Observational Study

Abortion is associated with knee osteoarthritis among older women in China

A STROBE-compliant article

Yan-Ting Meng, PhD\textsuperscript{a}, Yuan-Yuan Wang, MS\textsuperscript{b}, Yan-Hui Zhou, PhD\textsuperscript{a}, Jing-Xia Fu, MS\textsuperscript{a}, Ming-Zhu Chen, MS\textsuperscript{a}, Chen Xu, MS\textsuperscript{b}, Si Qin, MS\textsuperscript{b}, Yang Luo, MD\textsuperscript{a,*}  

Abstract

The current studies revealed inconsistent relationship between reproductive factors and osteoarthritis. Community-based research has not been conducted in China. The study was to examine the association of reproductive factors with the prevalence of knee osteoarthritis (OA).

Through a multistage stratified random sampling method, 10 streets or villages from 5 cities in Hunan province were randomly selected, a total 2746 eligible women aged 50 to 83 were recruited in this cross-sectional study. A structured questionnaire including demographic factors, socio-economic status, reproductive factors, and knee OA was used. According to the criteria of American College of Rheumatology, clinical knee OA was assessed by doctors in community or village health clinics for knee pain, age, morning stiffness, crepitus on active motion or for knee pain, morning stiffness, crepitus on active motion, and tenderness of the bony navigation of the joint. Self-reported age of menarche, parity, abortion history, and menopausal status were collected.

The prevalence of knee OA was 13.44%. Abortion is associated with knee OA (odds ratio [OR] = 1.271, 95% confidence interval [CI] = 1.007, 1.606), but age at menarche, parity, and menopausal status were not the factors. Furthermore, age (OR = 1.040, 95% CI = 1.020, 1.060), weight (OR = 1.019, 95% CI = 1.004, 1.035), higher education level (OR = 1.530, 95% CI = 1.121, 2.088), higher monthly household income (OR = 0.583, 95% CI = 0.441, 0.770 for 3000–4999 Y and OR = 0.599, 95% CI = 0.431, 0.833 for 5000 Y or more), and chronic gastritis (OR = 3.364, 95% CI = 2.548, 4.442) were associated with knee OA.

Abortion may increase the risk of knee OA. Special attention should be paid to women with a history of abortion, and women who are planning to abort should be informed of the risk of knee OA later in life. The relationship between abortion and knee OA should be interpreted with caution and further confirmed.

Abbreviations: CG = chronic gastritis, CI = confidence interval, NSAIDS = non-steroidal anti-inflammatory drugs, OA = osteoarthritis, OR = odds ratio, SD = standard deviation.

Keywords: cross-sectional study, osteoarthritis, prevalence, reproductive factor

1. Introduction

Osteoarthritis (OA) is an age-related joint disorder. As one of the most common sites of arthritis,\textsuperscript{[1]} knee OA brings a tremendous burden to the population because of pain and stiffness, which in turn leads to significant disability and requiring surgical intervention.\textsuperscript{[2]} Due to the increase in the size of the aging human population, knee OA has become one of the major global health problems.

The precise etiology of OA is unknown.\textsuperscript{[3]} Women have a higher prevalence and incidence of OA than men after 50 years old,\textsuperscript{[2,4,5]} around the same age of the menopausal transition.\textsuperscript{[6]} Reproductive factors, that is, menarche, parity, and menopause, may play a role in the risk of OA by influencing lifetime or acute exposure to estrogen or other sex hormones, although the nature of the effects of estrogen on the pathogenesis of OA remains uncertain.\textsuperscript{[7]}

