DR. SULTANA MONIRA HUSSAIN (Orcid ID : 0000-0001-7894-2485) DR. ANITA E WLUKA (Orcid ID : 0000-0001-8024-9049)



Female reproductive and hormonal factors and incidence of primary total knee arthroplasty due to osteoarthritis

Sultana Monira Hussain (MBBS, MPH, PhD)<sup>1</sup>\*, Yuanyuan Wang (MMed, MD, PhD)<sup>1</sup>\*, Graham G. Giles (PhD)<sup>1,2,3</sup>, Stephen Graves (FRACS, PhD)<sup>4</sup>, Anita E. Wluka(MBBS, FRACP, PhD)<sup>1</sup>, Flavia M. Cicuttini (MBBS, FRACP, PhD)<sup>1</sup>

\*Joint first authors

<sup>1</sup>Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC 3004, Australia <sup>2</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Carlton, VIC 3053, Australia <sup>3</sup>Cancer Epidemiology & Intelligence Division, Cancer Council Victoria, Melbourne, VIC

3004, Australia

<sup>4</sup>Australian Orthopaedic Association National Joint Replacement Registry, South Australian Health and Medical Research Institute, Adelaide, SA 5005, Australia

# Funding source

The recruitment of the Melbourne Collaborative Cohort Study was funded by VicHealth and Cancer Council Victoria. This study was further supported by Australian National Health and Medical Research Council (NHMRC) grants 209057, 251553, and 504711, and by infrastructure provided by Cancer Council Victoria. SMH is the recipient of NHMRC Early Career Fellowship (#1142198). YW and AEW are the recipients of NHMRC Career Development Fellowships (Clinical level 1, #1065464 and Clinical Level 2, #1063574,

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the <u>Version of Record</u>. Please cite this article as <u>doi: 10.1002/art.40483</u>

respectively). The funding sources had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

## Corresponding author and address for reprints

Dr Yuanyuan Wang School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia Tel: +61 3 9903 0353 Fax: +61 3 9903 0556 E-mail: <u>yuanyuan.wang@monash.edu</u>

Running head: Female reproductive & hormonal factors and risk of osteoarthritis

#### Abstract

**Objectives:** To examine the associations of female reproductive and hormonal factors with incidence of total knee arthroplasty (TKA) for osteoarthritis, and whether the associations differ according to overweight/obesity status.

**Design:** This study included 22,289 women in the Melbourne Collaborative Cohort Study. Data on age at menarche, pregnancy, parity, years of menstruation, oral contraceptive pill (OCP), menopausal status and hormone replacement therapy (HRT) were collected in 1990-1994. Incidence of TKA during 2001-2013 was determined by linking cohort records to the National Joint Replacement Registry. All analyses were adjusted for age, BMI at midlife, change in BMI (early reproductive age to midlife), country of birth, physical activity, smoking, and education.

**Results:** Over 12.7 years, 1,208 TKAs for osteoarthritis were identified. Ever pregnancy was associated with increased TKA risk (HR=1.32, 95%CI 1.06-1.63). Parity was positively associated with TKA risk (p for trend=0.003). OCP users had increased TKA risk than non-users (OCP<5 years, HR=1.25, 95%CI 1.08-1.45; OCP $\geq$ 5 years, HR=1.17, 95%CI 1.00-1.37). One year increase in menstruation was associated with 1% decreased TKA risk (HR=0.99, 95%CI 0.97-0.99). These associations remained significant only in normal weight women at early reproductive age. Current HRT users had increased TKA risk than non-users (HR=1.33, 95%CI 1.11-1.60); the association was significant only in non-obese women at midlife.

Conclusions: Reproductive and hormonal factors were associated with knee osteoarthritis

risk. These associations remained significant in normal weight women at early reproductive age and non-obese women at midlife. Further work is needed to understand the complex effect of these factors on knee osteoarthritis.

**Key words:** knee osteoarthritis, total knee arthroplasty, reproductive factors, oral contraceptive use, hormone replacement therapy

Knee osteoarthritis (OA) is a prevalent disabling disease with multifactorial aetiology including age, obesity, physical activity, malalignment, and genetics(1). Women have a higher prevalence and incidence of knee OA than men after the age of fifty years(2), suggesting a role for hormonal factors in the pathogenesis of OA. A number of studies have examined the association between reproductive and hormonal factors and knee OA, but the results are inconclusive. Increasing parity has been reported as a risk factor for radiographic knee OA and total knee arthroplasty (TKA) for OA(3, 4), whereas other studies find no association between parity and radiographic knee OA or TKA due to OA(5, 6). A large prospective cohort study reported increased risk of TKA associated with low age at menarche(4), contradicted by another large scale cohort study showing no association(6). No associations have been reported between the use of oral contraceptive pill (OCP) and knee cartilage volume(5), radiographic knee OA(7) or TKA(4, 6). While hormone replacement therapy (HRT) has been shown to be a protective factor for knee cartilage(8) and radiographic knee OA(9, 10), other studies have found no association of HRT with knee pain due to OA(11), knee cartilage(12), or TKA(6, 13). One study showed increased risk of TKA in relation to HRT(4). These discrepant findings may be attributable to the differences across studies in terms of the evaluation criteria for OA (symptomatic, radiographic, or TKA), classification of exposures, study populations, and study designs.

