codes may allow for potential misclassification.

Parazzini et al, reported that women (mean age – 53 years) experiencing natural (13%) and surgical (18%) menopause were more likely to self-report OA, compared to pre-menopausal

women. Women who used HT had 27% were less likely to report OA[207]. However, these associations failed to account for effect of any potential confounders.

Studies on the effect of HT on osteoarthritis have produced conflicting results. Arden et al, suggested that HT may have a protective effect on radiological signs of osteoarthritis[208]. While some studies have supported this hypothesis[207], the Women's Health Initiative showed no association between HT and hip or knee replacement[209]. Multiple studies have demonstrated a lack of association between oral contraceptive pill use and osteoarthritis[210-213].

In summary, the association between reproductive factors and osteoarthritis is unclear. The research is largely limited to knee OA, with conflicting results. Some studies were also limited by self-reported or clinical diagnosis of OA that could lead to potential misclassification bias. The peak incidence of hip and knee OA is between 70-79 years, Thus, studies on middle aged women may not adequately reflect these associations. To the best of our knowledge, no studies have assessed the association between reproductive history and hip OA in older women.

7.0 REPRODUCTIVE HEALTH AND BONE GEOMETRY

The aging process results in loss of structure and composition of the bone leading to osteoporosis[214]. Osteoporosis is a major health problem associated with low impact or osteoporotic fractures[215]. In 1 year, women are more likely to expericence fractures than myocardial infarction, coronary death or breast cancer, combined[216]. Fractures of the hip and vertebrae are associated with a significant increase in mortality and disability risk[217]. Women with history of hip fracture had an increased risk of subsequent hip fracture (2.3%/year)[218]. The cost of fractures is estimated to grow from $209 billion to $228 billion between 2006-2015 and 2016-2025 respectively[219]. Thus identification of risk factors and its prevention is key.

The female reproductive system largely influences the growth and development of the skeleton. From menarche to menopause, bones undergo constant modelling and remodeling[220]. This process occurs largely through the influence of estrogen on calcium balance and its effects on the bone[221]. With the menopausal transition, the levels of estrogen decrease resulting in loss of bone mineral content leading to osteoporosis and subsequently fractures[222]. Areal bone mineral density (aBMD) is the most commonly used measure to diagnose osteoporosis. However, aBMD does not account for bone size and geometry and fails to adequately reflect the ethnic/racial differences in fracture rates[223]. In addition, aBMD is limited by its 2-dimensional nature. Therefore, in addition to BMD, accounting for the geometry and structural properties of bone can better measure bone strength[224]. The Hip Structural Analysis (HSA) takes into account

bone geometry and predicts femoral neck strength[225] and fracture risk[226], independent of aBMD[227].

Attempts to understand the effect of hip geometry were made as early as 1975 by Phillips et al[228]. In 1984, Martin and Burr used dual energy photon absorptiometry as a non-invasive technique to understand the 3-dimensional structure of the bone from a 2 dimensional image[229]. Beck et al, further developed this method and applied them to newer Dual energy Xray Absorptiometry (DXA) images[230].

The Hip Structural Analysis (HSA) assesses the hip geometry at 3 anatomical sites on the femoral bone – the narrow neck, intertrochanteric region and the shaft. The main principle of the HSA is that pixel lines across the axis of the bone reflects the mineral in a cross-section from which the geometric properties can be measured[231]. Geometry is assessed in 5 profiles which are 1 pixel apart and then averaged at each region. Bone mineral density (BMD) is calculated as the average pixels in the region profiles. Cross sectional area (CSA) is assessed as a linear thickness (in cm^2) cross sectional bone surface divided by the average mineral content of a normal adult cortical bone (1.053 g/cm^2). Section modulus(SM), an indicator of the bending strength for maximum bending stress is computed as cross-sectional moment of inertia (CSMI) divided by the maximum distance from the section center to the cortical surface in the image plane (d_{max}). The outer diameter (OD) is the blur-corrected width of the bone. The buckling ratio (BR) is measured as a relative thickness of the cortex measured as an estimate of the cortical stability in buckling (lower is better). BR is estimated by modelling the cross section as a hollow circular annulus of the narrow neck with 60% of the CSA in the cortical shell.

Some reproductive factors have been studied in association with bone geometry in women. In a cross-sectional study of healthy postmenopausal women (N=87, aged 55-79 years),

greater parity was associated with significantly lower narrow neck CSA [β (95% CI) = -0.25(-0.09, -0.01)]. Longer duration of lactation (total lactation period over the life time) was associated with greater intertrochanteric BR [0.28(0.04, 0.27)] suggestive of higher fracture risk. In addition, longer duration of menopause was associated with greater narrow neck BR [0.24, 0.01, 0.29)]. These associations were independent of age, and BMI and the other reproductive factors[232]. Interestingly, women with >4 children had lower mean FN and spinal BMD compared to women with <2 children[232]. The association between parity and conventional BMD remains controversial. While some early studies suggested an inverse association[233, 234] between parity and BMD, more recent studies have demonstrated that parity and lactation have little effect on BMD or fracture risk[235]. One potential explanation for the association between parity and low BMD in the study could be due to greater BMI in women with greater parity. Lower BMI has been shown to be associated with lower BMD[236].

Laskey et al, reported similar association between lactation and hip geometry. In a longitudinal study of young women (48 lactating, 23 non-pregnant non-lactating) followed up for upto a year, lactating women showed significant decrease in BMD and CSA (narrow neck and intertrochanteric) from 2 weeks post-partum to peak lactation independent of weight. Lactating women also showed significant increase in BR that was explained by accoutning for weight. Interestingly, there was no significnat loss from 2 weeks post partum to post-lactation(>1 year). No associations were noted with non-pregnant non-lactating women[237]. These results are consistent with changes in conventional BMD. Lactation is known to be associated with temporary loss of FN BMD[235,238,239]. It has been postulated that the loss of BMD compensates for the increased calcium demand during lactation. This is supported by the ineffective apposition of the endocortical layers in girls but not boys, during puberty, so as to support pregnancies and

lactation[112,240]. In addition, breast feeding is associated with loss of body weight[241]. The changes in body weight could affect the skeleton through loading effects[242], and hence affect mineralization. Resumption of menstrual cycles after pregnancy has also been suggested as possible driver of bone health recovery after lactation[239].

Similar to changes in aBMD[127] and FN strength[243], the hip geometry showed accelerated change 2 years before the final menstrual period to 1 year after and continued to change in the post-menopausal period at a lower rate . We noted a decline in BMD, CSA and Section Modulus (SM) and an increase in outer diameter (OD) and buckling ratio (BR). This association was independent of body weight, smoking, and physical activity[244].

A large cross-sectinal study (N=1322) of post-menopausal Chinese women (aged 44-87 years) studied the association between years of menstruation (calculated as time between age at menarche to menopause) and hip geometry. They reported that longer years of menstruation and higher BMI were significantly associated with greater BMD, CSA and Cortical Thickness (CT) and lower OD and BR[245]. These associations were independet of age, body weight, height, eduation, physical activity, smoking status, oral calcium intake and age at menarche. Poor HSA measures may be attributed to lower cumulative exposure to estrogen, increased glucocorticoid levels, decreased anti-oxidant capacity and physical activity[246].

Few reproductive factors over the life course have been studied in relation to hip geometry. Many of these studies were limited by small study populations and cross-sectional design or with limited follow up time. Studies were also limited to certain populations, thus lacking strength to generalize the results. To the best of our knowledge, the association between reproductive factors and HSA levels during midlife has not been previously assessed. With the

high social and economic burden of fractures in older women, the association between reproductive factors and hip geometry needs to be further explored.

8.0 PAPER 1: ASSOCIATION BETWEEN REPRODUCTIVE FACTORS AND OBJECTIVE MEASURES OF PHYSICAL FUNCTION IN OLDER WOMEN: A LIFE COURSE HYPOTHESIS

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8.1 ABSTRACT

Objective: To assess association between reproductive history with level and rate of change of objective measures of physical function (PF) in older women.

Methods: The Study of Osteoporotic Fractures was a longitudinal study of women, aimed at understanding risk factors for fractures. To improve internal validity and reduce survivor bias, the analysis was limited to women 65-80 years at baseline with information on reproductive factors and 2 or more measures of PF [N=6154, Age, mean(SD)= 70.6(4.1) years, BMI=26.5(4.4) kg/m^2]. Outcomes were evaluated as both baseline levels and rate of change over 20 years to complete 5 chair stands, maximum grip strength and 6m gait speed. Linear mixed models were used to obtain subject specific rate of change for each PF measure over 20 years. Using the population mean and SD of each PF changes, women were classified into maintained, expected or accelerated change. Multinomial logistic regression models were then used to assess associations with reproductive history. Final models were adjusted for age, education, BMI, smoking, alcohol intake, physical activity, diabetes and stroke.

Results: Women who had later age at menarche [OR (95% CI) = 1.10(1.05, 1.16)], greater parity (total live births) [1.07(1.02, 1.12)] and breastfed their offspring [1.22(1.04, 1.42)] were more likely to maintain their grip strength. Conversely, women with a history of hysterectomy [0.85(0.73, 0.99)] & oophorectomy [0.85(0.73, 0.99)] were associated with accelerated loss of grip strength. No associations were noted with other reproductive factors.

Conclusion: Early life reproductive factors like menarche, parity, and breastfeeding are associated with grip strength change in later life. As grip strength is a measure of overall muscle strength (or weakness), further understanding of the underlying mechanisms could help design targeted interventions to prevent functional decline in later life.

8.2 INTRODUCTION

Preservation of functional status is a key marker of successful aging[20]. In addition to being a precursor of disability[247], low physical function is associated with greater mortality risk[248]. Women are more likely to report disability than men[5]. These differences point to many gender-specific biological and social factors that could contribute. For example, women are more likely to accumulate greater allostatic load from physiological insults and dysregulation across the life course[181,183,249]. Women are also subject to greater risk of several chronic diseases like arthritis, depression and osteoporosis[5]. In addition, greater predisposition to disability and functional decline may be related to socio-behavioral factors like education, smoking, and physical activity[6,7]. However, these factors account for only a fraction of the gender gap in disability[6,250]. In contrast, the effect of reproductive health on functional decline is poorly understood. Some studies have hypothesized that reproductive factors like early childbirth and greater parity, may be accountable for greater prevalence of functional limitations and earlier decline in physical function[183]. Early menarche[251], greater parity and early childbirth[252], lactation[253] and menopause[254], alter the physiologic and metabolic demands of the body. These alterations may be more permanent, increasing the risk for chronic diseases[12,255-256], thus increasing the risk of functional limitations. Few studies have extended support to this theory. In a study of middle aged women, parity ≥3 (vs 1-2 children) and first birth <18 years were associated with longer time to complete the chair stand test, independent of age, education, physical activity and menopausal status[184]. In NHANES (mean age ~70 years), natural menopause <45 years (vs ≥ 55 years) and surgical menopause were associated with slower gait speed and longer chair rise time respectively. These associations were independent of age, race, weight and education[101]. Conversely, young breastfeeding mothers' (mean age = 27 years) were

more likely to report better physical functioning, compared to non-breastfeeding mothers, independent of age, education, income and parity[257]. However, these studies were limited by cross-sectional design, self-reported physical function measures and/or failure to account for significant confounders like body mass index (BMI), physical activity and chronic diseases like diabetes. Little is known about these associations in older women. The effect of reproductive health on rate of functional decline older women is unknown.

Maintaining physical function is a key component of successful aging. With the increasing age of the population and the rising healthcare expenditures, there is a critical need to understand risk factors for functional decline and to prevent disability in older women. To the best of our knowledge, no other study has assessed the effect of reproductive health on the level and rate of change of objective measures of physical function later in life. Using the data from the Study of Osteoporotic Fractures (SOF), we aimed to assess these associations. We hypothesized that reproductive health, characterized by early age at menarche, nulliparity, non-breastfeeding, oral contraceptive (OC) use , early age at menopause, and history of hysterectomy or oophorectomy, would be associated with lower baseline levels as well as greater decline in physical functioning in older women.

8.3 METHODS

Study population:

The Study of Osteoporotic Fractures (SOF) is a multi-center longitudinal study of women recruited from 4 clinical centers: Baltimore, MD; Monongahela Valley near Pittsburgh, PA; Minneapolis, MN; and Portland, OR. SOF was originally designed to understand the risk factors

for fractures in women[258]. At baseline (1986-1988), 9704 community dwelling, ambulatory women aged 65 years or older were recruited through population based mailings, irrespective of osteoporotic status. Women with no history of bilateral hip replacement and ability to walk without assistance of another person were eligible to participate. The participants were followed with clinical visits and examinations approximately every 2 years for over 20 years (year 20: 2006-08). The study initially included only Caucasian women (N=9704) due to their higher incidence of fracture. African American (AA) women were recruited at year 10 (N=662). The study protocol was approved by the Institutional Review Boards at participating institutions and informed consent was obtained from all the participants.

Information on all reproductive factors/events were available for only Caucasian women. Hence for the current analyses, the population was limited to Caucasian women aged 65-80 years at baseline with 2 or more repeated measures of physical function. Women >80 years were excluded to limit survivor bias, improve internal validity and to maximize the follow up period[259]. In addition, outliers from age at menarche (<9 or >16 years) and menopause (<31 or >65 years) were excluded from the analyses to limit misclassification bias. The final study population consisted of 6154 women (Supplemental figure 8-2).

Compared to those who were included, the excluded women were older with a lower BMI (Age, mean(SD) = 83.37(2.18), BMI=25.46(3.65)). The excluded population had poorer physical functioning at baseline with longer time to complete the chair stand test (mean(SD) = 15.75(6.89) s), lower grip strength (18.96(3.85) kg), and slower gait speed (0.84(0.22) m/s). The age at menarche and menopause for all included and excluded ranged between 8-26 and 14-68 years respectively.

Study measures:

Physical function:

For the current study 3 objective measures of physical function were included - chair stands, grip strength, and gait speed[260]. Chair stand was measured as the number of seconds required to stand from a straight-back chair, 5 times, without using arms. Women who were unable to complete the chair stand test received an arbitrary value of 70 seconds was assigned (5 seconds greater than the highest value), to allow categorization of these women in the lowest quartile/accelerated loss group. Grip strength was measured from both hands, in standing position using a handheld isometric dynamometer (Preston Grip dynamometer, Takei Kiki Kogyo, Japan). Maximum grip strength recorded from right or left hand (in kilograms(kg)) was used for current analyses[261]. Gait speed (meters/second) was measured as the number of seconds needed to walk 6 meters, while walking at usual pace.

Reproductive factors:

The SOF study obtained information on multiple reproductive factors from questionnaires. Age at menarche and menopause were assessed as age at first and last menstrual periods respectively. Parity was reported as the total number of live births. Breast feeding (yes/no) was defined as having breastfed one or more children. Use of OCPs (yes/no) was self-reported as ever use of birth control pills. Hysterectomy and oophorectomy were self-reported as surgical removal of uterus and one or more ovaries respectively. All reproductive data except age at menarche (visit 2) were collected at baseline. Age at menarche, parity, and age at menopause were assessed as both continuous and categorical variables. Age at menarche was categorized into 4 groups – 9-10, 11-12, 13-14, 15-16 years. Similarly, age at menopause was categorized

into 5 groups - ≤40, 41-45, 46-50, 51-55 and >55 years. Parity was classified into 3 groups – nulliparous, 1-3 and >3 children.

Other measurements:

Other factors included in the analyses were collected at baseline. Demographic factors like age (years), and education (total number of years of education obtained) were obtained from questionnaires. BMI (kg/m^2) was calculated as weight in kilograms divided by height squared in meters. Smoking and alcohol consumption were self-reported. Smoking status was assessed as ever or never smoker. Alcohol intake was reported as total number of drinks per day in the last 30 days. Physical activity was assessed using a modified Harvard alumni questionnaire[262]. Women reported the distance and frequency they walked each day in city blocks or its equivalent. They also reported duration of activities like swimming, dancing, gardening, aerobics etc. in the last year. The physical activity was then calculated as a weighted estimate of total kilocalorie expenditure per week over the past year[263]. Physician diagnoses of diabetes and stroke was self-reported by the participants.

Statistical analyses:

Pearson coefficients were used to estimate correlations among the reproductive factors. Baseline characteristics were summarized as mean (SD) for continuous measures and frequencies (percentages) for categorical variables.

At baseline, associations between the reproductive factors and physical function were assessed using linear regression models. Women with history of hysterectomy were excluded in models assessing age at menopause since the latter could not be accurately estimated. In addition, nulliparous women were excluded from breastfeeding analyses.

To assess change over time, multiple approaches were used. Locally Weighted Scatterplot Smoothing (LOESS) regression models were used to examine the trajectories of physical function over time. From this, linear trajectories (increase in chair stand time and decline in grip strength and gait speed) were noted.

Next, we tested whether the population-average trajectory of each physical function measure overtime can be separated into distinct trajectories (e.g. not all study population follow the same trajectory of change in each physical function measure) using group based trajectory modeling[264]. Grip strength and gait speed showed similar group trajectories thus lacking evidence to demonstrate the existence of distinct trajectories of these physical function measures over time. Three distinct trajectory groups of time needed to complete chair stand test were identified [Supplemental figure 8-3]. Group 1 (N (%)= 4672 (83.6%)) maintained their chair stand for the duration of follow up. Group 2 women (579(12.2%)) maintained the chair stand time up until year 10, with steep increase in chair stand time thereafter. Group 3 (223(4.2%)) demonstrated a gradual increase in chair stand till year 4, followed by a steep increase in chair stand thereafter. Using multinomial logistic regression, we estimated the odds of belonging to the 3 groups with group 2 as our referent.

To further characterize our findings, we used linear mixed model analyses. Subject-specific slopes and intercepts for each physical function measure were estimated using random effects models. Repeated measures of each physical function assessments were modeled separately as a function of time. Fixed effect parameter of time since baseline provides an estimate of the population-average change in each physical function measure per year, while the random effect of time since baseline provides estimates of subject-specific deviation from the population-average. Using the estimated subject-specific slopes of change in physical function

per year, women were then categorized into “maintained”, “expected” and “accelerated” physical function change overtime. As chair stand time increases with age[265], women were considered to have maintained if their chair stand slope was ≤ mean, expected if the slope was within 1SD above the mean and accelerated if the slope was greater than 1 SD above the mean. Grip strength and gait speed decrease over time[155], thus women were considered as maintained if their respective slopes were ≥mean, expected if the slopes were within 1SD below the mean, and accelerated if the slopes were greater than 1SD below the mean. We used multinomial logistic regression to estimate the odds of having maintained or accelerated change in physical function with the expected group forming the referent group (figure 8-1). For chair stand test, the results from the mixed effect models were similar to those from group based trajectory modelling. Only results from the linear mixed models are presented below. Both cross-sectional and longitudinal analyses were conducted univariately and then adjusted for all the potential confounders.

8.4 RESULTS

Using Pearson correlation coefficients, we noted small but significant correlations between the reproductive factors ($p<0.05$) [Supplemental table 8-6]. Strong correlations included parity and breastfeeding ($r=0.17$) and hysterectomy and oophorectomy ($r=0.79$). The baseline characteristics of the population are summarized in Table 8-1.