There are some studies on reproductive factors and OA, but the conclusions are inconsistent. In addition to 2 reviews,\textsuperscript{[3,8]} recent research results are also conflicting. For instance, 2 cross-sectional studies and a longitudinal study showed that increased numbers of birth correlated with the risk of radiographic knee OA or joint replacement,\textsuperscript{[9–11]} but this contradicted another large prospective cohort study revealing no linkage between parity and knee or hip replacement.\textsuperscript{[12]} Menopausal status, age of menopause were not associated with knee or hip replacement.\textsuperscript{[13,14]} another study, however, found that women with longer periods had a lower risk of OA.\textsuperscript{[15]} The relationship of hormonal factors and OA may be too complex, or otherwise, yet to be determined.\textsuperscript{[8]}
China has the world’s largest elderly population. Among the population aged 60 and over, the prevalence of symptomatic knee OA was higher among women (15.0%), compared with men (5.6%). Some factors associated with knee OA in older adults include obesity, previous knee trauma, hand OA, women sex, and older age. Despite the literature on knee OA and reproductive factors in China, some limitations exist in the research, such as focusing on special groups including retired workers, selection bias (recruiting participants from hospital rather than communities). Meanwhile, knee pain and clinical knee OA were as outcome variables in their study, but there were various reasons for knee pain and stiffness, for instance, rheumatoid arthritis, a common inflammatory joint disease, also has knee pain and morning stiffness symptoms. Most importantly, the results based on data from >10 years ago may not reflect the present situation. Our study is based on data from a large-scale survey among general women in community, which may fill the gaps in existing research and provide the latest evidence.

Using the data, we mainly aimed to estimate the relationship between reproductive factors and knee OA. We hypothesized that reproductive factors were at least partially, if not completely, related to knee OA.

2. Methods

This study was prepared according to the strengthening the reporting of Observational Studies in Epidemiology (STROBE) Statement.

2.1. Study design

This study was a cross-sectional survey. Ethics approval was obtained from the Ethical Committee of Xiangya Nursing School, Central South University.

2.2. Participants and study size

This study was a conducted in collaboration with the Women’s Federation of Hunan provincial government from April to September 2018. The work assessed demographic information, social-economic status, reproductive factors, chronic diseases, and health-related knowledge of community residents, serving the needs of policy research on women health.

The survey took a multistage stratified random sampling to recruit participants. First, one city each in the East, West, South, North, and Central areas of Hunan was randomly selected to ensure the representativeness and comprehensiveness. Second, a district and a county, was chosen at random from each of the cities. Third, a street and a village were randomly selected from its district or county. Finally, according to the house number, 1200 participants were recruited by using the random number table. The eligibility criteria at recruitment included: women aged 10 and over; current residents in Hunan Province; and able to communicate the questionnaires independently or with the help of investigators. The participants’ verbal informed consent was obtained. Totally, 12,000 eligible women participated in the survey, and the response rate was 95.72%. We selected 3000 women aged 50 and over from the original database who were surveyed about their demographics, reproductive factors, and knee OA. Then we excluded 254 subjects based on the following exclusion criteria: 30 participants were excluded by age, and 224 participants were excluded with incomplete data. Finally, 2746 eligible women aged 50 and over were included in the analysis (Fig. 1).

2.3. Variables and measurement

2.3.1. Reproductive variables. Self-reported age of menarche, parity, abortion history, and menopausal status were collected. Age of menarche was recorded as a continuous variable. Parity was classified into 3 categories: (≤1), (2), and (≥3). Menopause is diagnosed after 12 months of amenorrhea resulting from the permanent cessation of ovarian function. We diagnosed menopause by asking participants about the menopausal status and the time of the last menstrual period. Both menopause status and abortion history were as dichotomous variable (no and yes).

2.3.2. Socioeconomic and chronic disease variables. Both age and weight were assessed as continuous variables. We categorized education level into 3 categories: elementary school or less, junior high school, and senior high school or higher. Average monthly household income was divided into 3 categories: <3000 Y, 3000 to 4999 Y, and ≥5000 Y. Average monthly personal income was classified into 3 categories: none, <3000 Y, and ≥3000 Y (1USD = 7.12 Y in September 2019). Both smoking and drinking were as dichotomous variable: no and yes. Chronic gastritis (CG) were self-reported, physician-diagnosed diseases which was confirmed by insurance records and treatment information.

2.3.3. Outcome variable. Clinical knee OA criteria was used in this study. Although some studies use radiographic knee OA that is, Kellgren and Lawrence radiographic grading scheme, which is an objective standard, radiographic usefulness relates more importantly to the exclusion of other diagnostic possibilities rather than the confirmation of OA, and the radiological findings of OA do not correlate well with their clinical symptoms. Clinical OA was defined by features in the history and on examination. As the widely recognized diagnostic criteria of OA, that is, the criteria of American College of Rheumatology, clinical knee OA is considered if the participant has knee pain plus at least 3 of the following 6 clinical findings: age >50 years, morning stiffness <30 minutes duration, crepitus on active motion, tenderness of the bony margins of the joint, bony enlargement on examination, and