A number of reproductive factors, such as menarche, parity, menopause, use of OCP and HRT, are associated with obesity(14), a major risk factor for knee OA. For example, women gain weight and central body fat at the menopausal transition(15). Thus, it is important to examine whether the associations between reproductive and hormonal factors and knee OA are modified and/or confounded by obesity as obesity may influence the hormonal status of an individual(16). This is of significant clinical and public health importance, given there is no cure for knee OA and we are faced with the global trend of increasing prevalence of knee OA and obesity. Established cohorts, such as the Melbourne Collaborative Cohort Study (MCCS), provide unprecedented opportunity to examine new hypothesis such sex steroid

hormones, metabolic syndrome, index-to-ring finger length ratio, body weight trajectories, gene mutations, physical activity, ethnicity, body adiposity in OA pathogenesis, because of the community-based recruitment of participants which was completely independent of musculoskeletal disease, the long follow-up and the richness of prospectively collected data(17). We aimed to determine (i) whether reproductive factors (age at menarche, pregnancy, parity, duration of menstruation in years) and OCP use increase the risk of TKA for OA, and whether the associations differ according to overweight status during early reproductive years (18-21 years); and (ii) whether menopause and HRT use increase the risk of TKA for OA, and whether the associations differ according to obesity status during midlife using the MCCS data.

# Participants and Methods

# Study participants

The MCCS is a prospective cohort study of 41,514 participants (24,469 women) aged 27-75 years (99.3% were aged 40-69 years), recruited via the electoral roll, advertisements and community announcements in local media in 1990-1994(18). Southern European migrants to Australia were deliberately oversampled to extend the range of lifestyle exposures and to increase genetic variation. The purpose of this study was to investigate prospectively the role of diet and other lifestyle factors in causing common chronic diseases(17). The study protocol was approved by the Cancer Council Victoria Human Research Ethics Committee. Of the recruited participants, 4.8% were excluded because they: died or left Australia prior to January 1, 2001; at the MCCS 2nd follow-up had reported a primary joint replacement prior to January 1, 2001; or had the first recorded procedure being a revision joint replacement as recorded in the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR). The current study examined data for 22,289 women.

#### Assessment of socio-demographic, comorbidity and anthropometric data

At baseline, socio-demographic factors including date of birth, country of birth, smoking, physical activity during leisure time, education level, physician diagnosed hypertension and diabetes were collected by face-to-face interviews. Height and weight were measured according to written protocols based on standard procedures. Body mass index (BMI) was calculated. Since the mean age of participants at baseline was 54.6 (S.D. 8.6) years, weight and BMI at study entry were termed as weight and BMI at midlife. Participants were asked

their weight between 18 and 21 years (early reproductive age). These data were previously published(19, 20). Change in BMI from early reproductive age to midlife was calculated.

### Assessment of reproductive and hormonal factors

At baseline, information was collected on age at menarche, ever being pregnant, number of live births (parity), menopausal status, age at menopause, and having had a hysterectomy or ovariectomy. Each woman was asked if she had ever taken HRT or OCP, and if so, for how long and whether they were using currently or a past user. Years of menstruation was calculated for women who experienced a natural menopause by deducting the age at menarche from the age at menopause.

# Incidence of total knee arthroplasty for osteoarthritis

The AOA NJRR collects information on prostheses, patient demographics, type and reason for arthroplasty. Data are collected from both public and private hospitals and validated using a sequential multi-level matching process against State and Territory Health Department unit record data. Following the validation process and retrieval of unreported records, the Registry collects an almost complete set of data relating to arthroplasties (>99%) in Australia(21). This study examined the first knee arthroplasty with a contemporaneous diagnosis of OA, as recorded in the AOA NJRR. If one person had multiple arthroplasties, such as bilateral knee arthroplasties, or both knee and hip arthroplasties, the first recorded procedure was considered the event. Matching of MCCS participants using first name, surname, date of birth, and sex, to the AOA NJRR in order to identify those who had an arthroplasty performed between 1 January 2001 and 31 December 2013 was using the Freely Extensible Biomedical Record Linkage (Febrl) system. The linkage study was approved by the Human Research Ethics Committee of Cancer Council Victoria and Monash University. Knee OA was defined as the first recorded primary total joint arthroplasty being a TKA for OA.