Baseline analyses – Univariately [Table 8-2], later age at menopause was associated with faster chair stand time. Menopause ≤40 years showed slower chair stand time compared to referent population [menopause 51-55 years]. Oophorectomy was associated with longer 0.3s longer chair stand time. These associations were no longer significant after adjusting for

confounders. In the fully adjusted model, menarche between 11-12 years was significantly associated with faster chair stand time compared to the referent population [menarche 13-14 years]. The reverse confounding effect was explained by age, BMI, smoking, diabetes and stroke.

In the fully adjusted models, Later age at menarche was associated with greater grip strength. Menarche between 11-12 years had significantly lower grip strength compared to referent population [menarche 13-14 years]. Parity 1-3 and ≥4 were associated with greater grip strength, compared to nulliparity. No significant associations were noted with the other menarche categories. Hysterectomy and oophorectomy were associated with lower grip strength. Menopause between 41-45 years was associated with greater grip strength compared to menopause between 51-55 years only in the final model. This suppressor effect was attributable to age and diabetes.

Univariately, breastfeeding, and hysterectomy were associated with slower gait speed while OC use and later age at menopause were associated with faster gait speeds. However, these associations were explained by adjusting for potential confounders.

Longitudinal analyses - Mean slope for chair time, grip strength and gait speed were 0.47s/year, -0.35kg/year and -0.02m/s/year respectively. The mean slope in the accelerated group was +2.19s/year (n=535), -0.38kg/year (n=915) and -0.03m/s/year (n=825) for chair stand, grip strength and gait speed respectively [Figure 8-1].

Univariately, later age at menopause were 3% less likely to have accelerated chair stand increase relative to expected increase. This association was largely explained by age, diabetes, and stroke. No significant associations were noted with other reproductive factors.

In the final models, women with later age at menarche (10%), or greater parity (7%) were

more likely to have maintained grip strength relative to expected group [Table 8-4]. Compared to nulliparous, women with 1-3 (91%) or >3 (115%) children were more likely to have maintained grip strength compared to expected group. Women with hysterectomy or oophorectomy were 15% less likely to have maintained grip strength. Women with oophorectomy [1.28(1.03, 1.58)] had 28% greater risk of accelerated loss of grip strength, compared to expected loss. No significant associations were noted with the other reproductive factors.

Univariately, women with greater parity (8%), and OC use (31%) had a greater likelihood of maintaining gait speed compared to expected loss [Table 8-5]. Compared to nulliparous women, women with >3 children were 50% more likely to maintain their gait speed relative to expected loss. Women with hysterectomy (13%) were less likely to have maintained gait speed. However, these associations did not remain significant in the fully adjusted models. No associations were noted with age at menarche, parity, breast feeding, age at menopause or oophorectomy.

No associations were noted with use or length of hormone therapy with any of our outcomes (results not shown).

8.5 DISCUSSION

We found selective reproductive factors may influence both the level and rate of change in grip strength in older women. At baseline, later age at menarche, and greater parity were associated with higher grip strength. Conversely, a history of hysterectomy or oophorectomy was associated with lower levels of grip strength. Longitudinally, women with a later age at

menarche, greater parity, and history of breastfeeding were more likely to maintain their grip strength while women who had hysterectomy or oophorectomy were less likely to maintain their grip strength, while a history of an oophorectomy was associated with a greater likelihood of accelerated loss of grip strength. These associations were independent of age, BMI, education, physical activity, smoking, diabetes and stroke. Our results support a life course perspective and highlights the association of multiple reproductive factors across life with grip strength in later life.

Gait speed[266], chair stand[266] and grip strength[267] have been linked to adverse health and mortality in later life. However, they reflect different physiologic processes. Successful completion of the chair stand reflects strength[268,269] of the proximal muscles, neuromuscular control as well as coordination and integration of cardiovascular and respiratory systems[191,270]. Walking entails muscle strength[101] as well as coordination[190]. Although grip strength is a simple isometric measure of upper body muscle strength[191], it is a known surrogate marker for various chronic diseases including cardiovascular disease and sarcopenia[271,272]. In addition, grip strength acts as a proxy for overall muscle strength[273] and is a predictor of functional limitation and disability[274,275]. Grip strength is also significantly correlated with arm, back, leg[276-278] and respiratory muscle strength[279].

Our study found significant results only with grip strength. We believe complex hormonal and biomechanical factors may mediate these associations. Early menarche, and other indicators of early biological maturity, is associated with greater adult BMI[280]. Obesity/overweight in early, middle or late adulthood has been linked to mobility limitations in old age[281].Thus, later age at menarche may indicate leaner, healthier population, retaining functional abilities in later life. On the other hand, greater parity[282] is associated with greater

body weight while breastfeeding is associated with postpartum weight loss[283]. This association differs by number of births, race and maternal BMI[282]. Interestingly, arm muscle area, an indicator of muscle mass, also increases in late pregnancy[284]. Coupled with an active lifestyle with young children, the increase in muscle mass could reflect as greater muscle strength in later life. Studies have also reported increase in BMI following hysterectomy/oophorectomy[285], increasing risk of functional limitations in later life. On the other hand, hysterectomy/oophorectomy may also be manifestations of underlying poor health.

In addition, the exposure to levels of hormones particularly estrogen, progesterone and testosterone vary across life. While the effect of sex-steroid hormones on muscle function remains unclear, studies have shown that these hormones may act independently[105] or along with other hormones[286] to affect physical functioning. Estrogen increases rapidly around menarche[251], and decreases around menopause[254]. Pregnancy is associated with increased levels of both estrogen and progesterone. High levels of progesterone can alter the effect of estrogen in the body[110] by blocking estrogen receptors[111]. Therefore, the effect of higher cumulative exposure to estrogen with greater parity, may be altered through high levels of progesterone. Together, these factors could be associated with greater grip strength. In addition, breast feeding reduces the synthesis of estrogen[112] and progesterone[113] while increasing the levels of follicle stimulating hormone[111]. These changes in hormones could have lasting effects on muscle structure and function. However, to completely understand the effect of hormones on physical function, repeated longitudinal assessment of hormones, especially in later life, is required. A life-course approach, by definition, aims to understand the long-term effects of biological and psycho-social processes from gestation to adult life[58]. However, accurately assessing these biological and

psycho-social influences over time can be challenging given requirements for detailed and comprehensive assessments over long period of follow up.

However, few studies have assessed the association between reproductive health and physical function levels in later life[257]. The results of our study are largely consistent with existing literature on reproductive health and physical function in early life[183,191,257]. In the recent years, there has been increasing research supporting the relationship between early life reproductive factors and later life health. Early age at menarche and menopause have been linked to increased risk of mortality[287] while later age at menarche, childbearing, breastfeeding, OC use have been related to decreased risk of all-cause mortality, lower circulatory and heart diseases[288]. Parity[289] and menopause[290] were inversely related to hip fractures. The findings from our study are consistent with these findings and extend the association to changes in grip strength in later life.

The strengths of our study include the large community population who were followed over 20 years. SOF collected information on multiple reproductive factors as well as objective assessments of multiple physical functions over time allowing for both cross-sectional and longitudinal analyses. However, the study has its limitations. Reproductive data was available only for Caucasian women. Thus, our results may not be generalizable to women of other race/ethnicities. Use of retrospective reports of reproductive health may be subject to recall bias. Since the women were 65 and older in 1986-88, there were few women who reported prior OC use; thus, limiting statistical power. Simultaneous comparisons of the many reproductive factors may also induce a problem of multiplicity/multiple comparisons i.e., statistical significance is likely due to chance. However, the consistent results in the cross-sectional and longitudinal analyses provides some validity. We were also unable to assess the effect of hormone levels in

later life on physical function. Despite these limitations, to the best of our knowledge, no studies have assessed the association between multiple reproductive factors and the level and rate of change of objective measures of physical function in later life.

8.6 CONCLUSION

Our study demonstrated possible influence of reproductive factors over the life course on grip strength in later life both cross-sectionally and over time. While later age at menarche and greater parity had protective effects, hysterectomy and oophorectomy may be associated with poorer grip strength in later life. These associations were independent of potential confounders and may be mediated through complex biomechanical, and hormonal pathways. Further studies are required to understand these pathways and provide appropriate interventional support to prevent functional decline and disability in older women.

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8.7 TABLES AND FIGURES

Table 8-1: Population characteristics

	All women (N=6154)	Menarche 9-10 (n=134)	Nulliparity (n=168)	Menopause <40 (n=289)	Hysterectomy (n=1666)	Oophorectomy (n=1595)
Age (years)	70.56(4.05)	70.70(4.11)	71.10(3.95)	71.35(4.21)	70.66(4.08)	70.42(3.99)
Education (years)	12.73(2.72)	13.23(2.64)	13.06(2.92)	12.33(2.65)	12.53(2.71)	12.50(2.69)
BMI (kg/m^2)	26.46(4.43)	27.16(4.49)	25.90(4.31)	26.33(4.49)	26.73(4.51)	26.68(4.58)
Ever smoker N(%)	2503(40.82)	64(47.76)	102(60.71)	128(44.44)	662(39.81)	661(41.52)
Alcohol consumption (total drinks/day)	1.01(0.84)	1.07(0.79)	1.21(0.85)	1.12(0.80)	1.02(0.78)	1.04(0.78)
Physical activity (kcal/week)	1521.59(1655.07)	2073.56(2985.82)	1649.82(1762.29)	1348.42(1405.81)	1509.19(1615.15)	1533.63(1677.38)
Diabetes N(%)	406(6.61)	15(11.19)	16(9.58)	25(8.71)	127(7.64)	115(7.22)
Stroke N(%)	161(2.63)	7(5.34)	5(3.03)	7(2.44)	58(3.50)	51(3.21)
Age at menarche (years)	12.98(1.36)	9.79(0.41)	12.88(1.49)	12.99(1.43)	12.91(1.34)	12.93(1.36)
Menarche (years) N(%)		N/A				
9-10	134(2.18)		8(4.76)	14(4.84)	32(1.92)	34(2.13)
11-12	2180(35.42)		62(36.90)	87(30.10)	649(38.96)	602(37.74)
13-14	3034(49.30)		73(43.45)	149(51.56)	778(46.70)	761(47.71)
15-16	806(13.10)		25(14.88)	39(13.49)	207(12.42)	198(12.41)
Parity	2.68(1.51)	2.60(1.58)	N/A	2.23(1.46)	2.60(1.45)	2.46(1.43)
Parity N(%)			N/A			
Nulliparous	168(3.23)	8(6.96)		16(7.48)	54(3.76)	70(5.23)
<=3	3805(73.14)	79(68.70)		163(76.17)	1073(74.77)	1014(75.73)
>3	1229(23.63)	28(24.35)		35(16.36)	308(21.46)	255(19.04)
Breast fed N(%)*	3551(70.36)	72(67.29)	N/A	131(66.16)	980(70.76)	880(69.18)
Oral contraceptive user N(%)	291(4.74)	9(6.72)	2(1.19)	3(1.04)	71(4.27)	71(4.46)
Age at menopause (years)	48.94(4.78)	48.17(6.01)	48.75(6.19)	38.32(2.22)	N/A	47.77(5.56)
Menopause (years) N(%)				N/A	N/A	
<=40	289(6.44)	14(13.73)	16(14.04)			31(12.06)
41-45	797(17.76)	18(17.65)	16(14.04)			49(19.07)
46-50	1782(39.71)	31(30.39)	36(31.58)			97(37.74)
51-55	1401(31.22)	32(31.37)	36(31.58)			72(28.02)
>55	219(4.88)	7(6.86)	10(8.77)			8(3.11)
Hysterectomy N(%)	1666(27.08)	32(23.88)	54(32.14)	0(0)	N/A	1338(83.94)
Oophorectomy N(%)	1595(26.34)	34(25.56)	70(42.68)	31(10.76)	1338(84.63)	N/A
Chair Stand Time time(sec)	12.12(4.71)	12.46(4.49)	12.49(4.51)	12.83(4.30)	12.20(4.28)	12.23(4.33)
Maximum grip strength (kg)	22.61(4.30)	22.31(4.44)	21.81(4.25)	22.31(4.69)	22.23(4.32)	22.33(4.33)
Gait speed (m/s)	1.04(0.21)	1.04(0.26)	1.05(0.21)	0.99(0.21)	1.03(0.21)	1.03(0.22)

*excluding nulliparous women

Table 8-2: Cross-sectional association between Reproductive factors and Physical function at baseline

	Chair Stand Time		Grip strength		Walk speed	
	Unadjusted model [β (95% CI)]	Multivariate model [β (95% CI)]	Unadjusted model [β (95% CI)]	Multivariate model [β (95% CI)]	Unadjusted model [β (95% CI)]	Multivariate model [β (95% CI)]
Age at menarche (cont.)	-0.002(-0.09, 0.08)	0.003(-0.09, 0.09)	**0.09(0.01, 0.17)**	**0.17(0.07, 0.26)**	0.001(-0.003, 0.01)	0.002(-0.002, 0.01)
Age at menarche						
9-10	0.28(-0.54, 1.10)	0.17(-0.69, 1.02)	-0.37(-1.11, 0.38)	-0.61(-1.50, 0.28)	-0.0004(-0.04, 0.04)	0.003(-0.04, 0.04)
11-12	-0.18(-0.44, 0.08)	**-0.29(-0.54, -0.03)**	-0.22(-0.46, 0.02)	**-0.31(-0.58, -0.04)**	-0.01(-0.02, 0.005)	-0.002(-0.01, 0.01)
13-14 [Ref]	Ref	Ref	Ref	Ref	Ref	Ref
15-16	-0.06(-0.42, 0.31)	-0.17(-0.53, 0.20)	0.12(-0.22, 0.45)	0.20(-0.18, 0.59)	-0.001(-0.02, 0.01)	0.01(-0.004, 0.03)
Parity (cont.)	-0.02(-0.11, 0.06)	0.02(-0.07, 0.10)	**0.19(0.11, 0.27)**	**0.14(0.05, 0.23)**	-0.001(-0.01, 0.003)	-0.003(-0.007, 0.001)
Parity [a]						
Nulliparous	Ref	Ref	Ref	Ref	Ref	Ref
1-3	-0.51(-1.20, 0.18)	-0.12(-0.80, 0.56)	**0.75(0.08, 1.42)**	**1.00(0.28, 1.73)**	-0.01(-0.04, 0.02)	-0.01(-0.04, 0.02)
>3	-0.44(-1.16, 0.28)	-0.01(-0.73, 0.70)	**1.29(0.59, 1.99)**	**1.23(0.47, 1.99)**	-0.01(-0.05, 0.02)	-0.02(-0.05, 0.02)
Breast fed [b]	-0.09(-0.36, 0.17)	-0.26(-0.54, 0.01)	0.08(-0.18, 0.34)	0.20(-0.10, 0.49)	**-0.02(-0.03, -0.003)**	-0.002(-0.02, 0.01)
Oral Contraceptive Pill use [c]	-0.55(-1.11, 0.003)	0.49(-0.03, 1.02)	**0.79(0.28, 1.30)**	-0.22(-0.77, 0.33)	**0.05(0.03, 0.08)**	-0.01(-0.04, 0.01)
Age at menopause (cont.)	**-0.03(-0.06, -0.01)**	-0.01(-0.04, 0.02)	0.02(-0.004, 0.05)	-0.02(-0.05, 0.01)	**0.003(0.002,0.004)**	0.001(-0.003, 0.002)
Menopause (years)						
≤40	**0.80(0.22, 1.39)**	0.38(-0.24, 0.99)	-0.48(-1.02, 0.06)	0.10(-0.53, 0.72)	**-0.06(-0.09, -0.04)**	-0.02(-0.05, 0.01)
41-45	0.09(-0.31, 0.49)	-0.08(-0.50, 0.34)	0.01(-0.36, 0.38)	**0.51(0.08, 0.93)**	**-0.02(-0.04, -0.003)**	-0.005(-0.01, 0.02)
46-50	-0.07(-0.40, 0.25)	-0.25(-0.59, 0.09)	-0.08(-0.38, 0.22)	0.29(-0.05, 0.63)	-0.01(-0.02, 0.01)	0.005(-0.01, 0.02)
51-55 [Ref]	Ref	Ref	Ref	Ref	Ref	Ref
>55	-0.38(-1.04, 0.27)	-0.21(-0.90, 0.48)	0.46(-0.16, 1.07)	0.45(-0.25, 1.15)	0.01(-0.02, 0.04)	-0.003(-0.04, 0.03)
Hysterectomy [e]	0.25(-0.01, 0.52)	0.09(-0.17, 0.36)	**-0.52(-0.76, -0.28)**	**-0.44(-0.71, -0.16)**	**-0.02(-0.03, -0.003)**	-0.002(-0.01, 0.01)
Oophorectomy [f]	**0.34(0.07, 0.61)**	0.14(-0.13, 0.41)	**-0.40(-0.65, -0.16)**	**-0.40(-0.68, -0.11)**	-0.01(-0.02, 0.003)	0.001(-0.01, 0.01)

Reproductive factors were modelled independently and then adjusted for confounders; *adjusted for age at menarche; [a] Ref - >3; [b] Excluding nulliparous women, Ref – never breastfed; [c] Ref – No Oral contraceptive use; [d] Ref- no HRT; [e] Ref- no hysterectomy; [f] Ref-no oophorectomy
Multivariate model – adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke

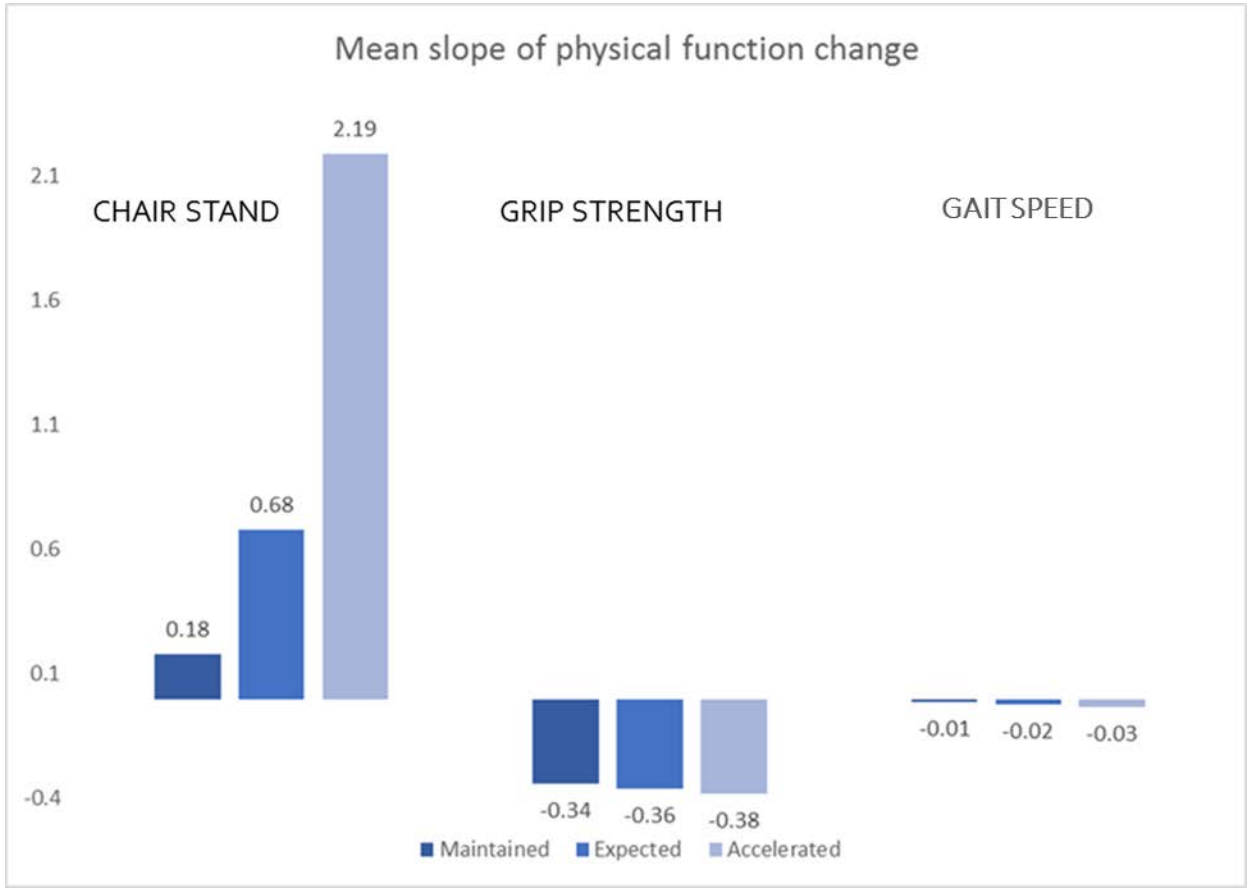


Figure 8-1: Mean slope of physical function change by category

Using subject specific linear mixed models, change in the physical function over time was assessed. Based on the mean and SD of change, women were categorized into 3 groups - maintained, expected and accelerated change. As chair stand (s) increases with time, +1SD change was used. For grip strength (kg) and gait speed (m/s) -1SD was used as they decrease over time.