---

Figure 1. Flow diagram.
a lack of palpable warmth of the synovium, which is 84% sensitive and 89% specific.\(^{[26]}\)

In our study, clinical knee OA was determined with the assessment of knee pain, age, morning stiffness, crepitus on active motion or with the assessment of knee pain, morning stiffness, crepitus on active motion, and tenderness of the bony navigation of the joint. Every participant was first asked whether she was often "troubled" with any kind of body pain. If the participant had knee pain, then the duration of pain, the presence and duration of morning stiffness were asked and recorded, and the crepitus on active motion or tenderness of the bony navigation of the joint were examined. The diagnosis of clinical knee OA was assessed by doctors in community or village health clinics. In addition, insurance records and treatment information of some participants who had been hospitalized were examined. Participants' related symptoms and examination results were recorded in the knee OA disease information subquestionnaire of a structured questionnaire.

2.4. Bias

To reduce potential sources of bias, the following measures were implemented. First, a face-to-face interview was conducted by investigators with a structured questionnaire. The investigators underwent standardized training, familiar with the objectives and methodology of the study. Second, the questionnaires were designed by many experts in gynecology, health promotion, and epidemiological background to make certain of its validation. Furthermore, a pilot test was conducted. Participants were interviewed in private using a pretested structured questionnaire. A total of 30 individuals participated in the pilot study. Questionnaire was modified based on the results of the pilot study, especially the description of questions and the answer options.

2.5. Statistical methods

The continuous data were expressed as mean±standard deviation (SD), and the categorical data were expressed in percentages. Normality of variables was assessed with the Shapiro Wilks test, and skewed data were analyzed using the Mann–Whitney U rank test. A chi-squared test was used for categorical variables and the Mann–Whitney U test for continuous variables to test statistical significance between the nonknee OA (code 0) and knee OA (code 1).

Logistic regression models were used to explore the factors related to knee OA by odds ratios (OR) and 95% confidence interval (CI). In Logistic model 1, non-reproductive factors (i.e., age, weight, education, household income, personal income, smoking, and chronic gastritis) were used as adjustment variables to estimate the correlation between each reproductive factor and knee OA. In Logistic model 2, non-reproductive factors and reproductive factors (i.e., age at menarche, parity, abortion, and menopausal status) were used to determine the adjusted relationship. The stepwise regression method was used to screen independent variables. The multivariate model 2 showed a good fit using the Hosmer and Lemeshow test (\(P = .66\)).

All statistics were performed using 2-sided tests, and statistical significance was pre-defined as \(P < .05\). The data were entered into a database that was developed using EpiData 3.0 independently by 2 individuals; SPSS 17.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

3. Results

Among the 2746 women aged 50 to 83, 369 (13.44%) had knee OA. The variables with statistical differences included age (\(P < .001\)), age at menarche (\(P = .01\)), household income (\(P < .001\)), personal income (\(P = .01\)), and CG (\(P < .001\)). There were no statistically significant variables such as weight, education, smoking, alcohol drinking, parity, abortion, and menopausal status (Table 1).

The multivariable logistic regression model 1 showed the relationship between knee OA and reproductive factors after adjustment for non-reproductive factors. Compared with those who were not exposed, those exposed to abortion had an increased risk of knee OA (OR = 1.271, 95% CI = 1.007, 1.605). Adjusted for reproductive and non-reproductive factors, the multivariable logistic regression model 2 revealed the adjusted relationship. The relationship between abortion and knee OA remained distinct (OR = 1.271, 95% CI = 1.007, 1.606) in model