#### Statistical analysis

Cox proportional hazards regression models were used to estimate the hazard ratios (HR) for TKA associated with each individual reproductive and hormonal factor with age as the time scale. BMI at midlife, change in BMI from early reproductive age to midlife, country of birth, physical activity, smoking, and education were included in all models. Additional adjustment was done for comorbidities [hypertension (yes/no), diabetes (yes/no)]. Follow-up for TKA (i.e. calculation of person-time) began at January 1, 2001, and ended at date of first TKA for This article is protected by copyright. All rights reserved

OA or date of censoring. Subjects were censored at either the date of first TKA performed for indications other than OA, the date of death, the date left Australia, or end of follow-up (i.e. December 31, 2013), whichever came first. Association between HRT use, duration of HRT use, age at menopause, years of menstruation and TKA was analysed only in women who experienced natural menopause at baseline and did not undergo an ovariectomy. To examine whether the relationship between reproductive factors, OCP and risk of TKA for OA was modified by overweight status, stratified analysis was performed based on overweight status at early reproductive age (18-21 years). Similarly stratified analysis was performed based on obesity status at midlife to examine the association between age at menopause, years of menstruation, HRT and risk of TKA. All these analyses were repeated on the subgroup of women who attended follow-up during 2004-7 (n=15,828) to examine whether the results changed after adjusting for change in BMI at midlife to 2004-7 follow-up.

Tests based on Schoenfeld residuals and graphical methods using Kaplan-Meier curves showed no evidence that proportional hazard assumptions were violated. All statistical analyses were performed using Stata 13.0 SE (StataCorp LP., College Station, TX, USA).

#### **Results**

Over an average of 12.7 (SD 2.9) years of follow-up, we identified 1,208 women with incident TKA for OA. Descriptive statistics of the participant characteristics are shown in Table 1. Women who received a TKA were older, had greater BMI at midlife and lower levels of education, were more likely to be overweight/obese during early reproductive life and obese at midlife, and to be born in Australia/New Zealand, and less likely to smoke than those who had no joint replacement. Those having a TKA were more likely to have been pregnant, have higher parity, and to be postmenopausal and current HRT users compared with those who had no joint replacement.

Table 2 shows reproductive and hormonal factors according to overweight status during early reproductive years, and menopausal status and HRT related factors according to obesity status at midlife. Women who were overweight/obese at early reproductive age had an earlier onset of menarche and shorter duration of OCP use compared with the normal weight women. Women who were obese at midlife were more likely to be postmenopausal, less likely to be current HRT users, and had shorter duration of HRT use compared with non-obese women.

The associations between reproductive and hormonal factors and risk of TKA are presented in Table 3. After adjustment, ever being pregnant was associated with increased risk of TKA (HR 1.32, 95% confidence interval (CI) 1.06-1.63). There was a positive linear association between parity and the risk of TKA. Using nulliparous women as the reference, the adjusted HRs were 1.10 (95% CI 0.83-1.47), 1.18 (95% CI 0.95-1.46), 1.25 (95% CI 1.01-1.55) 1.35 (95% CI 1.09-1.68) for parity 1, 2, 3, and  $\geq$ 4, respectively, p for trend 0.003. Women taking OCP had an increased risk of TKA compared with non-users (never OCP: reference; OCP<5 years: HR 1.25, 95% CI 1.08-1.45; OCP $\geq$ 5 years: HR 1.17, 95% CI 1.00-1.37). Years of menstruation was negatively associated with TKA risk (HR 0.99, 95% CI 0.97-0.99). All these associations remained significant in women with normal weight at early reproductive age, but not significant in women who were overweight/obesity despite the lower rate of TKA in normal weight group compared with the overweight/obese group (5.2% versus 7.1%). No association was observed between age at menarche and TKA.

Current HRT users had increased risk of TKA compared with non-users (HR 1.33, 95% CI 1.11-1.60). There was a linear association between increasing duration of HRT use and increased risk of TKA (never HRT use, reference; HRT<1 year, HR 1.12, 95% CI 0.91-1.39; HRT≥1 year, HR 1.30, 95% CI 0.99-1.72, p for trend 0.03). All the associations remained significant in women who were non-obese at midlife. There was a marginally significant association between HRT use and increased risk of TKA in the obese group (HR 1.38, 95% CI 0.99-1.92). There was a trend for a positive linear association between duration of HRT use and risk of TKA in non-obese women (p for trend 0.06). The rate of TKA was lower in the midlife normal/overweight women compared with the obese women (4.0% in normal/overweight versus 10.4% in obese). No association was observed between age at menopause and TKA. Additional adjustment for comorbidities did not change the results (data not shown). Likewise, the result of the subgroup analysis with additional adjustment for change in BMI at midlife to 2004-7 follow-up, were of similar direction and magnitude of those of total population as presented in Table 3 (Supplementary Table 1).