Table 8-3: Association between reproductive factors and rate of change of chair stand time

	Chair Stand Time				
	Unadjusted model [OR(95%CI)			Multivariate model [OR (95% CI)]	
	Maintained	Accelerated	Expected	Maintained	Accelerated
Age at menarche (cont.)	0.97(0.93, 1.01)	0.99(0.92, 1.07)	Ref	0.95(0.90, 1.00)	0.99(0.90, 1.09)
Age at menarche			Ref		
9-10	0.77(0.52, 1.15)	1.05(0.56, 1.97)		1.18(0.67, 2.08)	1.56(0.68, 3.59)
11-12	1.13(0.99, 1.30)	1.09(0.87, 1.36)		1.17(0.99, 1.40)	0.99(0.74, 1.32)
13-14 [Ref]	Ref	Ref		Ref	Ref
15-16	0.95(0.79, 1.14)	1.20(0.89, 1.36)		0.99(0.78, 1.25)	1.22(0.84, 1.76)
Parity (cont.)	1.02(0.97, 1.06)	0.99(0.92, 1.07)	Ref	0.99(0.94, 1.05)	1.00(0.91, 1.10)
Parity [a]			Ref		
Nulliparous	Ref	Ref		Ref	Ref
1-3	1.24(0.86, 1.78)	0.90(0.51, 1.58)		1.34(0.88, 2.03)	1.26(0.61, 2.59)
>3	1.21(0.83, 1.77)	0.81(0.45, 1.48)		1.12(0.72, 1.74)	1.11(0.51, 2.39)
Breast fed [b]	0.90(0.78, 1.04)	0.92(0.72, 1.18)	Ref	0.94(0.78, 1.13)	0.82(0.60, 1.11)
Oral Contraceptive Pill use [c]	1.24(0.92, 1.68)	1.11(0.68, 1.81)	Ref	0.80(0.56, 1.14)	1.65(0.95, 2.88)
Age at menopause (cont.)	1.01(0.99, 1.03)	**0.97(0.95, 0.99)**	Ref	0.99(0.98, 1.02)	0.98(0.95, 1.01)
Menopause (years)			Ref		
<=40	0.79(0.59, 1.08)	1.58(0.99,2.49)		0.95(0.65, 1.39)	1.14(0.62, 2.09)
41-45	0.88(0.72, 1.09)	1.19(0.84, 1.68)		1.06(0.81, 1.38)	1.23(0.80, 1.91)
46-50	0.94(0.79, 1.12)	0.94(0.79, 1.12)		1.07(0.87, 1.33)	1.12(0.78, 1.61)
51-55 [Ref]	Ref	Ref		Ref	Ref
>55	1.11(0.78, 1.59)	1.02(0.54, 1.90)		1.06(0.68, 1.65)	0.72(0.30, 1.72)
Hysterectomy [e]	0.90(0.79, 1.03)	0.99(0.80, 1.24)	Ref	0.90(0.76, 1.07)	0.90(0.68, 1.20)
Oophorectomy [f]	0.92(0.80, 1.05)	0.99(0.80, 1.25)	Ref	0.90(0.76, 1.07)	0.88(0.65, 1.18)

Reproductive factors were modelled independently and then adjusted for confounders; *adjusted for age at menarche; [a] Ref - >3; [b] Excluding nulliparous women, Ref – never breastfed; [c] Ref – No Oral contraceptive use; [d] Ref- no HRT; [e] Ref-no hysterectomy; [f] Ref-no oophorectomy

Multivariate model – adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke

Table 8-4: Association between reproductive factors and rate of change in grip strength

Grip Strength					
	Unadjusted model [OR(95%CI)			Multivariate model [OR (95% CI)]	
	Maintained	Accelerated	Expected	Maintained	Accelerated
Age at menarche (cont.)	**1.07(1.03, 1.12)**	0.97(0.92, 1.03)	Ref	**1.10(1.05, 1.16)**	0.95(0.88, 1.02)
Age at menarche					
9-10	0.71(0.48, 1.04)	1.01(0.86, 1.20)		0.67(0.41, 1.08)	0.81(0.40, 1.65)
11-12	**0.84(0.74, 0.95)**	0.87(0.68, 1.12)	Ref	**0.80(0.69, 0.92)**	1.08(0.88, 1.33)
13-14 [Ref]	Ref	Ref		Ref	Ref
15-16	1.06(0.89, 1.25)	0.87(0.68, 1.12)		1.05(0.85, 1.30)	0.80(0.58, 1.10)
Parity (cont.)	**1.08(1.04, 1.13)**	0.95(0.89, 1.01)	Ref	**1.07(1.02, 1.12)**	0.95(0.88, 1.03)
Parity [a]					
Nulliparous	Ref	Ref	Ref	Ref	Ref
1-3	**1.78(1.26, 2.51)**	1.04(0.68, 1.60)		**1.91(1.28, 2.85)**	1.15(0.69, 1.92)
>3	**2.15(1.50, 3.08)**	0.91(0.57, 1.44)		**2.15(1.41, 3.27)**	1.05(0.61, 1.84)
Breast fed [b]	1.10(0.97, 1.26)	0.95(0.79, 1.14)	Ref	1.14(0.97, 1.34)	0.79(0.63, 1.00)
Oral Contraceptive Pill use [c]	1.22(0.94, 1.57)	**0.51(0.32, 0.82)**	Ref	0.84(0.62, 1.12)	0.73(0.43, 1.24)
Age at menopause (cont.)	1.01(0.99, 1.02)	0.98(0.97, 1.00)	Ref	0.99(0.98, 1.01)	0.98(0.96, 1.00)
Menopause (years)					
<=40	0.79(0.60, 1.05)	1.32(0.91, 1.91)		0.96(0.68, 1.35)	1.24(0.78, 1/95)
41-45	0.94(0.78, 1.14)	0.96(0.73, 1.28)	Ref	1.13(0.89, 1.42)	0.96(0.68, 1.36)
46-50	0.99(0.85, 1.15)	1.09(0.87, 1.36)		1.15(0.95, 1.38)	1.03(0.78, 1.36)
51-55 [Ref]	Ref	Ref		Ref	Ref
>55	1.13(0.83, 1.55)	0.75(0.45, 1.26)		1.10(0.76, 1.60)	0.60(0.30, 1.19)
Hysterectomy [e]	**0.87(0.77, 0.98)**	**1.24(1.05, 1.47)**	Ref	**0.85(0.73, 0.99)**	1.22(0.99, 1.51)
Oophorectomy [f]	0.89(0.79, 1.01)	**1.20(1.01, 1.43)**	Ref	**0.85(0.73, 0.99)**	**1.28(1.03, 1.58)**

Reproductive factors were modelled independently and then adjusted for confounders; *adjusted for age at menarche; [a] Ref - >3; [b] Excluding nulliparous women, Ref – never breastfed; [c] Ref – No Oral contraceptive use; [d] Ref- no HRT; [e] Ref- no hysterectomy; [f] Ref-no oophorectomy

Multivariate model – adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke

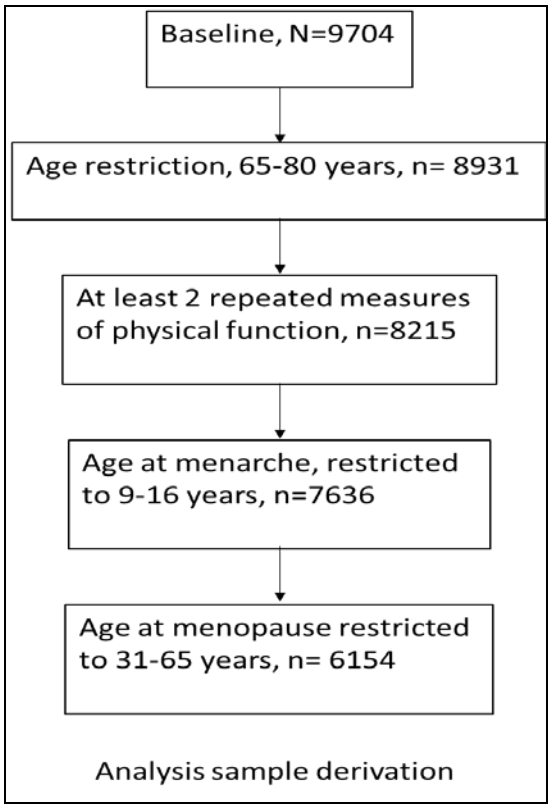
Table 8-5: Association between reproductive factors and rate of change in walk speed

	Walk speed				
	Unadjusted model [OR(95%CI)			Multivariate model [OR (95% CI)]	
	Maintained	Accelerated	Expected	Maintained	Accelerated
Age at menarche (cont.)	1.01(0.97, 1.05)	0.94(0.89, 1.00)	Ref	1.01(0.96, 1.06)	0.96(0.90, 1.04)
Age at menarche			Ref		
9-10	0.80(0.55, 1.17)	0.97(0.57, 1.66)		1.08(0.67, 1.74)	0.67(0.30, 1.48)
11-12	0.91(0.81, 1.03)	1.07(0.90, 1.27)		0.91(0.78, 1.05)	1.05(0.85, 1.30)
13-14 [Ref]	Ref	Ref		Ref	Ref
15-16	0.87(0.74, 1.03)	0.80(0.62, 1.04)		0.85(0.69, 1.04)	0.85(0.69, 1.04)
Parity (cont.)	**1.08(1.03, 1.12)**	1.01(0.95, 1.07)	Ref	1.05(0.99, 1.01)	0.98(0.91, 1.06)
Parity [a]			Ref		
Nulliparous	Ref	Ref		Ref	Ref
1-3	1.20(0.85, 1.69)	0.68(0.45, 1.05)		1.23(0.82, 1.84)	0.72(0.44, 1.18)
>3	**1.50(1.05, 2.15)**	0.71(0.45, 1.13)		1.40(0.92, 2.15)	0.69(0.40, 1.18)
Breast fed [b]	0.98(0.86, 1.12)	1.25(1.02, 1.53)	Ref	1.04(0.89, 1.22)	1.15(0.90, 1.47)
Oral Contraceptive Pill use [c]	**1.31(1.10, 1.70)**	1.14(0.77, 1.67)	Ref	0.91(0.67, 1.23)	1.15(0.73, 1.81)
Age at menopause (cont.)	1.01(0.99, 1.02)	0.99(0.98, 1.02)	Ref	0.99(0.97, 1.01)	0.98(0.96, 1.00)
Menopause (years)			Ref		
<=40	0.94(0.71, 1.23)	0.94(0.63, 1.42)		1.21(0.86, 1.71)	1.21(0.86, 1.71)
41-45	0.88(0.73, 1.07)	1.01(0.77, 1.33)		1.05(0.83, 1.33)	1.29(0.93, 1.79)
46-50	**0.83(0.71, 0.97)**	0.89(0.71, 1.12)		0.95(0.79, 1.14)	0.98(0.74, 1.29)
51-55 [Ref]	Ref	Ref		Ref	Ref
>55	0.86(0.63, 1.17)	0.94(0.60, 1.48)		0.81(0.55, 1.18)	0.92(0.52, 1.61)
Hysterectomy [e]	**0.87(0.77, 0.98)**	0.90(0.75, 1.07)	Ref	0.90(0.77, 1.04)	0.89(0.72, 1.11)
Oophorectomy [f]	0.89(0.78, 1.00)	0.88(0.73, 1.05)	Ref	0.86(0.74, 1.00)	0.89(0.71, 1.11)

Reproductive factors were modelled independently and then adjusted for confounders; *adjusted for age at menarche; [a] Ref - >3; [b] Excluding nulliparous women, Ref – never breastfed; [c] Ref – No Oral contraceptive use; [d] Ref- no HRT; [e] Ref- no hysterectomy; [f] Ref-no oophorectomy

Multivariate model – adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke

8.8 SUPPLEMENTAL TABLE AND FIGURES

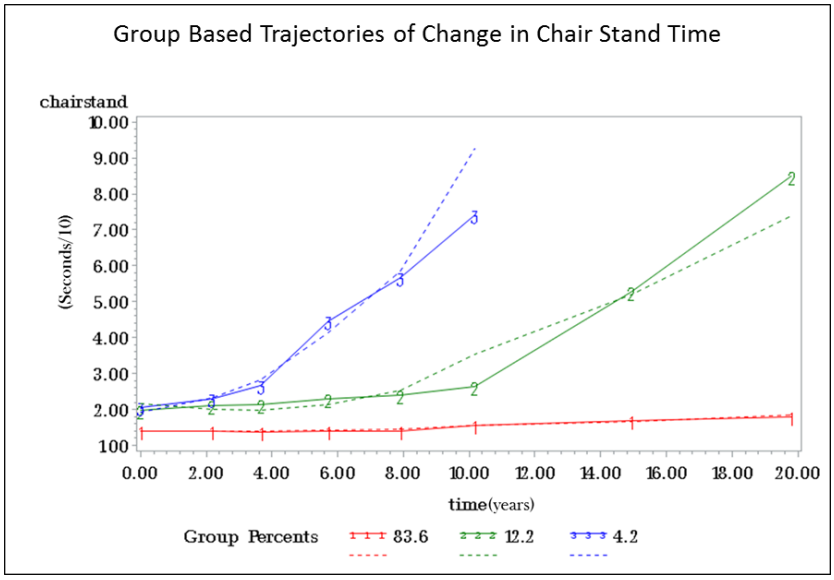


Supplemental Figure 8-2: Analysis sample derivation

Supplemental Table 8-6: Correlations between reproductive factors

	Menarche	Parity	Breastfeeding	OCP	Menopause	Hysterectomy	Oophorectomy
Menarche	1	0.02	**0.04**	**-0.04**	-0.01	**-0.03**	-0.02
Parity		1	**0.17**	**0.08**	**0.07**	**-0.04**	**-0.09**
Breastfeeding			1	**0.05**	**0.04**	0.01	-0.01
OCP				1	**0.08**	-0.01	-0.01
Menopause					1	N/A	**-0.06**
HRT						**0.04**	**0.06**
Hysterectomy						1	**0.79**
Oophorectomy							1

Bold indicates significance at $p<0.05$.



Supplemental Figure 8-3: Group based trajectories showing maintained (group 1), expected (group 2) and accelerated (group 3) change in chair stand time

9.0 PAPER 2: ASSOCIATION BETWEEN REPRODUCTIVE FACTORS AND PREVALENT AND INCIDENT RADIOGRAPHIC HIP OSTEOARTHRITIS

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9.1 ABSTRACT

Objective: To estimate the association between reproductive history and risk of prevalent and incident Radiographic Hip OA (RHOA) in older women.

Methods: Participants from the Study of Osteoporotic fractures with pelvic radiographs obtained at visit 1 and visit 5 (mean 8.3 years apart) were included in the study. RHOA was defined as presence of Minimal Joint Space ≤2.5mm at visit 1 (prevalent), visit 5 (incident) and total (visit 1+5). Information on reproductive history including age at menarche, parity, breastfeeding, age at menopause, hysterectomy and oophorectomy were collected from questionnaires. Women who reported extremes of age at menarche (<10 or >17) and/or menopause (<30 or >58) were excluded to limit bias and increase generalizability. Odds of RHOA and 95% confidence intervals for prevalent, incident and total RHOA were estimated using logistic regression. All reproductive factors were assessed independently – first by bi-variately and then adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke.

Results: Final study population consisted of 4502 women [mean(SD) age=70.7(4.7) years, BMI = 26.5(4.5) kg/m^2]. Compared to women with 2 children, women with 1 child had greater odds of incident [OR(95% CI) = 1.42(1.05, 1.94)] and total RHOA [1.32(1.08, 1.61)], independent of the covariates. Women with 4 children had significantly lower odds of total RHOA in unadjusted models [0.79(0.63, 0.99)], independent of the covariates. Breastfeeding was associated with lower odds of incident RHOA [0.76(0.61, 0.94)]. No significant associations were noted with other reproductive factors.

Conclusion: women with greater parity and a history breastfeeding were associated with a lower risk of RHOA in older Caucasian women, independent of age, BMI, education and physical

activity. Further research is required to understand underlying mechanisms and extend the findings to ethnically diverse populations

9.2 INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder in the United States. In 2010, OA accounted for about 6.7 million hospitalizations and 21.7 million ambulatory physician visits[291]. Compared to men, women have 45% greater risk of incident knee and 36% greater risk of radiographic hip OA (RHOA)[120]. Coupled with the longer life expectancy, OA in women, is associated with greater morbidity[292], poor quality of life[293], and high economic burden[294]. Determining risk factor for OA is an essential step to be able to design intervention studies that could delay the onset or reduce the severity of symptomatic OA.

Few risk factors have been established in the development of OA. Besides female gender and the wear and tear of aging, increased mechanical load on the joints (obesity)[140], joint injury and low Socio-Economic Status (SES) have been implied as major risk factors[295]. In some individuals, a component of inflammation may also be associated with the development or progression of OA[165]. Local fat hormones like leptin and adiponectin could mediate the inflammatory effect. While leptin has shown direct association with the severity of cartilage degeneration[296], adiponectin may inhibit the progression of osteoarthritis[297].