| Variables | Non-knee OA (n=2,377) | Knee OA (n=369) | \(P\) for trend |
|-----------|-----------------------|-----------------|---------------|
| Mean (SD)/n | \(\%\) | Mean (SD)/n | \(\%\) |
| Age       | 60.38 (6.21) | 61.64 (6.04) | <.001 |
| Weight, kg | 55.96 (7.44) | 56.50 (8.05) | .28 |
| Age at menarche | 14.68 (1.93) | 14.88 (1.86) | .01 |
| Education | Elementary or less | 1198 (50.40) | 189 (51.22) | .19 |
| Junior high school | 731 (30.75) | 99 (26.83) |
| Senior high school or higher | 448 (18.85) | 81 (21.95) |
| Household income* | <3000¥ | 1210 (50.90) | 233 (63.14) | <.001 |
| 3000–4999¥ | 704 (29.62) | 81 (21.95) |
| ≥5000¥ | 463 (19.48) | 55 (14.91) |
| Personal income† | None | 653 (27.47) | 109 (29.54) | .01 |
| <3000¥ | 1404 (59.07) | 231 (62.60) |
| ≥3000¥ | 320 (13.46) | 29 (7.86) |
| Smoking | No | 2280 (95.92) | 350 (94.85) | .34 |
| Yes | 97 (4.08) | 19 (5.15) |
| Alcohol drinking | No | 2207 (92.85) | 333 (90.24) | .08 |
| Yes | 170 (7.15) | 36 (9.76) |
| Parity | ≤1 | 672 (28.27) | 92 (24.93) | .39 |
| 2 | 999 (42.03) | 165 (44.72) |
| ≥3 | 706 (29.70) | 112 (30.35) |
| Abortion history | No | 1578 (66.39) | 226 (61.25) | .05 |
| Yes | 799 (33.61) | 143 (38.75) |
| Menopause status | No | 213 (8.96) | 25 (6.78) | .17 |
| Yes | 2164 (91.04) | 344 (93.22) |
| CG‡ | No | 2161 (90.91) | 276 (74.80) | <.001 |
| Yes | 216 (9.09) | 93 (25.20) |

Table 1

Characteristics of participants aged 50 years or older.

Notation: The Mann–Whitney U rank test and Chi-squared test were used to compare differences between non-knee OA and knee OA. OA = osteoarthritis, SD = standard deviation, CG = chronic gastritis.

* Monthly household income.
† Monthly personal income.
‡ CG was self-reported.
In the Zhou et al.[9] study, abortion was negatively associated with knee OA (OR 1.040, 95% CI 1.007, 1.060) and weight (OR 1.019, 95% CI 1.004, 1.035) were associated with an increased risk. Compared with elementary or less, senior high school or higher had a higher risk of knee OA (OR = 1.530, 95% CI = 1.121, 2.088). Using household income <3000 ¥ as reference, the adjusted ORs were 0.583 (95% CI = 0.441, 0.770) for the income of 3000 to 4999 ¥ and 0.599 (95% CI = 0.431, 0.833) for the income of ≥5000 ¥. CG was at increased risk of knee OA (OR = 3.364, 95% CI = 2.548, 4.442). No associations were observed for education with junior high school (OR = 1.024, 95% CI = 0.775, 1.352) with knee OA (Table 2).

### Discussion

In our study, we were surprised to find that abortion was associated with knee OA (OR = 1.271, 95% CI = 1.007, 1.606), which was consistent with the results of 2 studies including abortion variables.[9,10] In the Zhou et al.[9] study, abortion was not associated with the risk of knee OA, but the study focused on special groups including retired workers from hospital. They used knee pain and clinical knee OA as outcome variables, but there were various reasons for knee pain and stiffness, for instance, rheumatoid arthritis, a common inflammatory joint disease, also has knee pain and morning stiffness symptoms.[19,20] Moreover, the results based on data from >10 years ago may not reflect the present situation. In the Jung et al.[10] study, abortion is negatively associated with radiological knee OA. Radiographic usefulness relates more importantly to the exclusion of other diagnostic possibilities rather than the confirmation of OA,[24] and the radiological findings of OA do not correlate well with their clinical symptoms.[11,19,25]

The association between abortion and the prevalence of knee OA may be attributed to several factors. First, estrogen receptors have been found in normal and osteoarthritic cartilage, so estrogen may affect osteoarthritic cartilage metabolism.[29] Termination of pregnancy may exert influence on cartilage from sudden hormonal and physical changes, or that the women body adapts to the changes induced by repeated abortions.[10] Second, the relationship between abortion and knee OA may be mediated by socioeconomic status. Women who undergo spontaneous abortion are more likely to be of lower socioeconomic status and poorer.[30,31] Individuals with lower socioeconomic status are more likely to have knee OA,[27] and the results in our study also showed that women in lower-income households were associated with a higher prevalence of knee OA. Third, psychological problems such as depression may also mediate the relationship between abortion and knee OA. Pregnancy failure increases rates of subsequent mental health problems including depression, anxiety, and substance use disorders.[32,33] Depression was associated with increased knee pain,[34,35] and was also a significant predictor of increased knee pain.[36]