#### Discussion

Ever being pregnant, increasing parity, taking OCP, current HRT use and longer duration of HRT use were associated with increased risk of TKA for OA, while prolonged years of menstruation was associated with reduced risk. In subgroup analyses, all the associations This article is protected by copyright. All rights reserved between reproductive factors and TKA remained significant in normal weight but not for overweight/obese women at early reproductive years. Similarly, current HRT use was associated with increased risk of TKA in non-obese but not in obese women at midlife. No association was observed between age at menarche or age at menopause and TKA.

Consistent with two previous studies(3, 4), we found that pregnancy and parity increased the risk of TKA. This may be due to weight gain during pregnancy and postpartum weight retention(3, 4) which is common(22). We found normal weight women gained more weight from early reproductive age to midlife compared with the overweight/obese women. However, the association of pregnancy and parity with TKA was independent of BMI at midlife and change in BMI from early reproductive life to midlife. In subgroup analysis based on overweight status at early reproductive age (obesity is not common at this age), increased risk of TKA in relation to pregnancy and parity was seen in normal weight women, but not those overweight/obese despite a higher incidence of TKA in the overweight/obese women. These findings suggest that the relationship between pregnancy, parity and TKA for OA is complex and may not simply be mediated through increased weight gain associated with pregnancy and parity.

While neither age at menarche nor age at menopause was associated with TKA risk, increasing years of menstruation was associated with decreased risk of TKA for OA. This remained significant in women of normal weight in early reproductive life, but not those overweight/obese. There is no clear association between age at menarche and age at menopause, with studies reporting direct association, inverse association, or no association(23). Years of menstruation is a marker of prolonged reproductive life and active ovarian function(23). Hormonal depletion at the end of active reproductive period is linked to tissue damage and organ dysfunction(24), and increasing the risk of several diseases(25-27). The results of our study suggest a protective effect of prolonged reproductive life on decreased TKA risk.

Use of OCP increased the risk of TKA for OA in women of normal weight at early reproductive age, and current HRT use increased the risk of TKA for OA in women who were non-obese in midlife. The relationship between reproductive hormone supplementation and knee OA is complex. Although greater exposure to oestrogen may promote osteoarthritic changes by increasing cartilage damage(28), it is unclear whether hormone supplementations This article is protected by copyright. All rights reserved

increase circulating sex hormone to sufficient levels significantly to affect joint structure. In healthy women HRT user have more knee cartilage volume than non-users(8). The effect of exogenous hormones (OCP and HRT) on joint health can be affected by many factors, including age at starting OCP, the time elapsed from menopause to starting HRT and the duration of HRT use. We found that current HRT users started using HRT at an older age than past users (53.9 $\pm$ 7.0 years versus 50.3 $\pm$ 7.5 years, p=0.01). As the average age of menopause in developed countries is 51 years(29), these data suggest that the past HRT users began HRT at menopausal transition, whereas the current HRT users approximately 3 years after menopause. It may be that, analogous to other diseases(30, 31), starting HRT later in the menopause is associated with increased risk of knee OA. Alternatively, the association between HRT use and TKA may be due to non-biological factors with women on HRT having more access to health services, including TKA. However, we adjusted for confounders for TKA and Australians have universal cover so can readily access TKA(32, 33). Paradoxically, exposure to OCP increased, but prolonged years of menstruation decreased, the risk of knee OA. Along with oestrogen, other sex hormones might play a role in protecting women from knee OA development and progression. Prolonged years of menstruation increases the exposure to not only oestrogen, but also other endogenous sex hormones. The use of OCP might unfavourably change the circulatory levels of endogenous hormones thus affect joint health adversely. Further work will be needed to clarify this and the differences in OA outcomes based on the OCP type.

We observed significant associations between reproductive factors, taking OCP and the risk of TKA in normal weight but not overweight/obese women at early reproductive ages, and between current HRT use and TKA in normal/overweight but not obese women at midlife. The underlying mechanism might be explained by the association of reproductive factors with obesity(34), inflammation(35) and endothelial dysfunction(35, 36). Overweight/obese women have already been exposed to increased mechanical loading and are suffering from inflammation and endothelial dysfunction due to excessive fat mass, known risk factors for knee OA. This may mask any additional association between reproductive factors and TKA. If a person is obese, the excessive joint loading may be more likely to drive the OA pathogenesis and progression. These findings suggest that the influence of reproductive and hormonal factors on the risk of TKA due to OA is complex which warrants further investigation.