Despite a greater predilection for OA in women, little is understood about the role of sex-specific factors, particularly the reproductive health. Early age at menarche[298], greater parity[136], menopausal transition[137] and early bilateral oophorectomy[138] have been shown to be associated with obesity/overweight. Conversely, exclusive breastfeeding aides in postpartum weight loss

and return to pre-pregnancy weight[299]. Low ovarian function and low estrogen levels are also associated with greater inflammation[160]. Put together, these findings suggest a possible association between reproductive health and osteoarthritis via biomechanical and inflammatory pathways.

Few studies have evaluated associations between certain reproductive factors and risk of replacement or OA, predominantly at the knee. The Million Women Study reported that women with early menarche (≤ 11years) had a greater risk of hip (9%) and knee (15%) replacement compared to women with menarche at age 12, independent of age and body mass index (BMI)[201]. Wise et al, reported that greater parity (>=3 children) was associated with over 2.5 times greater risk of knee OA and knee replacement compared to one birth, independent of age and BMI[204]. Arden et al, suggested that hormone therapy (HT) may have a protective effect on osteoarthritis[208]. While some studies have supported this hypothesis[207], the Women's Health Initiative showed no association between HT and hip or knee replacement[209]. Some[207] but not all[201] studies demonstrated an association between age at menopause and OA risk. Overall, the association between reproductive health and OA is poorly understood. Many of these studies were limited by cross-sectional design or short duration of follow up, self-reported OA, and/or failed to account for the potential effect of important confounding variables like BMI.

Female reproductive health acts as the custodian of health and disease in later life[300]. It is important to understand the impact of reproductive health on OA in later life. The existing literature is largely limited to changes at the knee. To the best of our knowledge, associations between multiple reproductive factors and risk of Hip OA in older women have not been previously assessed. We hypothesized that women with early age at menarche, greater parity, non-breastfeeding, early age at menopause and non-HT users are at a greater risk of prevalent

and incident RHOA. Using the data from the Study of Osteoporotic Fractures, we aimed to understand these associations, independent of potential confounders.

9.3 METHODS

Study population:

Study of Osteoporotic Fractures (SOF) was a multi-center longitudinal study of women designed to understand the risk factors for osteoporotic fractures[258]. Women were recruited from 4 centers across the country (Baltimore, MD; Monongahela Valley near Pittsburgh, PA; Minneapolis, MN; and Portland, OR). Eligibility criteria included absence of bilateral hip replacement and ability to walk without assistance. At baseline (1986-1988), 9704 ambulatory women aged 65 years or older were enrolled. The participants were followed up biennially for over 20 years (year 20 exam 2006-08) with clinical visits and examinations. At baseline, only Caucasian women (N=9702) were included due to their higher risk of hip fractures. The study protocol was approved by the institutional review board of all sites and participants provided written informed consent.

The Hip Osteoarthritis cohort was an ancillary study to SOF. OA status was determined from pelvic radiographs. Radiographs were obtained at 2 visits – baseline and again at visit 5(1995-96). Radiographs from both baseline and visit 5 were available on 5987 women. At baseline, radiographs were obtained on all participants (n=9704). At visit 5, radiographs were obtained only on 61% of the baseline cohort (7847 women returned at visit 5 (80% of baseline)). Additional radiographs were obtained at home visits using portable X-ray machines in women who were unable to visit the clinic (n=467)[301]. As extremes of menarche and menopause are

known to be underlying markers for adverse health, the study was limited to menarche between 10-17 years (n=371) and menopause between 30-58 years (n=1113).

Of those who were excluded, 436 women had RHOA at baseline. The mean age and BMI of the excluded population was 71.3 years and 26.8 kg/m^2 respectively. The age at menarche and menopause ranged from 9-24 years and 17-62 years respectively. Thus, to improve the internal validity of our results, these women were excluded.

Study measures:

Radiographic Hip OA: Supine antero-posterior radiographs with 40 inches between the film and the focus were obtained at baseline and visit 5. The hips were internally rotated (15-30 degrees) with the X-ray positioned on the pubis symphysis[302]. The presence of RHOA was determined from radiographs using an atlas[303]. While many definitions for RHOA were available, for the current study we defined RHOA (Yes/No) based on Minimal Joint Space (MJS) $\leq$2.5mm[258]. MJS was measured as the shortest distance between the acetabulum and margin of the femoral head[258]. This definition has been previously shown to have high reproducibility[27] and high inter-reader reliability (κ statistic =0.71)[258].

Reproductive factors: Multiple reproductive factors across the life course were included to comprehensively characterize a woman's reproductive history. Age at menarche and menopause was self-reported as age at first and last menstrual periods respectively. During the reproductive period, information on parity (total number of live births), breast feeding (yes/no) and use of birth control pills (yes/no) was collected. Use of hormone therapy (HT) was self-reported as the use of oral estrogen as current, past or no HT use. Surgical removal of uterus (hysterectomy) and ovaries (oophorectomy) were recorded. All reproductive data except age at menarche (visit 2) was collected at baseline. Age at menarche, parity and age at menopause were

considered as continuous and categorical variables. Age at menarche was classified as 10-11, 12-13, 14-15 and 16-17 years. Age at menopause was classified in 5-year intervals as ≤40, 41-45, 46-50, 51-55 and >55 years. Parity was categorized as nulliparous (0), 1, 2, 3, 4 and 5-8 live births.

Other measurements:

Factors impacting the risk of RHOA were considered, including age at baseline (years), education, and BMI. Education was obtained from self-reported highest grade/year of school completed. BMI (kg/m^2) was calculated as weight (kilograms) divided by height square (meters). Smoking status was evaluated as never or ever smoker. Alcohol consumption was self-reported as total number of drinks per day in the last 30 days. A modified Harvard alumni questionnaire was used to assess physical activity[262]. Frequency and distance walked every day in city blocks or its equivalent was self-reported. In addition, duration of activities like gardening, dancing, swimming, aerobics etc. in the last year were reported. Physical activity was calculated as a weighted measure of average total kilocalories per week over the past year[304]. Diabetes and stroke were self-reported by the participants. Concurrent information on all factors except physical activity and alcohol consumption (from baseline) were used in the analyses.

Statistical methods:

Participants with data on reproductive factors and radiological RHOA were included in the study. Differences in characteristics of women with prevalent, incident and no RHOA was assessed using ANOVA and chi-squared tests for continuous and categorical variables respectively. Logistic regression was used to assess the association between the reproductive factors and RHOA. The odds of prevalent and incident RHOA were assessed at baseline and visit 5 respectively. Total RHOA was assessed as odds of all RHOA (incident and prevalent) at visit

5. The reproductive factors were assessed independently – first bi-variately and then adjusted for covariates (age, education, BMI, smoking, alcohol consumption, physical activity, diabetes and stroke) in the final model. Age at menarche, parity, and age at menopause were assessed both as continuous and categorical variables. Age at menarche was categorized by 2-year intervals. Parity was classified as nulliparous, 1, 2, 3, 4 and 5-8 children. Age at menopause was categorized by 5-year intervals as ≤40, 41-45, 46-50, 51-55 and >55 years. Women who reported hysterectomy were excluded from assessment of age at menopause due to limitations in accurately estimating age at menopause.

9.4 RESULTS

Characteristics of the population by OA status are summarized in Table 9-1. At baseline, 1265 women had prevalent RHOA with an additional 531 women developing RHOA by visit 5 (incident). By visit 5, 2706 women remained free of RHOA. Women with prevalent RHOA at baseline were significantly older, shorter and had fewer years of schooling compared to women in incident and no RHOA groups. No significant differences were noted for BMI, smoking, alcohol consumption, diabetes or stroke between prevalent, incident and no RHOA sub-cohorts. Interestingly, women without RHOA women had significantly greater parity compared to the other 2 groups with fewer nulliparous women and greater proportion of women with 4 children or more. Significant differences in parity were noted between prevalent (mean parity = 2.67(1.66)) and no RHOA (2.80(1.52)) populations. No significant differences were noted with any of the other reproductive factors by OA status.

Prevalent RHOA: In unadjusted models (table 9-2), greater parity was associated with 5% lower odds of RHOA [OR(95% CI) = 0.95(0.91, 0.99)]. However, no significant associations were noted using parity as a categorical variable. Menopause ≤40 years [1.28(1.01, 1.63)] was associated with 1.28 times greater odds of RHOA. HT use [0.87(0.76, 0.99)] was associated with 13% lower odds of RHOA. However, these associations were explained by age and education. No significant associations were noted with other reproductive factors.

Incident RHOA: Compared to women with 2 children, women with 1 child [1.44(1.06, 1.95)] had a 44% greater odds of incident RHOA in the unadjusted models. After accounting for potential confounders, the association remained significant [1.42(1.05, 1.94)]. No significant associations were noted with the other parity categories in the unadjusted or final models. Breast feeding [0.80(0.65, 0.99] was associated with 20% lower odds of incident RHOA. In the final model, a history of breastfeeding was associated with 24% lower odds of RHOA [0.76(0.61, 0.94]. No associations were noted with age at menarche, oral contraceptive pill use, HT use, age at menopause, hysterectomy or oophorectomy and incident RHOA.

Total RHOA: Combining women with either prevalent or incident RHOA (N= 1796) showed similar associations with parity, i.e., greater parity [0.95(0.91, 0.99)]. Parity was associated with 5% decreased odds of RHOA in the unadjusted models. The association was explained by accounting for age. Compared to parity of 2, women with 1 child [1.36(1.12, 1.66)] had 36% greater odds of RHOA, compared to women with 2 children. This association attenuated but remained significant in the final model [1.32(1.08, 1.61)]. Interestingly, compared to women with 2 children, women with 4 children had a 24% [0.76(0.61, 0.95)] decreased odds of OA in the unadjusted model. This association attenuated to 21% [0.79(0.63, 0.99)] after

adjustment for confounders. No associations were noted with age at menarche, breastfeeding, HT use, age at menopause or hysterectomy/oophorectomy and total RHOA.

9.5 DISCUSSION

Our study showed associations between early life reproductive factors like parity and breastfeeding on the development of RHOA in older age. Greater parity measured as a continuous variable was associated with lower risk of both prevalent and total RHOA. Compared to the referent (parity = 2), women having 1 child had greater risk of incident (42%) and total (32%) RHOA, while having 4 children had a lower risk of total (21%) RHOA. These associations were independent of age, education, BMI, smoking, alcohol consumption, physical activity, diabetes and stroke. Although not all parity groups reached significance, it is likely that the association between parity and risk of RHOA is non-linear with greatest risk among women with 1 child and lowest for women with 4 children. Additionally, history of breastfeeding was associated with 24% lower risk of incident RHOA independent of confounders and parity (results not shown). No associations were noted with the other reproductive factors. To the best of our knowledge, no other study has assessed the association between reproductive factors and RHOA in older women.

Current literature is limited to knee OA and knee/hip replacement. In a prospective study of middle aged women (mean age = 56 years) from the Million Women's Study, Lui et al[201], reported a 2% and 8% per birth increase in risk of hip and knee replacement respectively. Compared to nulliparous women, women with 4 or more children had a 10% greater risk of hip replacement. No significant associations were noted for women having 1, 2 or 3 children.

Conversely, 21% - 46% increased risk of knee replacement was noted for women with parity of 1- 4 or more. Women who underwent replacement were more likely to be older and of low SES. The authors attributed these associations largely to obesity and increases in BMI with greater parity and low SES. However, the due to limited information, the authors could not assess the association with risk of osteoarthritis, nor account for confounding effects of education and physical activity. Wise et al., studied women from the Multicenter Osteoarthritis Study cohort (MOST) (mean age = 62.6 years) and extended the findings to knee OA. Knee OA was assessed from X-ray radiographs using Kellgren/Lawrence grade ≥ 2. They reported that greater parity was associated with a greater risk of both incident radiologic knee OA and knee replacement[204]. These associations were independent of many confounders including BMI, pain, occupation, hormone therapy and any knee injury. The authors proposed a multi-hit model and suggested a combination of obesity and lifestyle factors resulting in an increased risk of OA. Increase in BMI with parity[203], and additional insults from caring for children during childbearing years could manifest as knee OA in older age. A recent Korean study (≥50 years) reported a stronger association between knee OA and parity in women who had undergone abortion (pregnancy ≤ 7 months)[305] [Knee OA, from X-ray radiographs, defined as Kellgren/Lawrence grade of 1 or more]. In addition, they also reported but failed to explain why the association was weaker in women with greater number of abortions. They hypothesized that sudden physical/hormonal changes from abortions could exert greater stress on cartilage than pregnancy only. Many other studies have demonstrated no association between parity and knee OA[211,212]. A few different reasons may be for the contradiction with existing studies on knee OA. The Million women study had limited information on other causes of RHOA like occupation history and joint injury. In addition to degenerative joint diseases like OA, repeated injury to the joint and occupation are

important risk factors for joint replacement[204]. Interestingly, studies in the United States have reported lower rates of joint replacement in lower SES men and women, potentially due to disparity in access to care[202]. This observation is contrary to England and Scotland where the healthcare system is centralized[306]. The MOST study included women with risk factors for knee OA including obesity, knee injury, and knee pain or stiffness in the last 30 days. Thus, it is likely that the sample was not representative of the general population[204].

In contrast to the findings at the knee joint, our results demonstrated a decreased risk of RHOA in older women with greater parity and breastfeeding. Biomechanical changes during pregnancy may be responsible for the differential association of parity between hip and knee OA. With the increase in weight during pregnancy, the center of gravity shifts upwards and forwards[307,308]. To control the center of gravity, the spine is thrown into lordosis (bending), resulting in greater biomechanical insults[307]. Increase in the lumbar lordosis and the anterior pelvis tilt could move the move the center of gravity to behind the hip joint and anterior to the knee joint[309]. Such a shift may could result in increased load at the knee joint[310] and slightly reduced load at the hip. In addition, the hormone relaxin, may produce ligament laxity in the pelvis and other joints[311] during late pregnancy. Relaxin, along with estrogen has shown to decrease inflammation in human cells[312] and arthritis induced rat models[313]. Additionally, in a small study of 68 women, Calguneri et al, demonstrated that with greater parity, correlation between relaxin and laxity was higher[314]. Put together, relaxin may play an important role in the association between greater parity and lower risk of RHOA via the inflammatory pathway. Similar mechanisms may be attributable to the association between breastfeeding and RHOA. Anti-inflammatory advantages of breastfeeding are well documented[163] and may be protective

against RHOA. No information on duration of breastfeeding was available to assess this association further.

It may be interesting to note that of all the reproductive factors, only parity differed significantly across the 3 RHOA groups. It is also important to note that SOF participants were relatively healthy and well-functioning at baseline, partly due to how the study was designed. Although greater parity was associated with slightly greater BMI, no significant association was noted between concurrent BMI and risk of RHOA. In addition, the sub-populations by parity groups were likely very small to demonstrate significant results. Nevertheless, a significant non-linear trend ($p<0.01$) between parity groups and prevalent, incident and total RHOA were noted. Interestingly, no associations were noted between HT use, age at HT initiation or duration of HT use.

The study had many strengths. The SOF study collected information on a large community based cohort of older women, around the age of peak incidence of RHOA[198]. We had information on a large number reproductive factors. We had no information on weight gain with each pregnancy. The study population was limited to Caucasian women. The results therefore, may not be generalizable to other race/ethnic groups. Radiographs were available only at baseline and visit 5. Thus, the timing of "incidence" of hip OA may not be accurately assessed. The reproductive history was assessed from questionnaires and maybe subject to recall bias. Simultaneous comparison of many reproductive factors may pose a problem of multiplicity. Nonetheless, to the best of our knowledge, no other studies have assessed have assessed the associations between reproductive history and radiologically defined RHOA.

In summary, women with greater parity and a history breastfeeding were associated with a lower risk of RHOA in older Caucasian women, independent of age, BMI, education and

physical activity. Future work should consider potential mechanisms linking parity and breastfeeding with RHOA (e.g., biomechanical changes during pregnancy and anti-inflammatory properties of breastfeeding) as well as extend this work to more ethnically diverse study populations.

9.6 TABLES

Table 9-1: Concurrent characteristics of the population by OA status

	Prevalent Hip OA (visit 1) (N=1265)	**Incident Hip OA (visit 5) (N=531)**	**No Hip OA (visit 5) (N=2706)**	**p-value**
Age (years)	71.52(5.03)	71.08(4.83)	70.3(4.41)	**<0.0001**
Education (years)	12.59(2.86)	13.13(2.69)	12.85(2.73)	**0.0004**
Height (cm)	158.45(6.17)	159.9(5.89)	159.69(5.86)	**<0.0001**
Weight (kg)	66.79(12.66)	67.68(11.65)	67.52(12.09)	0.17
BMI (kg/m^2)	26.59(4.73)	26.48(4.37)	26.47(4.45)	0.71
Ever smoker N(%)	455(36.14)	199(37.69)	1044(38.64)	0.31
Alcohol consumption (drinks/week adjusted for atypical drinks)*	1.82(3.91)	2.00(3.91)	1.88(3.78)	0.64
Physical activity (kcal/week last year)	1649.90(1653.11)	1805.46(1821.63)	1767.11(1589.47)	0.07
Diabetes N(%)	63(4.98)	24(4.53)	140(5.19)	0.81
Age at menarche (years)	13.06(1.37)	12.96(1.37)	13.02(1.37)	0.41
Menarche (years) N(%)				0.47
10-11	152(12.02)	62(11.68)	319(11.79)	
12-13	675(53.36)	310(58.38)	1504(55.58)	
14-15	371(29.33)	129(24.29)	735(27.16)	
16-17	67(5.30)	30(5.65)	148(5.47)	
Parity	2.67(1.66)	2.67(1.63)	2.8(1.52)	**0.0351**
Parity N(%)**				**0.0015**
Nulliparous	38(3.56)	13(2.97)	62(2.70)	
1	194(18.20)	82(18.72)	312(13.58)	
2	353(33.11)	136(31.05)	743(32.33)	
3	236(22.14)	113(25.80)	569(24.76)	
4	122(11.44)	46(10.50)	344(14.97)	
5-8	123(11.54)	48(10.96)	268(11.66)	
Breast fed N(%)*	736(69.04)	285(65.07)	1604(69.86)	0.14
Oral contraceptive user N(%)	57(4.52)	25(4.71)	143(5.29)	0.55
HT use, ever, N(%)	495(39.70)	226(43.13)	1155(43.19)	0.11
Age at HT initiation (years)	50.37(8.56)	49.42(7.28)	50.44(7.91)	0.23
Age at HT initiation, N(%)				0.16
≤50 years	280(59.70)	138(64.19)	642(57.42)	
>50 years	189(40.30)	77(35.81)	476(42.58)	
Duration of HT use (years)	7.50(8.23)	8.37(8.55)	7.29(7.74)	0.19
Duration HT use, N(%)				0.16
<=5 years	242(51.49)	95(44.19)	571(50.89)	
>5 years	228(48.51)	120(55.81)	551(49.11)	
Age at menopause (years)	48.14(5.31)	48.38(4.81)	48.3(5)	0.56
Menopause (years) N(%)				0.34
<=40	136(10.75)	39(7.34)	235(8.68)	
41-45	223(17.63)	107(20.15)	537(19.84)	
46-50	492(38.89)	212(39.92)	1045(38.62)	
51-55	368(29.09)	156(29.38)	795(29.38)	
>55	46(3.64)	17(3.20)	94(3.47)	
Hysterectomy N(%)	346(27.35)	140(26.37)	685(25.32)	0.39
Oophorectomy N(%)	305(24.72)	127(24.42)	657(24.92)	0.97