Age at menarche, parity, and menopausal status were not the factor of knee OA in our study. Although the variables with statistical differences included age at menarche, this effect disappeared in the multivariate models, leaving evidence of no relation. This is consistent with other studies.[37–39] Because early age of menarche has been associated with increased risk for other age-related chronic diseases.[40] It is possible that factors other than sex hormones influence the association with OA.[4] We did not observe any correlation between parity and knee OA, which is consistent with other studies.[12,38,41–44] Greater body weight during or after pregnancy may account for the increased OA risk in weight-bearing joints, and our results also showed that weight was associated with the prevalence. Menopause status did not increase the risk of knee OA. Menopausal status and age at menopause were not clearly associated with hip or knee OA replacement.[13,14] A moderate evidence was seen for no relation between knee OA and menopausal status.[45] Women experiencing surgical or natural menopause were at increased risk of OA, when compared with premenopausal women, however, there

| Variables                     | SE   | OR (95% CI)       | SE   | OR (95% CI)       |
|-------------------------------|------|-------------------|------|-------------------|
| Abortion                      | 0.119| 1.271 (1.007, 1.605) | 0.119| 1.271 (1.007, 1.606) |
| Age                           | 0.010| 1.040 (1.020, 1.060) | 0.008| 1.019 (1.004, 1.035) |
| Education                     |      |                   | 0.142| 1.024 (0.775, 1.352) |
| Junior high school            |      |                   | 0.159| 1.530 (1.121, 2.088) |
| Senior high school or higher  |      |                   |      |                   |
| Household income              |      |                   | 0.142| 0.583 (0.441, 0.770) |
| ≥3000 ¥                       |      |                   | 0.168| 0.599 (0.431, 0.833) |
| CG                            |      |                   | 0.142| 3.364 (2.548, 4.442) |

Table 2: Odds ratios (95% CI) for knee osteoarthritis.

Notation: Model 1: adjusted for age, weight, education, family income, personal income, smoking, and CG.

Model 2: adjusted for age, weight, education, family income, personal income, smoking, CG, age at menarche, parity, abortion, and menopausal status.

SE = standard error, CI = confidence intervals, OR = odds ratio, CG = chronic gastritis.

* Monthly household income.

† P<.05.

‡ CG was self-reported.
was no clear relationship of age at menopause with risk of OA. It has been postulated that the perimenopausal decrease of progesterone results in a transient period of exposure to unopposed estrogens that increases risk of OA. It remains unclear how the short-term hormonal imbalances or permanent declines in hormone concentrations contribute to the surge in OA that occurs around the age of menopause.

Age, weight, education, and family income were associated with increased prevalence of knee OA. Age and overweight are recognized the risk factors. In China, many old people think that knee OA is an inevitable illness associated with age, that not much can be done to modify its evolution. The reason for the correlation between education and knee OA are unclear, but the relationship may be mediated by physical activity. Weak quadriceps muscle is a possible cause of knee OA. Women with a higher level education are physical inactivity. A lower level physical activity combined with aging may result in weak quadriceps muscle, resulting in knee OA. Women in lower-income households were associated with a higher risk of knee OA. The possible assumption is that higher household income means women do not have to seek work, thus reducing the burden on their knees. Women typically work before marriage and withdraw from the job market at marriage or at childbirth, and then choose whether to continue working according to the situation. Family’s economic need is a factor affecting women’s employment pattern; for women with financial pressures at home, to continue working is certainly a necessary strategy.

The relationship between CG and increased prevalence of knee OA may be due to non-steroidal anti-inflammatory drugs (NSAIDS). Gastrointestinal injury is a common outcome after taking NSAIDS. However, we would like to emphasize the need to pay attention to the effect of CG on nutrient absorption in knee OA adjuvant therapy. Atrophic gastritis can cause malabsorption of calcium and fat-soluble vitamins (vitamins A, D, E, and K). Sufficient vitamin K status combined with sufficient vitamin D status was associated with better lower-extremity function in 2 knee OA cohorts. As a result, it is necessary to consider the treatment of chronic atrophic gastritis when carrying out the nutrition-assisted treatment of knee OA.