Our results need to be considered within the study's limitations. We defined OA based on arthroplasty. Arthroplasty for OA may be influenced by factors such as access to health care, socioeconomic status, and patient preference, in addition to disease severity. This study was carried out in Australia where there is universal health cover, so access to arthroplasty is available to all. Nevertheless, arthroplasty does reflect end-stage joint disease. We performed analysis with age as time scale and adjusted for BMI at midlife, change in BMI (early to midlife), country of birth, education, physical activity, smoking and comorbidity. TKA was ascertained from the AOA NJRR. We did not have accurate arthroplasty data prior to 2001. This may have resulted in non-differential misclassification of TKA. Participants were asked at midlife (40-69 years) to recall their weight at age 18-21 years, which may introduce bias by under reporting weight especially by overweight and obese women(37). However, we observed higher incidence of TKA in overweight/obese women at early reproductive age. In this study we examined weight at midlife (1990-4, baseline) and TKA between 2001-13. In the subgroup of women (n=15,828) with weight measured at the 2004-7 follow-up, there was strong correlation between weight measured at 1990-4 and 2004-7 (r=0.90), supporting the notion that weight trajectories tend to remain stable in healthy adult women(38). We repeated all the analyses in this subgroup-adjusting for change in BMI at midlife to 2004-7 follow-up and found results with similar direction and magnitude to those of the total population. However, we could not adjust for weight history of entire life since weight was not measured repeatedly throughout life including weight at the time of pregnancy. The self-reported reproductive and hormonal data were collected at baseline when included women were middle-aged. Any misclassification is most likely to be non-differential and would have underestimated the associations. Reproductive history and OCP use would not change, but HRT use and its duration might have changed during the follow-up. As duration of HRT use was associated with increased TKA risk, not updating the duration of HRT may have resulted in an underestimation of the association. Although we do not have data on types of OCP, the combined OCPs the most commonly used at that time (39). It remains possible that residual confounding contributed to the association between hormonal factors and risk of TKA.

Ever being pregnant, increasing parity, OCP use, current HRT use, and increasing duration of HRT use are risk factors for TKA due to OA, while prolonged years of menstruation decrease the risk. These findings add to the ongoing literature regarding the complex relationship of reproductive and hormonal factors and knee OA risk. Given the huge burden of knee OA and associated TKA in women worldwide, further studies are needed to understand the complex This article is protected by copyright. All rights reserved

association between reproductive factors and knee OA risk, and the role of obesity in this relationship.

#### Acknowledgements

The Melbourne Collaborative Cohort Study was made possible by the contribution of many people, including the original investigators and the diligent team who recruited the participants and who continued working on follow up. We would like to express our gratitude to the many thousands of Melbourne residents who participated in the study. For the data linkage, we would especially like to thank the Registry coordinator Ann Tomkins and statistician Lisa Miller from the Australian Orthopaedic Association National Joint Replacement Registry, and Ms Georgina Marr from Cancer Council Victoria.

#### References

1. Felson DT. Risk factors for osteoarthritis: understanding joint vulnerability. Clin Orthop Relat Res. 2004(427 Suppl):S16-21.

2. Felson DT. Epidemiology of hip and knee osteoarthritis. Epidemiol Rev. 1988;10:1-28.

3. Wise BL, Niu J, Zhang Y, Felson DT, Bradley LA, Segal N, et al. The association of parity with osteoarthritis and knee replacement in the multicenter osteoarthritis study. Osteoarthritis Cartilage. 2013;21(12):1849-54.

4. Liu B, Balkwill A, Cooper C, Roddam A, Brown A, Beral V. Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. Ann Rheum Dis. 2009;68(7):1165-70.

5. Wei S, Venn A, Ding C, Martel-Pelletier J, Pelletier JP, Abram F, et al. The associations between parity, other reproductive factors and cartilage in women aged 50-80 years. Osteoarthritis Cartilage. 2011;19(11):1307-13.

6. Hellevik AI, Nordsletten L, Johnsen MB, Fenstad AM, Furnes O, Storheim K, et al. Age of menarche is associated with knee joint replacement due to primary osteoarthritis (The HUNT Study and the Norwegian Arthroplasty Register). Osteoarthritis Cartilage. 2017;25(10):1654-62.

7. Sandmark H, Hogstedt C, Lewold S, Vingard E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis. 1999;58(3):151-5.

8. Wluka AE, Davis SR, Bailey M, Stuckey SL, Cicuttini FM. Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis. 2001;60.

9. Spector TD, Nandra D, Hart DJ, Doyle DV. Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford Study. Ann Rheum Dis. 1997;56(7):432-4.

10. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum. 1999;42(1):17-24.

11. Nevitt MC, Felson DT, Williams EN, Grady D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: The Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2001;44.

12. Zhang Y, McAlindon TE, Hannan MT, Chaisson CE, Klein R, Wilson PW, et al. Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: the Framingham Study. Arthritis Rheum. 1998;41(10):1867-73.

13. Cirillo DJ, Wallace RB, Wu L, Yood RA. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. Arthritis Rheum. 2006;54(10):3194-204.

14. Newby PK, Dickman PW, Adami HO, Wolk A. Early anthropometric measures and reproductive factors as predictors of body mass index and obesity among older women. Int J Obes (Lond). 2005;29(9):1084-92.

