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

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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≥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

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 ≥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≥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

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

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±7.0 years versus 50.3±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

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

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Table 1. Baseline characteristics of study participants

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

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†, 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†, years (n=12,332)	36.3 (5.5)	36.1 (5.1)	0.04
Hormone therapy‡, 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 (%) (n=11,238)			0.001
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

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

Early reproductive age (18 - 21years)			
	Normal weight n = **19,615**	Overweight/obese n = **2,674**	p
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, n (%)			<0.001
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†, years (n=12,332)	34.2 (6.3)	34.8 (6.1)	0.05
Postmenopausal women (n=12,332)			
	Normal and overweight **n=** 9,266	Obese **n=** 3,066	
Age at menopause†, years	49.3 (4.9)	49.2 (5.0)	0.04
Years of menstruation†, years	35.1 (5.7)	35.4 (5.6)	0.07
Hormone therapy‡, n (%) (n=12,300)			<0.001
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 (%) (n=11,238)			<0.001

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

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

	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Early reproductive age (18 - 21years)						
	All population n= 22,289		**Normal weight n= 19,615**		**Overweight/obese 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
≥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 (Postmenopausal women)						

	All population		Normal/overweight		Obese	
	n=12,332		**n=** 9,266		**n=** 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
≥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