In China, this is the first community-based study to examine the association of reproductive factors with knee OA. The results revealed that abortion increased the risk of knee OA. This study provided additional insights into potential preventive measures for knee OA. There is no satisfactory drug for OA treatment, and OA cannot be cured totally. Special attention should be paid to women with a history of abortion, and women who are planning to abort should be informed of the risk of knee OA later in life. The relationship between reproductive factors and knee OA should be interpreted with caution and further confirmed in longitudinal studies.

5. Conclusion
In summary, abortion may increase the risk of knee OA. Special attention should be paid to women with a history of abortion, and women who are planning to abort should be informed of the risk of knee OA later in life. The relationship between reproductive factors and knee OA should be interpreted with caution and further confirmed in longitudinal studies.

Acknowledgments
The authors want to express their special gratitude to the Women’s and Children’s Work Committee Office of Hunan government and the Department of Women and Children of Health Commission of Hunan who are helpful in recruiting participants. In the data entry stage, they thank the medical students of Central South University. They would like to thank Professor Zhao for his guidance on data analysis.

Author contributions
Conceptualization: Yan-Ting Meng, Yang Luo, Yuan-Yuan Wang.
Data curation: Yan-Ting Meng.
Formal analysis: Yan-Ting Meng.
Funding acquisition: Yang Luo.
Methodology: Yang Luo.
Resources: Yang Luo.
Validation: Yang Luo.
Writing – original draft: Yan-Ting Meng.
Writing – review & editing: Yang Luo, Yuan-Yuan Wang, Yan-Hui Zhou, Jing-Xia Fu, Ming-Zhu Chen, Chen Xu, Si Qin.

References
[1] Litwic A, Edwards MH, Dennison EM, et al. Epidemiology and burden of osteoarthritis. Br Med Bull 2013;105:185–99.
[2] Bjolma JW, Berenbaum F, Ladeber PB. Osteoarthritis: an update with relevance for clinical practice. Lancet 2011;377:2115–26.
[3] Stevens-Lapsley JE, Kohrt WM. Osteoarthritis in women: effects of estrogen, obesity and physical activity. Womens Health (Lond) 2010; 6:601–15.
[4] Felson DT. Epidemiology of hip and knee osteoarthritis. Epidemiol Rev 1988;10:1–28.
[5] Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis Cartilage 2005;13:769–81.
[6] Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012; 97: 1159–68.
[7] Hussain SM, Cigartini FM, Alyousef B, et al. Female hormonal factors and osteoarthritis of the knee, hip and hand: a narrative review. Climacteric 2018;21:132–9.
[8] de Klerk BM, Schiphof D, Groeneveld FP, et al. No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review. Rheumatol (Oxford) 2009;48:1160–5.
[9] Zhou M, Chen J, Wang D, et al. Combined effects of reproductive and hormone factors and obesity on the prevalence of knee osteoarthritis and knee pain among middle-aged or older Chinese women: a cross-sectional study. BMC Public Health 2018;18:1192.
[10] Jung YH, Shin JS, Lee J, et al. Influence of parity-related factors adjusted for abortion on knee osteoarthritis in Korean women aged 50 or older: a cross-sectional study. Maturitas 2015;82:176–83.
[11] Wise BL, Niu J, Zhang Y, et al. The association of parity with osteoarthritis and knee replacement in the Multicenter Osteoarthritis Study. Osteoarthritis Cartilage 2013;21:1849–54.
[12] Hellekant A, Nordsletten L, Johnsen MB, 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;25:1654–62.

[13] Wei S, Yenn A, Ding C, et al. The associations between parity, other reproductive factors and cartilage in women aged 50–80 years. Osteoarthritis Cartilage 2011;19:1307–13.

[14] Liu B, Balkwill A, Cooper C, et al. Reproductive history, hormonal factors and the incidence of hip and knee replacement for osteoarthritis in middle-aged women. Ann Rheum Dis 2009;68:1165–70.

[15] Hussain SM, Wang Y, Giles GG, et al. Female reproductive and hormonal factors and incidence of primary total knee arthroplasty due to osteoarthritis. Arthritis Rheumatol 2018;70:1022–9.

[16] Zhao Y, Hu Y, Smith JP, et al. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol 2014;43:61–8.

[17] Zhang Y, Xu L, Nevitt MC, et al. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: The Beijing Osteoarthritis Study. Arthritis Rheum 2001;44:2065–71.

[18] Blagojevic M, Jenks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.