15. Sutton-Tyrrell K, Zhao X, Santoro N, Lasley B, Sowers M, Johnston J, et al. Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation. Am J Epidemiol. 2010;171(11):1203-13.

16. Brown LM, Gent L, Davis K, Clegg DJ. Metabolic impact of sex hormones on obesity. Brain Res. 2010;1350:77-85.

17. Milne RL, Fletcher AS, MacInnis RJ, Hodge AM, Hopkins AH, Bassett JK, et al. Cohort Profile: The Melbourne Collaborative Cohort Study (Health 2020). Int J Epidemiol. 2017;46(6):1757-i.

18. Giles GG, English DR. The Melbourne Collaborative Cohort Study. IARC Sci Publ. 2002;156:69-70.

19. Wang Y, Wluka AE, Simpson JA, Giles GG, Graves SE, de Steiger RN, et al. Body weight at early and middle adulthood, weight gain and persistent overweight from early adulthood are predictors of the risk of total knee and hip replacement for osteoarthritis. Rheumatology (Oxford). 2013;52(6):1033-41.

20. Krishnan K, Bassett JK, Macinnis RJ, English DR, Hopper JL, McLean CA, et al. Associations between weight in early adulthood, change in weight and breast cancer risk in postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2013.

21. Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide: AOA; 2016.

22. Mannan M, Doi SA, Mamun AA. Association between weight gain during pregnancy and postpartum weight retention and obesity: a bias-adjusted meta-analysis. Nutr Rev. 2013;71(6):343-52.

23. Forman MR, Mangini LD, Thelus-Jean R, Hayward MD. Life-course origins of the ages at menarche and menopause. Adolescent Health, Medicine and Therapeutics. 2013;4:1-21.

24. Rocca WA, Shuster LT, Grossardt BR, Maraganore DM, Gostout BS, Geda YE, et al. Long-term effects of bilateral oophorectomy on brain aging: unanswered questions from the Mayo Clinic Cohort Study of Oophorectomy and Aging. Women's health (London, England). 2009;5(1):39-48.

25. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry. 2006;63(4):385-90.

26. Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology. 2014;82(3):222-9.

27. Svejme O, Ahlborg HG, Nilsson JA, Karlsson MK. Low BMD is an independent predictor of fracture and early menopause of mortality in post-menopausal women--a 34-year prospective study. Maturitas. 2013;74(4):341-5.

28. Felson DT, Nevitt MC. The effects of estrogen on osteoarthritis. Curr Opin Rheumatol. 1998;10(3):269-72.

29. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, et al. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. JAMA cardiology. 2016;1(7):767-76.

30. Salpeter SR, Walsh JM, Greyber E, Salpeter EE. Brief report: Coronary heart disease events associated with hormone therapy in younger and older women. A meta-analysis. J Gen Intern Med. 2006;21(4):363-6.

31. Salpeter SR, Walsh JM, Greyber E, Ormiston TM, Salpeter EE. Mortality associated with hormone replacement therapy in younger and older women: a meta-analysis. J Gen Intern Med. 2004;19(7):791-804.

32. Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 2009;68(4):490-6.

33. Hussain SM, Cicuttini FM, Bell RJ, Robinson PJ, Davis SR, Giles GG, et al. Incidence of total knee and hip replacement due to osteoarthritis in relation to circulating sex steroid hormone concentrations in women. Arthritis & rheumatology (Hoboken, NJ). 2014;66(8):2144-51.

34. Lovejoy JC. The influence of sex hormones on obesity across the female life span. J Womens Health. 1998;7(10):1247-56.

35. Jabbour HN, Sales KJ, Catalano RD, Norman JE. Inflammatory pathways in female reproductive health and disease. Reproduction (Cambridge, England). 2009;138(6):903-19.

36. Campesi I, Occhioni S, Tonolo G, Cherchi S, Basili S, Carru C, et al. Ageing/Menopausal Status in Healthy Women and Ageing in Healthy Men Differently Affect Cardiometabolic Parameters. Int J Med Sci. 2016;13(2):124-32.

37. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. Maternal and child health journal. 2007;11(2):137-44.

38. Heo M, Faith MS, Pietrobelli A. Resistance to change of adulthood body mass index. Int J Obes. 2002;26:1404.

39. Richters J, Grulich AE, de Visser RO, Smith AM, Rissel CE. Sex in Australia: contraceptive practices among a representative sample of women. Aust N Z J Public Health. 2003;27(2):210-6.