*significant difference between prevalent vs no RHOA; *excluding nulliparous women

Table 9-2: Association between reproductive factors and risk of hip OA

		Prevalent Hip OA (N=1265)		Incident Hip OA (N=531)		Total hip OA (N=1796)	
		Unadjusted [OR (95% CI)]	Fully adjusted[1] [OR (95% CI)]	Unadjusted [OR (95% CI)]	Fully adjusted[1] [OR (95% CI)]	Unadjusted [OR (95% CI)]	Fully adjusted[1] [OR (95% CI)]
Age at menarche	Continuous	1.03(0.98, 1.08)	1.01(0.96, 1.06)	0.97(0.91, 1.04)	0.98(0.91, 1.05)	1.01(0.96,1.05)	1.00(0.96, 1.05)
Age at menarche	10-11 12-13 [ref] 14-15 16-17	1.07(0.87, 1.32) Ref 1.15(0.99, 1.34) 1.01(0.75, 1.36)	1.06(0.86, 1.31) Ref 1.10(0.94,1.28) 0.95(0.71, 1.29)	0.94(0.70, 1.27) Ref 0.85(0.68, 1.07) 0.98(0.65, 1.48)	0.92(0.68, 1.24) Ref 0.83(0.66, 1.05) 1.02(0.67)	1.04(0.86, 1.25) Ref 1.04(0.91, 1.20) 0.99(0.76, 1.30)	1.02(0.84, 1.24) Ref 1.01(0.87, 1.16) 0.97(0.74, 1.28)
Parity	Continuous	**0.95(0.91, 0.99)**	0.97(0.92, 1.01)	0.94(0.88, 1.01)	0.96(0.90, 1.03)	**0.95(0.91, 0.99)**	0.97(0.93, 1.01)
Parity	0 1 2 [ref] 3 4 5-8	1.26(0.84, 1.90) 1.23(0.99, 1.52) Ref 0.86(0.71, 1.05) **0.78(0.61, 0.99)** 0.97(0.76, 1.24)	1.30(0.85, 1.96) 1.17(0.95, 1.45) Ref 0.88(0.72, 1.07) 0.81(0.64, 1.04) 1.01(1.03, 1.06)	1.15(0.61, 2.14) **1.44(1.06, 1.95)** Ref 1.09(0.83, 1,43) 0.73(0.51, 1.05) 0.98(0.68, 1.40)	1.14(0.60, 2.15) **1.42(1.05, 1.94)** Ref 1.13(0.85, 1.48) 0.74(0.51, 1.07) 1.07(0.51, 1.07)	1.27(0.86, 1.88) **1.36(1.12, 1.66)** Ref 0.94(0.79, 1.12) **0.76(0.61, 0.95)** 1.00(0.80, 1.26)	1.29(0.87, 1.92) **1.32(1.08, 1.61)** Ref 0.97(0.81, 1.16) **0.79(0.63, 0.99)** 1.07(0.85, 1.34)
Breast feeding	Yes No [ref]	0.99(0.86, 1.16) Ref	0.94(0.81, 1.10) Ref	**0.80(0.65, 0.99)** Ref	**0.76(0.61, 0.94)** Ref	0.92(0.80, 1.06) Ref	0.87(0.75, 1.00) Ref
Oral contraceptive use	Ever Never[ref]	0.86(0.64, 1.18) Ref	1.07(0.78, 1.46) Ref	0.88(0.57, 1.37) Ref	0.97(0.62, 1.51) Ref	0.86(0.65, 1.14) Ref	1.03(0.77, 1.37) Ref
Hormone Therapy use	Ever Never [ref]	**0.87(0.76, 0.99)** Ref	0.96(0.83, 1.10) Ref	1.00(0.83, 1.21) Ref	1.02(0.84, 1.24) Ref	0.92(0.81, 1.04) Ref	0.98(0.87, 1.12) Ref
Age at menopause	Continuous	0.99(0.98, 1.01)	0.99(0.98, 1.01)	1.00(0.98, 1.02)	1.00(0.98, 1.02)	1.00(0.99, 1.01)	1.00(0.99, 1.01)
Age at menopause	<=40 41-45 46-50 51-55 [ref] >55	**1.28(1.01, 1.63)** 0.90(0.74, 1.09) 1.01(0.86, 1.19) Ref 1.07(0.74, 1.54)	1.18(0.92, 1.50) 0.86(0.71, 1.05) 0.97(0.82, 1.14) Ref 1.07(0.74, 1.55)	0.87(0.59, 1.27) 1.03(0.79, 1.36) 1.05(0.83, 1.31) Ref 0.94(0.54, 1.61)	0.87(0.59, 1.28) 1.03(0.78, 1.35) 1.04(0.83, 1.31) Ref 0.97(0.56, 1.68)	1.12(0.89, 1.40) 0.93(0.78, 1.12) 1.03(0.89, 1.19) Ref 1.03(0.74, 1.45)	1.10(0.87, 1.38) 0.91(0.76, 1.09) 1.00(0.86, 1.16) Ref 1.06(0.75, 1.49)
Hysterectomy	Yes No [ref]	1.10(0.95, 1.27) Ref	1.10(0.95,1.28) Ref	1.05(0.85, 1.30) Ref	1.06(0.74, 1.83) Ref	1.09(0.95, 1.24) Ref	1.09(0.95, 1.25) Ref
Oophorectomy	Yes No [ref]	0.99(0.85, 1.16) Ref	1.01(0.87, 1.18) Ref	0.98(0.79, 1.22) Ref	1.00(0.80, 1.25) Ref	0.98(0.85, 1.13) Ref	1.01(0.87, 1.16) Ref

[1]Fully adjusted model – adjusted for age, BMI, education, smoking, alcohol consumption, physical activity, diabetes and stroke
*adjusted for age at menarche; [a] Ref - >3; [b] Ref – never breastfed; [c] Ref – No Oral contraceptive use; [d] Ref- no HRT; [e] Ref- no hysterectomy; [f] Ref-no oophorectomy

10.0 PAPER 3: ASSOCIATION BETWEEN REPRODUCTIVE FACTORS, SEX HORMONES AND CHANGE IN HIP GEOMETRY ACROSS THE MENOPAUSAL TRANSITION: STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

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10.1 ABSTRACT

Objective: To understand the associations of reproductive factors and sex-hormones with hip geometry [from Hip Structural Analysis (HSA)] relative to the final menstrual period (FMP).

Methods: At baseline, 1947 women from SWAN bone cohort were included. For longitudinal analyses (spanning across 10 years), women with information on final menstrual period (FMP) and more than 1 DXA scan were included (N=900). Hormone therapy users were excluded from the analyses. HSA parameters at femoral narrow neck [Bone Mineral Density (BMD), Cross Sectional Area (CSA), Section Modulus (SM), Outer Diameter (OD) and Buckling ratio (BR)] were obtained from 2D DXA scans and normalised to baseline values. Reproductive factors (menarche, parity, breastfeeding, age at first and last birth, and OC use) were self-reported. Sex hormones [estradiol (E2), Follicle Stimulating Hormone (FSH), testosterone (T) and Sex-Hormone Binding Globulin (SHBG)] were measured from blood samples drawn annually. Associations between reproductive factors and pre-menopausal HSA were assess using linear regression models. Mixed effects linear model with random slopes were used to estimate the rate of change in HSA. Changes in HSA were assessed over 3 phases, 5 to 2 years before FMP (pre-transmenopausal), 2 before to 1 years after FMP (transmenopausal), 1 to 5 years after FMP (postmenopausal). Reproductive factors and sex-hormones were assessed independently and subsequently adjusted for baseline age, race, education, smoking, physical activity, and time varing BMI and diabetes status.

Results: At baseline, later age at last birth and OC use were associated with greater CSA and lower OD levels respectively. Over the 10 year period, only breastfeeding was associated with accelerated decline in BMD (-2.21%/10 years), and CSA(-1.82%) and accelerated increase in OD(0.59%) and BR(0.25%). Doubling of FSH and SHBG were associated with faster loss of

BMD, CSA and SM with accelerated increase in BR cumulatively. However, these associations were not consistent across all phases. These associations were independent of covariates. Associations with SHBG were independent of E2 or T levels.

Conclusions: Doubling of FSH and SHBG were associated with unfavourable HSA changes cumulatively but not all phases of the menopausal transition. Further research to understand the underlying mechanisms could help design targetted interventions to prevent bone loss and fractures in later life.

10.2 INTRODUCTION

Bones undergo constant modelling and remodeling across female reproductive life[220]. Reproductive events including menarche[315], pregnancy[316,317], breastfeeding[316,317] and menopause[318] are endocrinologically charged and bear significant effects on bone health. Nearly a third of peak bone mineral density (BMD) is gained around menarcheal age[220]. Pregnancy and lactation represent periods of increased calcium demand, with increase in intestinal calcium absorption and bone resorption and decrease in calcium excretion to accommodate this need[316,317,319,320]. Decline in estradiol (E2) and rise in follicle stimulating hormone (FSH) over the Menopausal Transition (MT), have been shown to be associated with accelerated loss of lumbar spine BMD starting 1 year before to 2 years after final menstrual period (FMP)[129]. Thus increasing the risk of fractures in the post-menopausal period. Hip fracture is of the most common osteoporotic fractures in older women, with significant functional limitations and high 1-year mortality (>20%) following it[321,322].

However, fracture risk and bone strength depends on both density and bone quality, i.e., bone microarchitecture and geometry[323]. Areal BMD (aBMD), a 2 dimensional measure of bone, fails to account for the bone size and geometry. These structural components, may be a predictor of fracture risk in postmenopausal women[324]. Some[227], but not all[325] studies have shown this association to be independent of aBMD. While the impact of female reproductive health on aBMD have been well studied[317,318,326], few studies have assessed the association between reproductive health and bone geometry. Fels Longitudinal Study assessed metacarpal hip geometry from radiographs and reported that later age at menarche was associated with greater bone strength in young adulthood.This association was independent of prepubertal bone strength[315]. A cross-sectional study of 87 women in India (aged 55-79 years) reported inverse association between parity and cross sectional area (CSA) at narrow neck of the femur[232]. A longitudinal study of lactating mothers reported significant decline in femoral BMD and CSA from 2 weeks postpartum to peak lactation, independent of BMI[237]. Longer years of menstruation in postmenopausal Chinese women (mean age = 59.6 years) was also associated with more stable bone geometry[245]. However, little is known about the effect of these reproductive factors on change in hip geometry during the menopausal transition.

Previous findings from Study of Women's Health Across the Nation (SWAN), has shown that during the menopausal transition (MT), change in hip geometry parallels change in aBMD[127] and Femoral Neck (FN) strength[243]. Hip geometry, measured by Hip Structural Analysis (HSA)[230], showed accelerated change starting 2 years before to 1 year after menopause which continued for 4 more years[244]. Accelerated increase in Buckling Ratio (BR) and Outer Diameter (OD), coupled with accelerated loss of BMD, Cross Sectional Area (CSA) and Section Modulus (SM) during the MT could result in cortical instability. Change in sex-steroid hormones were significantly associated with the change in aBMD at the lumbar spine. However the effect of

reproductive factors and sex-steroid hormones on the HSA change during MT is unknown. Using data from the SWAN, we assessed the associations between reproductive factors and sex-steroid hormones with pre-menopausal HSA levels and the rate of change HSA during the MT in midlife women.

10.3 METHODS

Study population:

SWAN is an ongoing, community based, multi-center, longitudinal study of midlife women designed to study the biological, physiological and psycho-social changes during their middle years[327]. The study was started in 1994 and is currently in its 22nd year. The study recruited 3302 participants from 7 sites across the US – Ann Arbor, MI; Boston, MA; Oakland, CA Chicago, IL; Los Angeles, CA; Newark, NJ & Pittsburgh, PA. Women were eligible to participate in the study if they had - (1) at least 1 menstrual period within the past 3 months; (2) not pregnant or breast feeding; (3) an intact uterus and at least 1 ovary; (4) no hormone therapy use within the past 3 months. The study protocol was approved by the institutional review board and informed consent was obtained from all the participants.

Only 5 out of 7 sites - Los Angeles, CA; Ann Arbor, MI; Boston, MA; Oakland, CA; & Pittsburgh, PA sites were included in the bone cohort (N=2335 from visit 1 - visit3). Black women were recruited from Ann Arbor, Boston, Chicago and Pittsburgh sites. Japanese and Chinese women were recruited from Los Angeles and Oakland sites respectively. White women were enrolled at all the sites. Women could participate in the bone study if they were (1) enrolled in the SWAN main cohort (2) weighed <136 kg (machine limit) and (3) provided informed

consent. As an extension to the bone study, hip bone strength was also measured across the menopausal transition. For the current study, baseline population included 1947 women with information on reproductive factors. Women who had a date for the final menstrual period (FMP) were included in longitudinal analyses. Additionally, women were excluded if they reported hormone therapy use or had only 1 DXA scan in 10 years (n=27). The longitudinal evaluation included 900 women (supplementary figure 10-1).

Compared to the FMP cohort, the women who were excluded were slightly younger and heavier at baseline [mean(SD) age of 46(2.7)years, BMI 27.59(6.8)kg/m^2]. Nearly 81% of this population had more than high school education, compared to ~76% in the FMP cohort. At baseline, women who were excluded had slightly higher BMD, CSA and SM and lower OD and BR, compared to the FMP cohort. Interestingly, those who were excluded had lower levels of E2, FSH, T and SHBG at baseline.

Study measures:

DXA scans:

Femoral Neck (FN) DXA scans were obtained at every clinic visit using OsteoDyne's Hip Positioner System (Osteodyne Inc, NC) and Hologic QDR scanners (Hologic, Inc., Bedford, MA). The Oakland and Pittsburgh sites upgraded from 2000 to 4500 Hologic scanner at visit 8. The other 3 sites used 4500A scanner model from baseline to visit 10. Scans on 40 women from the 2000 and 4500A machines were used to develop calibration equations. In collaboration with Synarc Inc, quality check was conducted through everyday phantom measurements, central review of scans flagged for problems, cross site calibration of scans with anthropometric spine

standard biannually, local review of all scans and central review of random scans (5%). FN measurement variability in vivo was 0.016 g/cm^2(2.2%)[318].

Hip geometry (HSA):

HSA was measured from de-identified DXA scans using software developed at Johns Hopkins School of Medicine[231]. HSA software uses bone mass image from the DXA scan to produce areal mass (g/cm^2) using pixel values[231]. It analyzes the geometry at 3 locations on the femoral bone –shaft, inter-trochanteric and Narrow Neck (NN) regions. For the current analyses only NN measures were used. NN represents the narrowest diameter of the FN. Five measures of HSA at the NN were included – Bone Mineral Density(BMD), Cross Sectional Area (CSA), Outer Diameter (OD), Section Modulus (SM) and Buckling Ratio (BR). BMD was measured as the mean pixels in the region profiles. CSA was the cortical equivalent of cross-sectional bone surface area not including the soft tissue and trabecular space. OD was measured as width of mass profile after blur correction. SM, an indicator of maximum bending stress was measured as a composite measure of cross sectional moment of inertia and distance from outer cortex to the mass center. BR is a measure of cortical stability in buckling. It was measured as the relative thickness of the cortex[231].

To account for the differences in geometry between the QDR 2000 and QDR4500 scanners, a linear correction was undertaken. The correction factor was calculated as the ratio of NN BMD from QDR 2000 to QDR 4500 prior to visit 8. No significant differences in age, weight, and height were noted between the QDR 2000 and QDR 4500 scanners. The resulting correction was then applied to the measures from QDR2000 scanner only. To account for any residual error, all analysis was adjusted for scanner type.

Reproductive factors:

SWAN collected data on multiple reproductive factors. Age at menarche was defined as the age when the periods or menstrual cycles started. Age at menarche was assessed as a continuous and categorical variable (9-10, 11-12, 13-14, 15-16 years) to understand differences between groups. Parity was self-reported as the total number of pregnancies that resulted in a livebirth. Parity was assessed continuously and subsequently categorized as nulliparous, 1-3 births and ≥4 births. For livebirths, data on breastfeeding (yes/no) and duration of breastfeeding (months) for each child was self-reported at baseline. Total duration of breastfeeding was calculated as the sum of breastfeeding duration for all livebirths, in years. Age at first and last birth (years) was also self-reported at baseline. Self-reported use of oral contraceptive pill (yes/no) at baseline was included.

Age at FMP was self-reported on annual follow up interviews as the age at last menstrual period reported immediately before being classified as postmenopausal (12 consecutive months of amenorrhea).

Sex-steroid hormones:

Fasting blood draw was scheduled to occur before 10AM in early follicular phase in (day 2-5) of the menstrual cycle in menstruating women. Blood draw was arranged within 2 months of recruitment at baseline and every follow up visit thereafter[91]. Fasting blood samples were drawn on day 2-5 of the menstrual cycle in menstruating women. If a timed sample (before 10 AM in early follicular phase) was not obtainable after 2 attempts, a random sample was drawn within 90 days of the baseline visit anniversary. Hormone levels were measured at the Central Ligand Assay Satellite Services (CLASS) Laboratory, University of Michigan. Estradiol (E2) levels were measured using modified ACS-180 (E2-6) immunoassay (Bayer Diagnostics Corp,

Norwood, MA). E2 was measured in duplicate and average of the 2 levels was used. Averaged intra and inter-assay coefficients of variation were 6.4% and 10.6% respectively[91,329]. Serum Follicle-Stimulating Hormone (FSH) was measured using a 2-site chemiluminometric manual assay kit (Bayer diagnostics). Intra and inter-assay coefficient of variation were 6% and 12% respectively[91]. Lower limit of detection (LLD) ranged from 1-7 pg/ml and 0.4-1 mIU/ml for E2 and FSH respectively.

Testosterone (T) levels were assessed using the ACS-180 total T immunoassay[329]. The intra and inter-assay coefficients of variation were 9.7% and 11.3% respectively[329]. Serum Sex-Hormone Binding Globulin (SHBG) concentrations were measured using 2 site chemiluminescent immunoassay. Intra and inter-assay variability coefficients were 9.9% and 6.1% respectively. LLD for T and SHBG ranged between 2-2.2 ng/dL and 1.9-3.2 nM respectively[329]. Any assay below the LLD was set to a random level between 0 and the LLD. Cycle day of sample collection was recorded as within or outside of the follicular phase (day 2-5) for regular menstrual cycles and as unknown for non-menstruating or irregularly menstruating women.