[19] Fitzcharles MA, Lussier D, Shir Y. Management of chronic arthritic pain in the elderly. Drugs Aging 2010;27:471–90.

[20] Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med 2007;120:936–47.

[21] Greendale GA, Lee NP, Arriola ER. The menopause. Lancet 1999;353:571–80.

[22] Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national health and nutrition examination survey (HANES I). Am J Epidemiol 1988;128:179–89.

[23] Koh J, Suh Y. Female reproductive and hormonal factors and incidence of radiographic knee osteoarthritis. Osteoarthritis Cartilage 2020;28:5427.

[24] Cabrera J. Do we need radiographs to diagnose osteoarthritis? Best Pract Res Clin Rheumatol 2006;20:27–38.

[25] Peat G, Thomas E, Duncan R, et al. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. Ann Rheum Dis 2006;65:1363–7.

[26] Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.

[27] Tang X, Wang S, Zhan S, et al. The prevalence of symptomatic knee osteoarthritis in China: results from the China health and retirement longitudinal study. Arthritis Rheumatol 2016;68:648–53.

[28] Fang EF, Scheibe-Knudsen M, Jahn HJ, et al. A research agenda for aging in China in the 21st century. Aging Res Rev 2015;24:197–205.

[29] Rachette P, Corvol M, Bardin T. Estrogens, cartilage, and osteoarthritis. Osteoarthritis Cartilage 2010;18:24–33.

[30] Iijima H, Aoyama T, Fukutani N, et al. Psychological health is associated with knee pain and physical function in patients with knee osteoarthritis: an exploratory cross-sectional study. BMC Psychol 2018;6:19.

[31] Riddle DL, Kong X, Fitzgerald GK. Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2011;19:1095–101.

[32] Schouten JS, Van Den Ouwerda FA, Valkenburg HA. Natural menopause, oophorectomy, hysterectomy and the risk of osteoarthritis of the dip joints. Scand J Rheumatol 1992;21:196–200.

[33] Cooley HM, Stankovich J, Jones G. The association between hormonal and reproductive factors and hand osteoarthritis. Maturitas 2003;45:257–63.

[34] Remsberg KE, Demerath EW, Schuberth CM, et al. Early menarche and the incidence of hip and knee replacement for osteoarthritis in elderly white women: a case-control study. Br J Rheumatol 1998;37:1198–202.

[35] Karlson EW, Mandll LA, Aweh GN, et al. Total hip replacement due to osteoarthritis: the importance of age, obesity, and other modifiable risk factors. Am J Med 2003;114:93–8.

[36] Dawson J, Juszczak E, Thorogood M, et al. An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. J Epidemiol Community Health 2003;57:823–30.

[37] Parazzini F, Progetto Menopausa Italia Study Group. Menopausal status, hormone replacement therapy use and risk of self-reported physician-diagnosed osteoarthritis in women attending menopause clinics in Italy. Maturitas 2003;46:207–12.

[38] Spector TD, Campion GD. Generalised osteoarthritis: a hormonally mediated disease. Ann Rheum Dis 1989;48:523–7.

[39] Segal NA, Glass NA. Is quadriceps muscle weakness a risk factor for incident or progressive knee osteoarthritis? Physican Sports Med 2011;39:44–50.

[40] He XZ, Baker DW. Differences in leisure-time, household, and work-related physical activity by race, ethnicity, and education. J Gen Intern Med 2005;20:259–66.

[41] Yi CC, Chen WY. The linkage between work and family: Female’s employment patterns in three Chinese societies. J Comp Fam Stud 2002;33:451–74.

[42] Waite LJ. Working wives and the family life cycle. Am J Sociol 1980;86:272–94.

[43] Tramier MR, Moore RA, Reynolds DJ, et al. Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain 2000;85:169–82.

[44] Saltzman JR, Russell RM. The aging gut. Nutritional issues. Gastroenterol Clin North Am 1998;27:309–24.

[45] Sheu MK, Looser RF, McAllinon TE, et al. Sufficient vitamin K status combined with sufficient vitamin D status is associated with better lower extremity function: a prospective analysis of two knee osteoarthritis cohorts. Arthritis Care Res 2018;70:1150–9.

[46] Li YS, Xiao W, Liao W. Cellular aging towards osteoarthritis. Mech Ageing Dev 2017;162:80–4.