<b>—</b>	Total knee	No joint	р
	replacement	replacement	
	n = 1208	n = 21081	
Age, years	57.6 (7.3)	54.4 (8.6)	< 0.001
Body mass index at midlife, kg/m <sup>2</sup>	29.7 (5.3)	26.5 (4.8)	< 0.001
Overweight/obese at early reproductive	191 (15.8)	2,483 (11.8)	< 0.001
life, n (%)			
Obesity at midlife, n (%)	501 (41.5)	4,335 (20.6)	< 0.001

Table 1. Baseline characteristics of study participants

Country of birth, n (%)			< 0.001
Australia/United Kingdom	979 (81.0)	16179 (76.8)	
Italy/Greece	229 (19.0)	4902 (23.2)	
Education, n (%)			< 0.001
Primary and some secondary	821 (68.5)	13029 (62.4)	
Completed secondary & degree/diploma	378 (31.5)	7866 (37.6)	
Vigorous physical activity, n (%)			0.03
None	968 (80.1)	16942 (80.4)	
1-2 times/week	153 (12.7)	2513 (11.9)	
>=3 times/week	87 (7.2)	1622 (7.7)	
Smoking, n (%)			< 0.001
Non-smoker	886 (73.3)	14549 (69.0)	
Ex-smoker	261 (21.6)	4594 (21.8)	
Current smoker	61 (5.1)	1935 (9.2)	
Diabetes, n (%)	31 (2.6)	638 (3.0)	0.002
Hypertension, n (%)	380 (31.5)	4506 (21.4)	< 0.001
Age at menarche, years	13.0 (1.7)	13.1 (1.6)	0.004
Ever pregnant, n (%)	1110 (91.9)	18729 (88.9)	< 0.001
Parity, n (%)			< 0.001
0	126 (10.5)	3002 (14.2)	
1	85 (7.1)	1815 (8.6)	
2	337 (27.9)	6948 (33.0)	
3	335 (27.8)	5411 (25.7)	
≥4	323 (26.8)	3892 (18.5)	
Duration of oral contraceptive use, n (%)			0.002
0 (never use)	526 (44.0)	8,516 (41.5)	
Any use <5 years	357 (30.4)	5,921 (28.8)	
≥5 years	291 (24.8)	6,092 (29.7)	
Postmenopause <sup>†</sup> , n (%)	848 (76.9)	11484 (58.3)	< 0.001
Age at menopause†, years	49.3 (5.0)	49.3 (4.9)	0.18
Years of menstruation <sup>†</sup> , years (n=12,332)	36.3 (5.5)	36.1 (5.1)	0.04
Hormone therapy <sup>‡</sup> , n (%) (n=12,300)			< 0.001
Never	600 (71.2)	8,280 (72.3)	

Past	85 (10.1)	1,293 (11.3)	
Current	158 (18.7)	1,884 (16.4)	
Duration of hormone therapy‡, n (%)			0.001
(n=11,238)			
0 (never use)	600 (78.3)	8,280 (79.1)	
Any use <1 year	108 (14.1)	1,513 (14.5)	
≥1 year	58 (7.6)	679 (6.5)	
Ovariectomy, n (%)	149 (44.2)	1938 (44.2)	0.94

Values are reported as mean (SD), or number (%)

† only those having natural menopause (n=12,332)

‡ only those having natural menopause and HRT data not missing

Author Manus

-

Early reproductive age (18 - 21 years)					
	Normal weight Overweight/obes		р		
<b>—</b>	n = <b>19,615</b>	n = <b>2,674</b>			
Age at menarche, years	13.1 (1.6)	12.9 (1.8)	< 0.001		
Ever pregnant, n (%)	17,494 (89.2)	2,345 (87.8)	0.03		
Parity, n (%)			0.47		
0	2,722 (13.9)	406 (15.2)			
1	1,672 (8.5)	228 (8.6)			
2	6,427 (32.8)	858 (32.1)			
3	5,067 (25.8)	679 (25.5)			
≥4	3,718 (19.0)	497 (18.6)			
Duration of oral contraceptive use,			< 0.001		
n (%)					
0 use	7,576 (39.7)	1,466 (56.1)			
Any use to <5 years	5,653 (29.6)	625 (23.9)			
≥5 years	5,859 (30.7)	524 (20.0)			
Years of menstruation <sup>†</sup> , years	34.2 (6.3)	34.8 (6.1)	0.05		
(n=12,332)					
Postmenopau	isal women (n=12,	,332)			
0	Normal and	Obese			
$\mathbf{O}$	overweight	<b>n</b> = 3,066			
	<b>n</b> = 9,266				
Age at menopause <sup>†</sup> , years	49.3 (4.9)	49.2 (5.0)	0.04		
Years of menstruation <sup>†</sup> , years	35.1 (5.7)	35.4 (5.6)	0.07		
Hormone therapy‡, n (%)			< 0.001		
(n=12,300)					
Never	6,406 (69.3)	2,474 (80.9)			
Past	1,111 (12.0)	267 (8.7)			
Current	1,725 (18.7)	317 (10.4)			
Duration of hormone therapy‡, n			< 0.001		
(%) (n=11,238)					