Other factors:

Information at baseline including age, race, education were self reported on questionnaires at baseline. Four races/ethnicities were self reported as – black, white, Chinese and Japanese. Education was classified as high school or less and greater than high school. Anthropometric measures like height (cm), weight (kg) and body mass index(kg/m^2) was obtained at each follow up clinic visit. Smoking status was self reported at baseline as current, past or never smokers. Baseline physical activity was quantified using modified Baecke score. The score is a measure of active living, home and recreational activity[330]. Diabetes status was

obtianed at every follow up visit as self reported diabetes status, fasting glucose level and/or use of anti-diabetic medication.

Statistical Analyses:

Baseline associations between reproductive factors, sex hormones and hip geometry were estimated using linear regression models. The associations were assessed independently and subsequently adjusted for potential confounders at baseline (age, race, site, education, BMI, smoking status, physical activity and diabetes).

Longitudinal assessment: HSA measures were assessed as percent change from baseline during the menopausal periods and overall[$\{\frac{Time1-Time0}{Time0}\}$*100]. To assess the associations between reproductive factors, sex hormones and hip geometry over MT we used linear mixed models. Time was centered around the final menstrual period (FMP) such that FMP is time 0. Step 1 - Locally weighted scatterplot smoothing (LOESS) curves were used to determine the trajectory of the HSA measures. Step 2 - Based on the curves, 2 distinct knots – 2 years before FMP and 1 year after FMP were noted. Appropriateness of the knots was tested using null models at 6 month increments. With these knots, the changes in hip geometry were assessed at 3 distinct phases – (1) premenopausal (5 years before to 2 years before FMP), (2) transmenopausal (2 years before to 1 year after FMP) and (3)post-transmenopausal (1 year to 5 years after FMP). Step 3- Using piecewise linear mixed regression, the associations of the reproductive factors and sex hormones (annually obtained repeated measures) with the rate of change of each HSA measures were estimated[244]. Rate of change in HSA measures over time were estimated using intereaction with time segments. To account for between women heterogeneity, random slopes were allowed. The associations were assessed in 2 models. Model 1 was adjusted for site, scanner change and baseline value and subsequently adjusted for potential confounfers - age,

race, education, BMI, smoking status, physical activity and diabetes. Baseline values for age, race and education were used. BMI and diabetes were used as time varying measures. Variation in smoking and physical activity over time was not associated with any of the HSA measures and hence baseline values were used in the analyses. Change in DXA scanner and baseline value of the HSA measure were also accounted for. In addition to phase specific slopes, cumulative change over the 10 years was assessed. Reproductive factors and sex hormones were modelled as independent predictors for each HSA measure.

For baseline and longitudinal assessments, nulliparous women were excluded from models assessing breastfeeding, age at first and last birth. Repeated measures of hormones were used. Given the skewed distribution of the hormones, they were log transformed to base 2. The transformation to log base 2 allows for a more intuitive interpretation compared to the natural log - one unit increase in log base 2 of the hormones is equal to doubling of the untransformed hormone level[8]. Models assessing hormones were additionally adjusted for cycle day on which the blood was drawn. SHBG models were additionally adjusted for E2 levels.

10.4 RESULTS

At baseline [Table 10-1], the mean age of the cohort was 46.38 years with a mean BMI of 27.55 kg/m^2. Nearly 50% of the population was White with ~27% Blacks. Over 78% of the women had more than high school education with 15% current smokers. The average age at menarche was 12.48 years with nearly 71% of the cohort having 1-3 children. Post exclusion of nulliparous women, 69% of the women breastfed their offspring, for an average duration of about 3/4th of a year.

Baseline analyses:

Later age at menarche, greater parity, later age at last birth, and breastfeeding were associated with significantly lower BMD and CSA, in the unadjusted models [Table 10-2]. Later age at first birth was associated with lower BMD and CSA. In the fully adjusted model, no significant associations were noted with BMD. The associations were explained by age, race, BMI and physical activity. After adjusting for confounders, later age at last birth was associated with greater CSA. No other reproductive factors/ hormones were associated with CSA.

In the unadjusted models, T doubling was associated with greater OD. This association remained significant in the multivariable model. Only in the fully adjusted model, OC use was associated with lower OD. This reverse confounding effect was explained by smoking. No associations were noted with the other reproductive factors or hormones.

In the unadjusted models, later age at menarche, later age at first birth and ever breastfeeding were associated with lower SM while greater parity was associated with greater SM. Doubling of FSH and SHBG were associated with lower SM. After accounting for confounders, later age at menarche was associated with greater SM. This reversal was explained by race, BMI, physical activity.

Later age at menarche, greater parity, breastfeeding and longer duration of breastfeeding were associated with greater BR. Greater FSH, T, and SHBG levels were associated with greater BR. In the fully adjusted models, associations with FSH and SHBG were attenuated but remained significant. No associations were noted with the other reproductive factors or hormones.

Longitudinal assessment:

In the fully adjusted models [Tables 10-3], only age at first birth and breastfeeding were significantly associated with change in BMD. Later age at first birth was associated with

significant decline in the transmenopausal period (-0.04%/year) but not cumulatively. over 10 years. Breastfeeding was associated with greater declines inBMD during the transmenopausal period (-0.50) and cumulatively (-2.21%/10 years). Doubling of FSH (-0.30%/year) was associated with greater BMD loss in the transmenopausal and postmenopausal period respectively. These associations also reflected cumulatively over 10 years (-1.12 for FSH and -0.86 for SHBG). Adjusting for E2 levels, slightly attenuated association between SHBG and BMD cumulatively (-0.84). No associations were noted with other reproductive factors/ hormones.

Similar patterns were noted for CSA [Tables 10-4]. Later age at first birth was associated with greater loss in the transmenopausal period (-0.04). No significant cumulative association was noted. Breastfeeding was associated with significant greater CSA loss cumulatively (-1.82%/10 years). Doubling of E2 was associated with lower CSA loss (+0.14%/year) in the transmenopausal period but not cumulatively. Conversely, doubling of FSH was associated with greater loss of CSA in the transmenopausal period (-0.28) and over 10 year (-1.16%/10 years). Doubling of SHBG was associated with greater loss of CSA in the postmenopausal period (-0.23%/year) and cumulatively (-0.73%/10 years). Other hormones/ repoductive factors were not significantly associated with change in CSA.

Few associations were noted with OD in the fully adjusted models [Table 10-5]. Compared to nulliparous women, women with parity ≥ 4 children showed lower increase in OD (-0.33) in the transmenopausal period. However this association was not mirrored cumulatively. Compared to menearche between 11-12 years, earlier menarche (9-10 years) showed greater increase in OD in the pre-transmenopausal period while later menarche (13-14 years) had significnatly lower rates of increase in the post-menopausal period. No associations were noted in the transmenopausaly or cumulatively. Breastfeeding was associated with greater OD

cumulatively (+0.59%/10 years). Doubling of SHBG was associated with increase in OD in the transmenopausal period (+0.08%/year) and cumulatively (0.22%/10 years).

After adjusting for the confounders, later age at menarche (+0.14%/year) was associated with greater increases in SM in the post-menopausal period (table 10-6). This association was not reflected in the cumulative change. Compared to the 3rd quartile, women with the highest quartile of age at FMP had greater loss of SM. Similar to BMD and CSA, doubling of E2 was associated with lower transmenopausal loss (+0.17), while FSH doubling was associated with greater loss in the transmenopausal period (-0.39) and cumulatively (-2.03%/10 years). Doubling of SHBG was associated with greater SM loss in the postmenopausal period (-0.31%/year) and cumulatively (-0.90%/10 years). No associations were noted with T.

In the fully adjusted models, parity ≥4 was associated with greater increase in BR during the pre-transmenopausal period, as compared to nulliparous women (table 10-8). No associations were noted in the trans- and post-menopausal periods or cumulatively. Later age at first birth was associated with greater rates of BR increase in the transmenopausal period (+0.60%/year) and cumulatively (+0.25%/10 years). Ever breastfeeding (+3.87%/10 years) and longer duration of breastfeeding (+1.36%/10 years) were associated with greater increase in BR cumulatively. FSH doubling was associated with BR increase in the postmenopausal (+0.89%/year) and cumulatively (+2.96%/10 year). SHBG doubling was associated with greater in BR in the transmenopausal (+0.40%/year), postmenopausal (+0.46%/year) and reflecting (+2.46%/10 years). No associations were noted with other reproductive factors or hormones.

10.5 DISCUSSION

Our study found that specific reproductive factors like age at first birth, breastfeeding, and hormone levels of FSH and SHBG significantly influenced premenopausal hip geometry characteristics, and the rate of change of hip geometry measures, particularly around the FMP. At baseline, later age at menarche was associated with greater premenopausal OD and SM, while later age at last birth was associated with greater premenopausal CSA level. OC use was associated with greater premenopausal OD levels. Over the 10 year period, only breastfeeding was associated with accelerated decline in BMD, CSA and SM and accelerated increase in OD and BR. Longer duration of breastfeeding and later age at first birth were associated with greater increase in BR. In the transmenopaual period, later age at first birth and breastfeeding were associated with accelerated loss of BMD and greater increase in BR. These associations were independent of age, race, BMI, education, physical activity, smoking and diabetes.

At baseline, doubling of FSH was associated with greater premenopausal OD and BR levels while doubling of SHBG was associated with greater premenopausal BR levels. Cumulatively over 10 years, doubling of FSH and SHBG were associated with accelerated decline in BMD, CSA and SM and accelerated increase in BR. SHBG doubling also showed accelerated increase in OD. These associations were independent of age, race, BMI, education, physical activity, smoking and diabetes. In the transmenopausal period, doubling of FSH was associated with greater decline in BMD and CSA, while doubling of SHBG was associated with accelerated increase in OD and BR. Doubling of E2 in the transmenopausal period was associated with decelerated decline in CSA and SM. Together, these findings are consistent with structural instability and fracture risk accompanying the MT. To the best of our knowledge, no

other studies have demonstrated an association between several reproductive factors and level and rate of change in hip geometry measures at midlife.

Both pregnancy and lactation have been known to cause short-term BMD loss (up to 5%)[331,332]. During this time, the maternal skeleton compensates for the increased calcium demand. In addition to increased caclium absororption from the gut and decreased calcium excretion, hormonal changes could result in increased bone resorption. These changes are accompanied by increase in parathyroid hormone-related protein levels[333] and low estrogen levels[334]. These changes however, may be transient and reversed post-delivery[335], typically within 6-12 months. However, studies have reported that bone mass may likely not return to baseline levels, with longer duration of breastfeeding[336]. Nevertheless, the long-term effects remain ambiguous. While some studies have reported protective[337] or no associations[338], more recent studies have reported unfavorable effects on BMD in later life[326].

Using the Women's Health Inititative (mean age = 63.6), Crandall et al[339], reported significant trend for assocation between later age at first birth and greater hip fracture risk, that was explained by adjusting for many confounders including age, race, BMI, education and physical activity. Contrary to their hypothesis, breastfeeding was associated with a lower risk of hip fractures. The Leisure World Cohort Study[340] of older women (mean age = 73 years) reported that compared to first birth before 20 years, later age at first birth (30+years) was associated with lower risk of spine fracture but not hip fractures. Associations with breastfeeding were not assessed. These associations were independent of age, BMI and history of fractures. However, important confounders like education and physical activity were not accounted for[340]. Prior work in SWAN reported that, longer duration of breastfeeding and greater parity were associated with lower spine BMD and greater impact strength indices respectively[235]. These associations were independent of age, BMI, physical activity and bone adverse medications[235].

Our results support the hypothesis that pregancy and lactation influence bone re-modelling in later life and extend the evidence to hip geometry in midlife.

MT studies have demonstrated association between higher FSH[341,342], lower E2[341,342] with lower BMD. SHBG, binds to E2 and T and hence lowering the bioavailable E2/T concentrations. High SHBG levels are associated with low BMD and an increased risk of fracture[130,343,344]. Interestingly, a prior SWAN study, reported that higher FSH in the pre-trans and transmenopausal periods, and lower E2 in the post-menopausal periods were associated with faster spine BMD loss. At the femoral neck, transmenopausal high FSH levels were associated with greater BMD loss[129]. Our results mirror these findings and strengthen evidence for association between higher FSH and SHBG levels, with greater cortical instability as measured by lower BMD, CSA, SM and greater BR.

Despite the highly regulatory role of estrogen on bone metabolism[1], our results did not establish significant associations with E2, particularly in the transmenopausal period. Given the large variation in E2 during the menstrual cycle[129], a single annual measure may therefore not refelct these levels adequqtely. Thus it is likely that FSH is a better measure of ovarian aging during this period[129], strengthening the eneed for better measures of ovarian aging during the MT[8]. Similarly, no associations were noted with T cumulatively. Some[345] but not all studies[346] have shown significant associations between T and BMD. It is likely that androgens play a role in bone metabolism as precursors to E2, and not directly[347]. We also showed that higher SHBG was associated with poorer hip geometry, independent of E2 and T (results not shown) levels. The exact mechanism of SHBG on the bone is unclear. SHBG levels are directly related to estrogen levels and may serve as a proxy for E2[348]. Although SHBG has greater affinity for androgens then estrogen and is thus a better marker of androgenecity[349], our study showed SHBG associations were independent of T. Thus, SHBG may act directly via the androgen

receptors to activate bone loss[350]. Together, these findings support the hypothesis that hormonal changes during the MT, produces accelerated changes in hip geometry, increasing its susceptibility to fractures. Additionally, no associations were noted with calcium and vitamin D for any of the HSA measures (results not shown).

Our study was limited by HSA estimation from 2 dimensional DXA scans. However, HSA estimation from 2D images are comprable with that of QCT measures[351]. Reproductive history was collected via questionnaires, and may be subject to recall bias. Multiple simultaneous comparisons may limit the power of statistical inferences. However, the consisitency of results across the HSA factors, strenghens our findings to some extent. Blood samples for hormone assays were collected in the early follicular phase, which may not be ideal for all the hormones mesaured. However, all analyses accounted for cycle day of blood draw. In addition, one of the limitations of E2 and T estimation is that it did not detect LLD in the postmenopausal period. Strengths of our study include large, multi-ethnic, community-based population with longitudinal assessment of FMP, information on an array of reproductive factors and multiple measures of hip geometry.

In conclusion, early life reproductive factors including older age at first birth and breastfeeding and greater premenopausal FSH and SHBG levels were associated with levels and accelerated unfavourable changes in HSA measures across the MT (10 years). Our results strengthen exisiting literature and provide better understanding of reproductive factors influencing hip geometry and cortical stability during the MT. Further studies with advanced measures of ovarian aging could provide better understanding of the bone health during the MT. Early identification of women at risk for accelerated change in bone geometry is important to prevent fractures.

10.6 TABLES

Table 10-1: Baseline characteristics of the study population

Characteristics	Baseline (N=1941)
Age (years)*	46.38(2.67)
Race/Ethnicity	
Black N(%)	517(26.55)
Chinese N(%)	220(11.30)
Japanese N(%)	240(12.33)
White N(%)	970(49.82)
Education	
High school or less	421(21.62)
Greater than high school	1526(78.38)
Height (cm)*	162.30(6.52)
Weight (kg)*	72.69(19.33)
BMI (kg/m^2) *	27.55(6.82)
Smoking status	
Current smokers N(%)	291(15.06)
Past smokers N(%)	494(25.57)
Never smokers N(%)	1147(59.37)
Physical activity score (range 3-14) *	9.95(1.91)
Age at menarche	12.48(1.45)
Age at menarche	
9-10	153(8.14)
11-12	802(42.66)
13-14	757(40.27)
15-16	168(8.94)
Parity	1.88(1.35)
Parity	
Nulliparous	370(19.06)
1-3	1374(70.79)
4 or more	197(10.15)
Age at first birth (years)**	25.54(6.15)
Age at last birth (years)**	30.78(5.83)
Breastfeeding (YES)**	1077(68.56)
Duration of breastfeeding (years)**	0.74(1.27)
Use of oral contraceptive pills (YES)	1431(74.03)
Estradiol (pg/ml) ***	54.95(33.25, 86.55)
FSH (mlU/ml) ***	16.2(11.20, 26.5)
Testosterone (ng/dl) ***	41(29.40, 54.9)
SHBG (nM) ***	41(28.00, 57.99)
NN BMD (g/cm^2) *	1.06(0.18)
NN CSA (cm^2) *	2.99(0.53)
NN OD (cm) *	2.96(0.20)
NN SM (cm^3) *	1.36(0.30)
NN BR *	7.60(1.43)

*mean ± SD; narrow neck (NN) Bone mineral density (BMD); Cross Sectional Area (CSA); Outer Diameter (OD); Section modulus (SM); Buckling Ratio (BR); **excluding nulliparous women; ***Median (Q25, Q75)

Table 10-2: Cross-sectional association between reproductive factors/hormones and NN HSA measures at baseline