Table 2: Reproductive and hormonal factors at age 18-21 years and at midlife accordingto overweight or obesity status

0 use	6,406 (76.5)	2,474 (86.4)
Any use to <1 year	1,344 (16.1)	277 (9.7)
≥1 year	624 (7.5)	113 (4.0)

Values are reported as mean (SD), or number (%)

† only those having natural menopause (n=12,332)

‡ only those having natural menopause and HRT data not missing

Manusc Auth

	Hazard ratio	P value	Hazard ratio	P value	Hazard ratio	P value	
t	(95% CI)		(95% CI)		(95% CI)		
Early reproductive age (18 - 21years)							
	All population Normal weight		Overweight/obese				
0	n= 22,289		n= 19,615		n= 2,674		
Age at menarche, years	1.00 (0.97, 1.04)	0.91	1.02 (0.98, 1.06)	0.34	0.91 (0.82, 1.00)	0.06	
Ever pregnant (Yes vs. No)	1.32 (1.06, 1.63)	0.01	1.40 (1.10, 1.78)	0.01	0.93 (0.57, 1.53)	0.78	
Parity categories							
0	1.00		1.00		1.00		
1	1.10 (0.83, 1.47)	0.50	1.04 (0.76, 1.42)	0.80	1.43 (0.71, 2.87)	0.32	
2	1.18 (0.95, 1.46)	0.14	1.18 (0.93, 1.49)	0.17	1.12 (0.64, 1.96)	0.69	
3	1.25 (1.01, 1.55)	0.04	1.24 (0.98, 1.57)	0.07	1.26 (0.73, 2.20)	0.41	
≥4	1.35 (1.09, 1.68)	0.01	1.38 (1.09, 1.74)	0.01	1.07 (0.61, 1.90)	0.81	
P for trend	0.003		0.002		0.91		
Duration of oral contraceptive use, categories							
0 use	1.00		1.00		1.00		
Any use to <5 years	1.25 (1.08, 1.45)	0.002	1.37 (1.17, 1.60)	< 0.001	0.72 (0.47, 1.11)	0.13	
$\geq$ 5 years	1.17 (1.00, 1.37)	0.05	1.25 (1.05, 1.48)	0.01	0.85 (0.54, 1.33)	0.49	
Years of menstruation years (n=12,332)	0.99 (0.97, 0.99)	0.01	0.98 (0.97, 1.00)	0.01	0.99 (0.96, 1.02)	0.61	
	At midlife (Postme	enopausal v	vomen)				

 Table 3. Associations between reproductive and hormonal factors and risk of total knee arthroplasty for osteoarthritis\*

	All population n=12,332		Normal/overweight n= 9,266		Obese	
					<b>n</b> = 3,066	
Age at menopause, years (n=12,332)	0.99 (0.97, 1.01)	0.42	1.00 (0.97, 1.03)	0.99	0.98 (0.95, 1.01)	0.18
Years of menstruation (n=12,332)	0.99 (0.97, 0.99)	0.01	0.98 (0.97-0.99)	0.03	0.99 (0.97-1.00)	0.10
Hormone therapy (n=12,300)						
Never	1.00		1.00		1.00	
Past	0.99 (0.79, 1.25)	0.94	0.86 (0.64, 1.17)	0.34	1.20 (0.84, 1.73)	0.31
Current	1.37 (1.14, 1.64)	0.001	1.39 (1.12, 1.74)	0.003	1.38 (0.99, 1.92)	0.054
Duration of hormone therapy (n=11,238)						
0 use	1.00		1.00		1.00	
Any use to <1 year	1.12 (0.91, 1.39)	0.27	1.05 (0.80, 1.36)	0.73	1.29 (0.91, 1.84)	0.15
$\geq 1$ year	1.30 (0.99, 1.72)	0.06	1.36 (0.99, 1.89)	0.06	1.21 (0.71, 2.05)	0.49
P for trend	0.03		0.06		0.19	

\*adjusted for body mass index at midlife, change in body mass index (early to midlife), country of birth, education levels, vigorous physical

activity, and smoking status

Autho

# **University Library**



# A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

# Author/s:

Hussain, SM;Wang, Y;Giles, GG;Graves, S;Wluka, A;Cicuttini, FM

# Title:

Female Reproductive and Hormonal Factors and Incidence of Primary Total Knee Arthroplasty Due to Osteoarthritis

# Date:

2018-07

# Citation:

Hussain, S. M., Wang, Y., Giles, G. G., Graves, S., Wluka, A. & Cicuttini, F. M. (2018). Female Reproductive and Hormonal Factors and Incidence of Primary Total Knee Arthroplasty Due to Osteoarthritis. [Abstract]. ARTHRITIS & RHEUMATOLOGY, 70 (7), pp.1022-1029. https://doi.org/10.1002/art.40483.

# Persistent Link: http://hdl.handle.net/11343/284021