	Unadjusted model [β(95% CI)]				
Characteristics	**NN BMD**	**NN CSA**	**NN OD**	**NN SM**	**NN BR**
Age at menarche	**-0.02(-0.02, -0.01)**	**-0.04(-0.06, -0.02**)	0.002(-0.004, 0.01)	**-0.02(-0.02, -0.01)**	**0.08(0.03, 0.12)**
Age at menarche					
9-10	**0.07(0.04, 0.10)**	**0.19(0.10, 0.28)**	-0.01(-0.05, 0.02)	0.07(0.02, 0.12)	**-0.29(-0.54, -0.05)**
11-12	**0.03(0.01, 0.05)**	**0.09(0.04, 0.15)**	0.01(-0.01, 0.03)	0.05(0.02, 0.08)	-0.08(-0.22, 0.06)
13-14	Ref	Ref	Ref	Ref	Ref
15-16	-0.01(-0.04, 0.01)	-0.04(-0.13, 0.05)	0.01(-0.03, 0.04)	-0.01(-0.06, 0.04)	0.20(-0.04, 0.44)
Parity	**0.02(0.01, 0.02)**	**0.04(0.03, 0.06)**	-0.003(-0.01, 0.003)	**0.02(0.01, 0.03)**	**-0.13(-0.18, -0.08)**
Parity					
Nulliparous	Ref	Ref	Ref	Ref	Ref
1-3	**0.02(0.004, 0.04)**	0.05(-0.01, 0.11)	-0.02(-0.04, 0.004)	0.01(-0.02, 0.05)	**-0.36(-0.53, -0.20)**
4 or more	**0.08(0.05, 0.11)**	**0.22(0.13, 0.31)**	-0.004(-0.04, 0.03)	**0.09(0.04, 0.14)**	**-0.50(-0.74, -0.25)**
Age at first birth (years) [A]	**-0.01(-0.01, -0.004)**	**-0.01(-0.02, -0.01)**	0.0003(-0.001, 0.002)	**-0.01(-0.01, -0.003)**	0.02(0.01, 0.03)
Age at last birth (years) [A]	**-0.002(-0.003, -0.001)**	**-0.01(-0.01, -0.001)**	0.0004(-0.001, 0.002)	-0.002(-0.004, 0.001)	0.01(-0.001, 0.02)
Breastfeeding (YES) [A]	**-0.04(-0.05, -0.02)**	**-0.11(-0.17, -0.05)**	-0.01(-0.03, 0.01)	**-0.04(-0.07, -0.01)**	**0.18(0.03, 0.32)**
Duration of breastfeeding [A] (years)	**-0.01(-0.01, -0.001)**	-0.02(-0.04, 0.002)	0.004(-0.003, 0.01)	-0.004(-0.01, 0.01)	**0.05(0.0002, 0.10)**
Oral contraceptive pills (YES)	**0.02(0.003, 0.04)**	0.05(-0.0004, 0.11)	-0.01(-0.03, 0.01)	0.02(-0.01, 0.05)	-0.12(-0.27, 0.02)
Estradiol (pg/ml) *	-0.01(-0.01, 0.001)	-0.02(-0.04, 0.003)	-0.002(-0.01, 0.01)	-0.01(-0.02, 0.0001)	0.03(-0.03, 0.08)
FSH (mlU/ml) *	**-0.02(-0.02, -0.01)**	**-0.03(-0.06, -0.01)**	0.01(-0.00001, 0.02)	**-0.01(-0.03, -0.002)**	**0.13(0.07, 0.19)**
Testosterone (ng/dl) *	-0.001(-0.01, 0.01)	0.01(-0.02, 0.04)	**0.02(0.003, 0.03)**	0.01(-0.005, 0.03)	**0.09(0.01, 0.18)**
SHBG (nM) *	**-0.03(-0.04, -0.02)**	**-0.08(-0.11, -0.05)**	-0.002(-0.05, 0.01)	**-0.04(-0.05, -0.02)**	**0.18(0.10, 0.25)**
SHBG[C]	**-0.03(-0.04, -0.02)**	**-0.08(-0.11, -0.05)**	-0.002(-0.01, 0.001)	**-0.04(-0.05, -0.02)**	**0.17(0.09, 0.25)**
	Multivariable model [β (95% CI)] [B]				
Age at menarche	-0.0004(-0.01, 0.005)	0.07(-0.01, 0.02)	**0.01(0.001, 0.02)**	**0.01(0.002, 0.02)**	0.03(-0.02, 0.07)
Age at menarche					
9-10	-0.001(-0.03, 0.03)	-0.04(-0.13, 0.05)	-0.04(-0.07, 0.004)	-0.05(-0.10, 0.002)	0.04(-0.20, 0.27)
11-12	0.01(-0.01, 0.03)	0.02(-0.03, 0.06)	-0.01(-0.03, 0.01)	0.004(-0.02, 0.03)	-0.05(-0.18, 0.08)
13-14	Ref	Ref	Ref	Ref	Ref
15-16	0.003(-0.02, 0.03)	0.01(-0.07, 0.09)	0.01(-0.03, 0.04)	0.02(-0.02, 0.07)	0.10(-0.12, 0.32)
Parity	0.0001(-0.01, 0.01)	-0.002(-0.02, 0.02)	-0.002(-0.01, 0.01)	-0.001(-0.01, 0.01)	-0.03(-0.08, 0.02)

Table 10-2 Continued					
Parity					
Nulliparous	Ref	Ref	Ref	Ref	Ref
1-3	-0.003(-0.02, 0.02)	-0.01(-0.06, 0.04)	-0.003(-0.03, 0.02)	-0.004(-0.04, 0.03)	-0.11(-0.26, 0.04)
4 or more	-0.01(-0.04, 0.02)	-0.02(-0.11, 0.07)	-0.001(-0.04, 0.04)	-0.01(-0.06, 0.04)	-0.08(-0.32, 0.17)
Age at first birth (years) [A]	0.001(-0.001, 0.002)	0.003(-0.001, 0.01)	0.001(-0.001, 0.003)	0.001(-0.001, 0.004)	0.0002(-0.01, 0.01)
Age at last birth (years) [A]	0.001(-0.001, 0.001)	**0.005(0.002, 0.01)**	0.002(-0.004, 0.004)	0.002(-0.0003, 0.005)	0.001(-0.01, 0.01)
Breastfeeding (YES) [A]	0.01(-0.01, 0.03)	0.02(-0.04, 0.08)	-0.02(-0.04, 0.01)	-0.01(-0.05, 0.02)	-0.02(-0.17, 0.13)
Duration of breastfeeding [A] (years)	0.003(-0.003, 0.01)	0.01(-0.01, 0.03)	0.002(-0.01, 0.01)	0.004(-0.01, 0.01)	0.01(-0.03, 0.06)
Oral contraceptive pills (YES)	-0.03(-0.02, 0.01)	-0.03(-0.08, 0.02)	**-0.02(-0.05, -0.002)**	-0.02(-0.05, 0.01)	-0.01(-0.15, 0.13)
Estradiol (pg/ml) *	-0.002(-0.01, 0.004)	-0.01(-0.03, 0.01)	-0.002(-0.01, 0.01)	-0.01(-0.02, 0.005)	-0.01(-0.06, 0.04)
FSH (mlU/ml) *	-0.01(-0.01, 0.00001)	-0.01(-0.03, 0.01)	**0.01(0.0002, 0.02)**	-0.001(-0.01, 0.01)	**0.09(0.03, 0.15)**
Testosterone (ng/dl) *	-0.01(-0.02, 0.004)	-0.003(-0.03, 0.03)	0.01(-0.001, 0.02)	0.004(-0.01, 0.02)	0.04(-0.04, 0.12)
SHBG (nM) *	-0.01(-0.01, 0.003)	-0.01(-0.04, 0.01)	0.01(-0.01, 0.02)	-0.004(-0.02, 0.01)	0.04(-0.03, 0.11)
SHBG[C]	-0.01(-0.01, 0.004)	-0.01(-0.04, 0.02)	0.01(-0.01, 0.02)	-0.002(-0.02, 0.01)	0.05(-0.03, 0.12)

*log base 2, adjusted for cycle day; [A] – excluding nulliparous women; [B]- adjusted for age, race (ref=Caucasian), site, BMI, education(ref=<=HS), smoking(ref=non-smoker), physical activity, diabetes (ref=non-diabetic); [C]- adjusted for log transformed E2;

Table 10-3: Rate of change of baseline normalized NN BMD in relation to FMP (fully adjusted models)

NN BMD[1]	**Rate of change (slope) in each FMP-defined Phase (%/year) [2]**			**Cumulative Change[b] (%)[3]** Mean (95% CI), **-10.67(-11.29, -10.05)**
	Pre-transmenopause (Prior to 2 years before FMP) Mean[b] (95% CI), -0.001(-0.07, 0.07)	**Transmenopause (2 years before to 1 years after FMP)** Mean[b] (95% CI), **-1.84(-2.01, -1.66)**	**Postmenopause (1 years after FMP and beyond)** Mean[b] (95% CI), **-1.66(-1.82, -1.49)**	
Age at menarche	-0.02(-0.08, 0.04)	0.06(-0.08, 0.19)	0.06(-0.07, 0.20)	0.30(-0.18, 0.77)
Age at menarche				
9-10	0.11(-0.25, 0.47)	-0.09(-0.87, 0.69)	0.08(-0.69, 0.84)	0.02(-2.73, 2.77)
11-12	0.02(-0.16, 0.19)	-0.09(-0.49, 0.31)	-0.19(-0.59, 0.21)	-0.69(-2.09, 0.70)
13-14	Ref	Ref	Ref	Ref
15-16	0.03(-0.28, 0.34)	0.09(-0.62, 0.80)	-0.22(-0.91, 0.46)	0.02(-2.46, 2.43)
Parity	-0.03(-0.09, 0.03)	-0.03(-0.16, 0.11)	-0.06(-0.20, 0.07)	-0.29(-0.75, 0.18)
Parity				
Nulliparous	Ref	Ref	Ref	Ref
1-3	-0.01(-0.21, 0.20)	-0.09(-0.54, 0.35)	0.07(-0.39, 0.53)	-0.26(-1.82, 1.30)
4 or more	-0.29(-0.60, 0.03)	0.04(-0.67, 0.75)	-0.35(-1.12, 0.42)	-1.11(-3.63, 1.41)
Age at first birth (years) [A]	0.001(-0.01, 0.02)	**-0.04(-0.07, -0.004)**	0.03(-0.01, 0.06)	-0.10(-0.22, 0.02)
Age at last birth (years) [A]	-0.01(-0.02, 0.01)	-0.03(-0.06, 0.01)	0.01(-0.02, 0.04)	-0.10(-0.22, 0.02)
Breastfeeding (YES) [A]	-0.04(-0.24, 0.17)	**-0.50(-0.95, -0.06)**	-0.06(-0.49, 0.36)	**-2.21(-3.72, -0.71)**
Duration of breastfeeding [A] (years)	-0.03(-0.09, 0.03)	-0.05(-0.19, 0.10)	-0.07(-0.23, 0.10)	-0.37(-0.91, 0.16)
Oral contraceptive pills (YES)	0.05(-0.12, 0.22)	-0.13(-0.52, 0.27)	0.15(-0.24, 0.54)	-0.10(-1.47, 1.28)
Estradiol (pg/ml) [B]	0.01(-0.07, 0.09)	0.10(-0.01, 0.21)	-0.15(-0.38, 0.07)	0.11(-0.38, 0.60)
FSH (mlU/ml) [B]	0.03(-0.06, 0.12)	**-0.30(-0.45, -0.15)**	0.01(-0.23, 0.24)	**-1.12(-1.75, -0.50)**
Testosterone (ng/dl) [B]	-0.09(-0.20, 0.02)	0.12(-0.09, 0.32)	-0.05(-0.27, 0.18)	0.20(-0.47, 0.87)
SHBG (nM) [B]	0.01(-0.08, 0.10)	-0.13(-0.29, 0.04)	-0.18(-0.37, 0.004)	**-0.86(-1.39, -0.34)**
SHBG[C]	-0.002(-0.09, 0.09)	-0.11(-0.28, 0.05)	-0.19(-0.38, 0.002)	**-0.84(-1.37, -0.31)**

Table 10-4: Rate of change of baseline normalized NN CSA in relation to FMP (fully adjusted models)

NN CSA[1]	Rate of change (slope[a]) in each FMP-defined Phase (%/year) [2]			Cumulative Change[b] (%)[3]
	Pre-transmenopause (Prior to 2 years before FMP) Mean[b] (95% CI) -0.003(-0.07, 0.07)	**Transmenopause (2 years before to 1 years after FMP)** Mean[b] (95% CI) **-1.45(-1.63, -1.27)**	**Postmenopause (1 years after FMP and beyond)** Mean[b] (95% CI) **-1.59(-1.76, -1.42)**	Mean[b] (95% CI), **-9.01(-9.63, -8.39)**
Age at menarche	-0.03(-0.09, 0.03)	0.07(-0.07, 0.21)	0.11(-0.03, 0.21)	0.43(-0.06, 0.91)
Age at menarche				
9-10	0.22(-0.16, 0.59)	-0.30(-1.12, 0.51)	-0.04(-0.87, 0.79)	-0.86(-3.69, 1.97)
11-12	0.04(-0.14, 0.22)	-0.04(-0.46, 0.38)	-0.31(-0.74, 0.12)	-0.70(-2.14, 0.73)
13-14	Ref	Ref	Ref	Ref
15-16	0.07(-0.25, 0.39)	0.12(-0.62, 0.86)	-0.24(-0.99, 0.50)	0.14(-2.38, 2.66)
Parity	-0.02(-0.08, 0.04)	-0.06(-0.20, 0.08)	-0.05(-0.20, 0.10)	-0.37(-0.85, 0.11)
Parity				
Nulliparous	Ref	Ref	Ref	Ref
1-3	-0.004(-0.21, 0.20)	-0.17(-0.63, 0.30)	0.03(-0.47, 0.53)	-0.22(-1.05, 0.62)
4 or more	-0.23(-0.54, 0.09)	-0.26(-1.00, 0.48)	-0.22(-1.05, 0.62)	-0.61(-2.22, 0.99)
Age at first birth (years) [A]	0.0005(-0.01, 0.02)	**-0.04(-0.07, -0.00001)**	0.02(-0.01, 0.06)	-0.10(-0.22, 0.02)
Age at last birth (years) [A]	-0.01(-0.02, 0.01)	-0.03(-0.07, 0.01)	0.01(-0.02, 0.05)	-0.01(-0.23, 0.02)
Breastfeeding (YES) [A]	-0.003(-0.21, 0.20)	-0.40(-0.87, 0.06)	-0.10(-0.55, 0.35)	**-1.82(-3.37, -0.27)**
Duration of breastfeeding [A] (years)	-0.03(-0.08, 0.03)	-0.03(-0.19, 0.12)	-0.08(-0.26, 0.10)	-0.33(-0.89, 0.23)
Oral contraceptive pills (YES)	0.06(-0.12, 0.23)	-0.16(-0.57, 0.26)	0.20(-0.22, 0.63)	-0.11(-1.53, 1.32)
Estradiol (pg/ml) [B]	0.004(-0.08, 0.09)	**0.14(0.03, 0.26)**	-0.15(-0.39, 0.09)	0.27(-0.24, 0.79)
FSH (mlU/ml) [B]	0.03(-0.06, 0.13)	**-0.28(-0.44, -0.13)**	-0.05(-0.30, 0.21)	**-1.16(-1.81, -0.51)**
Testosterone (ng/dl) [B]	-0.09(-0.20, 0.02)	0.11(-0.10, 0.32)	-0.06(-0.30, 0.18)	0.14(-0.54, 0.83)
SHBG (nM) [B]	-0.01(-0.10, 0.08)	-0.05(-0.22, 0.13)	**-0.22(-0.42, -0.02)**	**-0.65(-1.19, -0.11)**
SHBG[C]	-0.02(-0.11, 0.08)	-0.04(-0.21, 0.14)	**-0.22(-0.43, -0.02)**	**-0.62(-1.17, -0.08)**

[1] adjusted for site, baseline value and DXA scanner, race, education, BMI, diabetes, smoking, physical activity; 2 Rate of change (slope) in percentage of baseline value of the index of interest. Negative values mean faster decline, and positive values mean slower decline; 3 Cumulative change during the years spanning the final menstrual period [Median time (years) of first visit – Median time (years) of last visit]. A – excluding nulliparous women; Blog base 2, adjusted for cycle day; C- adjusted for log transformed E2

Table 10-5: Rate of change of baseline normalized NN OD in relation to FMP (fully adjusted models)

NN OD[1]	Rate of change (slope[a]) in each FMP-defined Phase (%/year) [2]			Cumulative Change[b] (%)[3]
	Pre-transmenopause (Prior to 2 years before FMP) Mean[b] (95% CI), -0.01(-0.03, 0.01)	**Transmenopause (2 years before to 1 years after FMP)** Mean[b] (95% CI), **0.44(0.38, 0.50)**	**Postmenopause (1 years after FMP and beyond)** Mean[b] (95% CI), **0.11(0.06, 0.16)**	Mean[b] (95% CI), **1.95(1.73, 2.18)**
Age at menarche	-0.01(-0.02, 0.01)	0.01(-0.04, 0.06)	**0.05(0.003, 0.09)**	0.12(-0.06, 0.31)
Age at menarche				
9-10	**0.10(0.002, 0.19)**	-0.18(-0.47, 0.10)	-0.13(-0.38, 0.12)	-0.79(-1.85, 0.27)
11-12	Ref	Ref	Ref	Ref
13-14	0.02(-0.03, 0.06)	0.06(-0.09, 0.20)	**-0.15(-0.28, -0.01)**	-0.02(-0.57, 0.52)
15-16	0.03(-0.05, 0.11)	0.05(-0.21, 0.30)	-0.04(-0.27, 0.19)	0.16(-0.79, 1.11)
Parity	0.01(-0.01, 0.02)	-0.04(-0.09, 0.01)	0.03(-0.02, 0.08)	-0.10(-0.28, 0.08)
Parity				
Nulliparous	Ref	Ref	Ref	Ref
1-3	0.01(-0.04, 0.07)	-0.11(-0.27, 0.06)	0.01(-0.14, 0.17)	-0.37(-0.98, 0.23)
4 or more	0.05(-0.03, 0.13)	**-0.33(-0.59, -0.08)**	0.16(-0.10, 0.42)	-0.92(-1.90, 0.06)
Age at first birth (years) [A]	-0.0005(-0.005, 0.004)	0.003(-0.01, 0.02)	-0.005(-0.02, 0.01)	0.002(-0.04, 0.05)
Age at last birth (years) [A]	0.0001(-0.004, 0.004)	-0.004(-0.02, 0.01)	0.004(-0.01, 0.02)	-0.01(-0.05, 0.04)
Breastfeeding (YES) [A]	0.03(-0.02, 0.09)	0.11(-0.06, 0.27)	0.05(-0.09, 0.19)	**0.59(0.03, 1.15)**
Duration of breastfeeding [A] (years)	0.01(-0.01, 0.02)	0.01(-0.04, 0.07)	0.02(-0.03, 0.07)	0.10(-0.10, 0.29)
Oral contraceptive pills (YES)	-0.01(-0.05, 0.04)	-0.03(-0.17, 0.12)	0.06(-0.07, 0.19)	0.003(-0.53, 0.54)
Estradiol (pg/ml) [B]	-0.002(-0.02, 0.02)	0.03(-0.01, 0.08)	-0.01(-0.10, 0.07)	0.11(-0.08, 0.29)
FSH (mlU/ml) [B]	-0.01(-0.03, 0.02)	0.03(-0.03, 0.09)	-0.02(-0.10, 0.06)	0.07(-0.17, 0.30)
Testosterone (ng/dl) [B]	0.01(-0.02, 0.03)	-0.03(-0.09, 0.03)	0.02(-0.05, 0.08)	-0.08(-0.28, 0.13)
SHBG (nM) [B]	-0.01(-0.04, 0.01)	**0.09(0.03, 0.15)**	-0.04(-0.10, 0.03)	**0.24(0.04, 0.44)**
SHBG[C]	-0.01(-0.04, 0.01)	**0.09(0.03, 0.15)**	-0.04(-0.10, 0.03)	**0.24(0.04, 0.44)**

[1] adjusted for site, baseline value and DXA scanner, race, education, BMI, diabetes, smoking, physical activity; [2] Rate of change (slope) in percentage of baseline value of the index of interest. Negative values mean faster decline, and positive values mean slower decline; [3] Cumulative change during the years spanning the final menstrual period [Median time (years) of first visit – Median time (years) of last visit]. [A] – excluding nulliparous women; [B]log base 2, adjusted for cycle day; [C-] adjusted for log transformed E2

Table 10-6: Rate of change of baseline normalized NN SM in relation to FMP (fully adjusted models)

NN SM[1]	Rate of change (slope[a]) in each FMP-defined Phase (%/year) [2]			Cumulative Change[b] (%)[3]
	Pre-transmenopause (Prior to 2 years before FMP) Mean[b] (95% CI), -0.01(-0.11, 0.09)	**Transmenopause (2 years before to 1 years after FMP)** Mean[b] (95% CI), **-1.09(-1.32, -0.86)**	**Postmenopause (1 years after FMP and beyond)** Mean[b] (95% CI), **-1.33(-1.54, -1.11)**	Mean[b] (95% CI), **-7.03(-7.80, -6.25)**
Age at menarche	-0.05(-0.14, 0.04)	0.09(-0.10, 0.28)	**0.14(-0.05, 0.32)**	0.54(-0.08, 1.16)
Age at menarche				
9-10	0.47(-0.07, 1.01)	-0.71(-1.80, 0.38)	-0.09(-1.14, 0.95)	-2.07(-5.69, 1.55)
11-12	-0.02(-0.28, 0.24)	-0.05(-0.61, 0.51)	-0.34(-0.88, 0.21)	-0.90(-2.73, 0.94)
13-14	Ref	Ref	Ref	Ref
15-16	0.09(-0.38, 0.55)	-0.05(-1.04, 0.94)	-0.22(-1.16, 0.72)	-0.47(-3.68, 2.74)
Parity	-0.03(-0.12, 0.06)	-0.11(-0.29, 0.08)	-0.01(-0.19, 0.18)	-0.50(-1.11, 0.10)
Parity				
Nulliparous	Ref	Ref	Ref	Ref
1-3	0.02(-0.29, 0.32)	-0.43(-1.06, 0.19)	0.06(-0.57, 0.69)	-1.57(-3.62, 0.47)
4 or more	-0.32(-0.79, 0.15)	-0.64(-1.62, 0.35)	0.18(-0.87, 1.23)	-2.84(-6.14, 0.47)
Age at first birth (years) [A]	0.002(-0.02, 0.03)	-0.03(-0.08, 0.02)	0.02(-0.02, 0.06)	-0.08(-0.23, 0.08)
Age at last birth (years) [A]	-0.01(-0.03, 0.01)	-0.02(-0.07, 0.03)	0.01(-0.03, 0.06)	-0.07(-0.23, 0.08)
Breastfeeding (YES) [A]	0.08(-0.24, 0.40)	-0.49(-1.10, 0.12)	0.18(-0.38, 0.74)	-1.45(-3.41, 0.51)
Duration of breastfeeding [A] (years)	-0.02(-0.10, 0.07)	-0.03(-0.23, 0.18)	0.04(-0.17, 0.26)	-0.06(-0.76, 0.64)
Oral contraceptive pills (YES)	0.13(-0.14, 0.39)	-0.25(-0.80, 0.30)	-0.08(-0.61, 0.45)	-0.90(-2.72, 0.91)
Estradiol (pg/ml) [B]	0.02(-0.10, 0.15)	**0.17(0.005, 0.33)**	-0.24(-0.54, 0.06)	0.24(-0.43, 0.92)
FSH (mlU/ml) [B]	0.03(-0.11, 0.17)	**-0.39(-0.61, -0.17)**	-0.27(-0.59, 0.04)	**-2.03(-2.86, -1.19)**
Testosterone (ng/dl) [B]	-0.11(-0.28, 0.05)	0.20(-0.09, 0.50)	-0.12(-0.43, 0.18)	0.34(-0.57, 1.26)
SHBG (nM) [B]	-0.04(-0.17, 0.10)	-0.05(-0.29, 0.19)	**-0.31(-0.56, -0.05)**	**-0.87(-1.60, -0.15)**
SHBG[C]	-0.05(-0.18, 0.09)	-0.03(-0.27, 0.21)	**-0.31(-0.56, -0.06)**	**-0.83(-1.56, -0.11)**

[1] adjusted for site, baseline value and DXA scanner, race, education, BMI, diabetes, smoking, physical activity; [2] Rate of change (slope) in percentage of baseline value of the index of interest. Negative values mean faster decline, and positive values mean slower decline; [3] Cumulative change during the years spanning the final menstrual period [Median time (years) of first visit – Median time (years) of last visit]. [A] – excluding nulliparous women; [B]log base 2, adjusted for cycle day; [C-] adjusted for log transformed E2

Table 10-7: Rate of change of baseline normalized NN BR in relation to FMP (fully adjusted models)

NN BR[1]	Rate of change (slope[a]) in each FMP-defined Phase (%/year) [2]			Cumulative Change[b] (%)[3]
	Pre-transmenopause (Prior to 2 years before FMP) Mean[b] (95% CI), 0.05(-0.02, 0.13)	**Transmenopause (2 years before to 1 years after FMP)** Mean[b] (95% CI), **3.02(2.71, 3.33)**	**Postmenopause (1 years after FMP and beyond)** Mean[b] (95% CI), **3.83(3.39, 4.26)**	Mean[b] (95% CI), **19.84(18.58, 21.09)**
Age at menarche	0.03(-0.03, 0.10)	-0.15(-0.36, 0.06)	-0.09(-0.40, 0.22)	-0.70(-1.65, 0.26)
Age at menarche				
9-10	0.02(-0.37, 0.41)	-0.39(-1.58, 0.80)	-0.12(-1.91, 1.67)	-1.76(-7.26, 3.74)
11-12	-0.04(-0.23, 0.14)	0.49(-0.12, 1.11)	0.42(-0.50, 1.34)	2.73(-0.07, 5.52)
13-14	Ref	Ref	Ref	Ref
15-16	-0.06(-0.39, 0.28)	-0.15(-1.24, 0.93)	0.55(-1.02, 2.11)	0.37(-4.52, 5.25)
Parity	0.05(-0.02, 0.12)	-0.08(-0.29, 0.12)	0.20(-0.11, 0.52)	0.17(-0.78, 1.12)
Parity				
Nulliparous	Ref	Ref	Ref	Ref
1-3	0.05(-0.17, 0.28)	-0.07(-0.76, 0.62)	0.02(-1.04, 1.08)	-0.13(-3.31, 3.04)
4 or more	**0.43(0.09, 0.78)**	-0.54(-1.64, 0.56)	0.66(-1.13, 2.45)	0.03(-5.18, 5.24)
Age at first birth (years) [A]	-0.001(-0.02, 0.02)	**0.06(0.01, 0.11)**	0.01(-0.07, 0.09)	**0.25(0.02, 0.48)**
Age at last birth (years) [A]	0.02(-0.00001, 0.03)	0.02(-0.04, 0.07)	0.04(-0.04, 0.12)	0.17(-0.07, 0.41)
Breastfeeding (YES) [A]	0.14(-0.10, 0.38)	0.44(-0.24, 1.11)	0.92(-0.05, 1.90)	**3.87(0.93, 6.81)**
Duration of breastfeeding [A] (years)	0.06(-0.01, 0.12)	0.14(-0.09, 0.36)	0.34(-0.06, 0.75)	**1.36(0.26, 2.45)**
Oral contraceptive pills (YES)	-0.02(-0.21, 0.17)	-0.32(-0.93, 0.29)	-0.0003(-0.91, 0.91)	-1.33(-4.11, 1.46)
Estradiol (pg/ml) [B]	-0.08(-0.17, 0.01)	0.03(-0.12, 0.19)	-0.29(-0.82, 0.24)	-0.61(-1.69, 0.47)
FSH (mlU/ml) [B]	0.04(-0.06, 0.14)	0.21(-0.004, 0.42)	**0.89(0.32, 1.46)**	**2.96(1.39, 4.00)**
Testosterone (ng/dl) [B]	0.05(-0.07, 0.17)	-0.02(-0.32, 0.28)	-0.11(-0.62, 0.40)	-0.20(-1.50, 1.09)
SHBG (nM) [B]	-0.04(-0.14, 0.06)	**0.40(0.15, 0.65)**	**0.46(0.04, 0.88)**	**2.43(1.40, 3.46)**
SHBG[C]	-0.03(-0.13, 0.07)	**0.39(0.14, 0.64)**	**0.45(0.03, 0.87)**	**2.39(1.36, 3.41)**

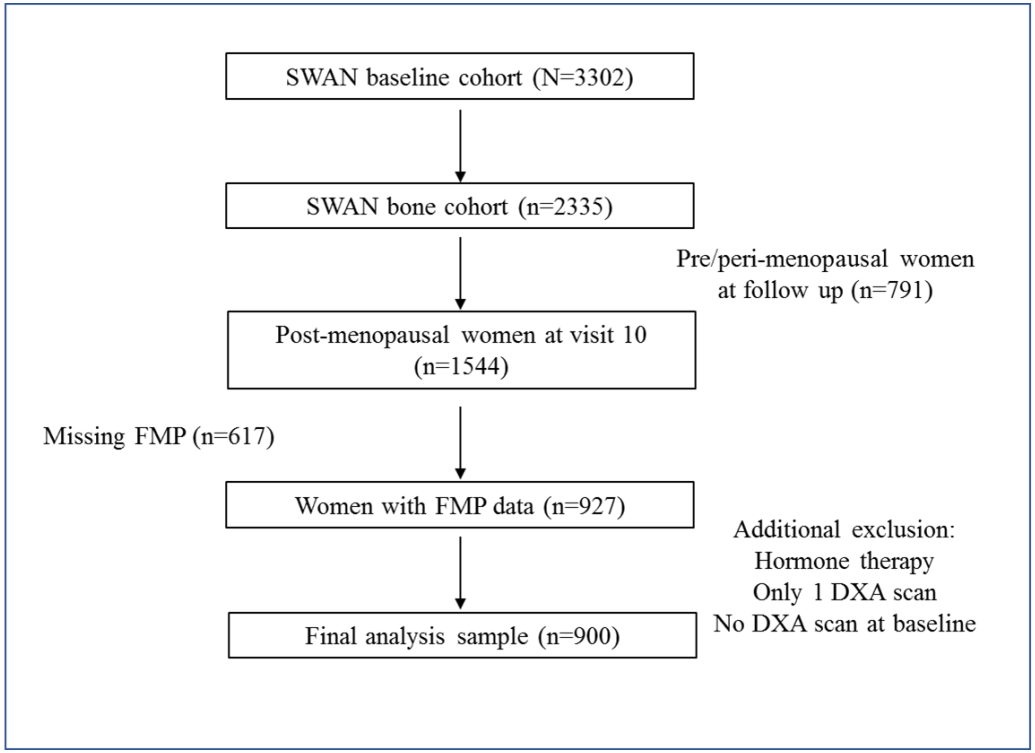
[1] adjusted for site, baseline value and DXA scanner, race, education, BMI, diabetes, smoking, physical activity; [2] Rate of change (slope) in percentage of baseline value of the index of interest. Negative values mean faster decline, and positive values mean slower decline; [3] Cumulative change during the years spanning the final menstrual period [Median time (years) of first visit – Median time (years) of last visit]. [A] – excluding nulliparous women; [B]log base 2, adjusted for cycle day; [C]- adjusted for log transformed E2

10.7 SUPPLEMENAL TABLE AND FIGURE

Supplemental Table 10-8: Correlation between reproductive factors, hormones and HSA measures

	Menarche	parity	Age at first birth	Age at last birth	Ever breastfed	Duration of breast-feeding	Ever OCP	Average E2	FSH	T	SHBG	BMD	CSA	Width	Section modulus	Buckling ratio
Menarche	1															
parity	-0.03	1														
Age at first birth	0.02	**-0.41**	1													
Age at last birth	0.004	**0.18**	**0.66**	1												
Ever breastfed	-0.003	0.03	**0.36**	**0.36**	1											
Duration of breastfeeding	-0.02	**0.27**	**0.18**	**0.33**	**0.46**	1										
Ever OCP	-0.04	0.005	-0.09	-0.07	-0.07	-0.08	1									
Average E2	-0.02	0.01	-0.01	0.01	-0.01	0.02	-0.02	1								
FSH	0.03	-0.06	0.05	-0.01	0.01	-0.0001	-0.02	-0.4	1							
T	-0.04	-0.01	0.01	0.01	-0.001	0.003	0.02	0.04	-0.08	1						
SHBG	0.05	-0.02	0.02	0.03	-0.001	0.02	-0.07	**0.21**	0.06	-0.05	1					
BMD	-0.09	**0.11**	**-0.19**	-0.08	-0.11	-0.05	0.07	0.1	**-0.33**	0.01	**-0.15**	1				
CSA	-0.09	0.1	**-0.16**	-0.06	-0.1	-0.04	0.07	0.08	**-0.3**	0.01	**-0.15**	**0.93**	1			
Width	-0.01	-0.02	0.05	0.03	-0.0004	0.04	-0.0008	-0.04	0.05	-0.004	0.004	**-0.1**	**0.27**	1		
Section modulus	-0.08	0.07	**-0.11**	-0.04	-0.07	-0.02	0.06	0.05	**-0.24**	0.004	**-0.12**	**0.77**	**0.93**	**0.48**	1	
Buckling ratio	0.04	-0.07	**0.14**	0.07	0.08	0.06	-0.05	**-0.13**	**0.34**	-0.004	**0.14**	**-0.78**	**-0.60**	**0.44**	**-0.41**	1

*bold if $p<0.05$ and correlation coefficient > |0.1|



Supplemental Figure 10-1: Analysis sample derivation

11.0 DISCUSSION

11.1 SUMMARY, CONCLUSIONS AND FUTURE RESEARCH

The main objective of the dissertation was to investigate the role of reproductive factors and sex-hormones on musculoskeletal aging as characterized by decline in physical functioning, risk of hip OA and change in bone geometry in later life. In a cohort of Caucasian women (65-80 years) followed over 20 years, we found that early life reproductive factors like later age at menarche, greater parity and breastfeeding were associated with a greater likelihood of maintaining grip strength over time. Conversely, women who underwent hysterectomy or oophorectomy were more likely to experience accelerated loss of grip strength. These associations were independent of age, education, BMI and physical activity. No associations of reproductive factors with chair stand time or grip strength. These findings are in support of our hypothesis that reproductive factors are associated with level and rate of change of physical function in later life. Lifestyle factors associated with child rearing could contribute to the association between perinatal factors and grip strength.

In our second paper, we examined the associations between reproductive factors and risk of RHOA. Contrary to existing literature on knee OA, we found that greater parity and breastfeeding were associated with lower risk of incident and total RHOA in the SOF Caucasian population. No associations were noted with the other reproductive factors. These associations were independent of age, education, BMI and physical activity. We postulate that with the

increase in weight during pregnancy, the center of gravity shifts forwards and upwards, increasing the load at the knee joint and decreasing the load on the hip joint[309]. In addition, anti-inflammatory properties of breastfeeding may protect women against RHOA. Together, these findings support our hypothesis that reproductive factors are associated with joint health in later life.

Finally, we investigated the associations of reproductive factors, sex hormones with the level and rate of change of hip geometry as measured by HSA. At baseline, later age at last birth was associated with greater NN CSA while OC use was associated with lower OD. Over the course of the MT, few factors were associated with change in hip geometry. Breastfeeding was associated with faster decline in BMD, and CSA and increase in OD and BR over the 10-year period. Later age at first birth was associated with an increased trans-menopausal decline in BMD, CSA and increase in BR. Doubling of FSH and SHBG were associated with faster decline in BMD, CSA and SM along with accelerated increase in BR over the 10-year period. These associations were independent of age, race, education, BMI, smoking, physical activity and diabetes. These findings parallel the changes in aBMD[129] and support the hypothesis that reproductive factors are associated with level and rate of change of hip geometry in midlife women.

The findings from these papers shed light on the role of reproductive factors on musculoskeletal aging. Using a life course approach, we demonstrated the associations between important early life reproductive events (menarche, parity, breastfeeding and surgical interventions like hysterectomy and oophorectomy) with later life changes in bone and muscle health. In addition to lifestyle factors related to child rearing, changes in body composition, hormones and immunological pathways may play important roles in mediating these

associations. However, our understanding of these mechanisms is limited. Life course epidemiology is an emerging field of research. Attempts are underway to understand the life course origins of disease and age-related disorders in later life. Therefore, future studies are needed to better understand the underlying pathways relating reproductive health with musculoskeletal health in later life. With a clear understanding of mechanistic pathways, it may be possible to use these reproductive factors as markers for successful musculoskeletal aging.

Through this dissertation, we demonstrated that few select reproductive factors were associated with musculoskeletal health and aging in later life. While greater parity and breastfeeding were associated with greater likelihood of maintaining grip strength and lower risk of hip OA in older SOF women, later age at first birth and breastfeeding were associated with unfavorable trans-menopausal changes in hip geometry measures in midlife SWAN women. Despite the significant non-linear trend, few parity groups demonstrated significant association with the risk of radiographic hip OA. In addition to perinatal factors, later life surgeries like hysterectomy and oophorectomy were associated with lower grip strength in SOF population. Barring the perinatal factors, particularly breastfeeding, no common factors were noted across the 3 papers. It is important to note that due to cohort differences in the distribution of parity in the 3 studies, parity was assessed differently. SWAN women were younger and more likely to have fewer children compared to the much older SOF women. In addition, the lack of associations between BMI/ weight/ change in BMI or weight was not associated with risk of RHOA. Given these factors, the results from the 3 studies should be interpreted with some caution and are not comparable. To increase the generalizability of these results, similar studies with long durations of follow up are needed to understand the effect of the reproductive factors on musculo-skeletal functioning in later life in other multi-ethnic populations across the globe.

These results shall aid in not only understanding the effect of reproductive health in later life but also in deducing meaningful clinical implications and intervention design.

It is important to weight these results against the limitations. Due to availability of reproductive information, the associations of reproductive health with functional decline and RHOA were limited to Caucasian women. These findings may not be generalizable to other studies. Additionally, reproductive data was collected from questionnaires and may be subject to recall bias. However, studies have reported high reliability for reproductive health collected through questionnaires[352]. Given the vast number of reproductive factors that were assessed independently, it is likely that some of the results were just a result of chance i.e. multiplicity. However, consistent associations with specific reproductive factors across the studies, suggests little role of chance. The strengths of our studies include large sample sizes, information on various reproductive factors, and objective or radiological outcome measures obtained over long follow up periods.

11.2 OVERALL IMPACT AND PUBLIC HEALTH SIGNIFICANCE

In 2013, the World Health Organization (WHO) recommended an integrated and life course approach to health and disease in women[353]. In accordance, our study aimed at understanding associations between reproductive factors from menarche to menopause with changes in bone and muscle in later life. This dissertation focused on understanding the long-term effects of reproductive health on musculo-skeletal aging. To the best of our knowledge, this is the first study to assess and compare all the reproductive milestones in relation to

musculoskeletal aging. The novelty of the study lies in the life course approach to identify the reproductive risk factors for musculoskeletal aging and disease. Through this, we hoped to –

1. Understand the associations between of multiple factors of reproductive health and musculoskeletal health independent of confounders like age, BMI, smoking and physical activity
2. Characterize the effects of these reproductive factors on both structural and functional aspects of musculoskeletal health
3. Understand the effect of reproductive and ovarian aging on the musculoskeletal system beyond chronological aging

The population of the world in increasing rapidly. With this increase in the older population, higher population of women are more likely to suffer from disability and functional limitations. These factors represent a major healthcare and economic burden. Expenditure on musculoskeletal disorders are greater than cost of cardiovascular, breast cancer and stroke combined[354]. Thus, it is important to understand the risk factors and underlying mechanisms contributing to functional decline, and disability. Major consequences of these limitations include morbidity and mortality.

The work from this dissertation has important public health implications. Using a life-course approach, our findings established associations between reproductive health and musculoskeletal aging. Accumulation of physiological insults could contribute to poor musculoskeletal health in later life. Understanding the underlying mechanisms could help identify these “at risk” women for future disability and design appropriate interventions to prevent functional decline and disability, and subsequently lower the healthcare expenditures.

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