Osteoarthritis and Cartilage 25 (2017) 1654–1662

Osteoarthritis and Cartilage

Age of menarche is associated with knee joint replacement due to primary osteoarthritis (The HUNT Study and the Norwegian Arthroplasty Register)

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ARTICLE INFO

Article history:
Received 1 February 2017
Accepted 30 June 2017

Keywords:
Osteoarthritis
Reproductive history
Hormonal therapies
Hip joint replacement
Knee joint replacement

SUMMARY

Objective: To investigate whether parity, age at menarche, menopausal status, age at menopause, use of oral contraceptives (OC) or use of hormone replacement therapy (HRT) were associated with total knee replacement (TKR) or total hip replacement (THR) due to primary osteoarthritis.
Method: In a prospective cohort study of 30,289 women from the second and third surveys of the Nord-Trøndelag Health Study, data were linked to the Norwegian Arthroplasty Register (NAR) in order to identify TKR or THR due to primary osteoarthritis. Cox proportional hazards models were used to estimate the hazard ratios (HRs).
Results: We observed 430 TKRs and 675 THRs during a mean follow-up time of 8.3 years. Increasing age at menarche was inversely associated with the risk of TKR (P-trend < 0.001). Past users and users of systemic HRT were at higher risk of TKR compared to never users (HR 1.42 (95% confidence interval (CI) 1.06–1.90) and HR 1.40 (95% CI 1.03–1.90), respectively). No association was found between parity, age at menarche, menopausal status, age at menopause, oral contraceptive use or HRT use and THR.
Conclusion: We found that increasing age at menarche reduced the risk of TKR. Past users and users of systemic HRT were at higher risk of TKR compared to never users. Parity did not increase the risk of THR or TKR.

Introduction

Osteoarthritis is probably the result of a complex interplay between genetic, cellular and biomechanical factors. A better understanding of the risk factors and, thereby, groups at risk, would make it possible to target effective public health preventions[1].

There is a rise in osteoarthritis prevalence in women after menopause[2]. The findings from epidemiologic studies on reproductive history (parity, age at menarche, menopausal status and age at menopause) and hormonal factors (oral contraceptives (OC) and hormone replacement therapy (HRT)) in relation to osteoarthritis have been conflicting. Increasing parity has been reported as a risk factor for radiographic osteoarthritis in the knee[3] as well as total knee replacement (TKR) and total hip replacement (THR)[4]. However, some studies have not found any association between parity and radiographic joint space narrowing, osteophytes or changes in either cartilage volume or cartilage defects[5]. A large,

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http://dx.doi.org/10.1016/j.joca.2017.06.010

prospective cohort study reported that low age at menarche increased the risk of TKR[4], but this finding has not yet been confirmed by other studies. The use of OC has not been associated with osteoarthritis in most studies[5–8], except one that reported a possible increased risk of THR[9]. HRT has been shown to have a protective effect on osteoarthritis in some studies[7,10,11], while others have found it to have no effect[12–15] or even adverse effects[4].

The aim of this study was to investigate the association between reproductive history and use of hormonal therapies and the risk of TKR or THR due to osteoarthritis in a prospective cohort study.

Methods

In the Nord-Trøndelag Health Study (HUNT)[16] all inhabitants of Nord-Trøndelag county ≥ 20 years of age were invited to participate in three surveys: HUNT1 (1984–1986), HUNT2 (1995–1997) and HUNT3 (2006–2008)[17]. In total, 35,280 women participated in HUNT2 (75.5% of those invited), and 27,758 in HUNT3 (58.7% of those invited)[17]. Our study only included baseline data from HUNT2 or HUNT3 as these surveys included questionnaire and interview data on reproductive history and covariates. We included women aged ≥30 years at baseline, and our study population consisted of 11,746 participants from HUNT2, 20,459 participants of both HUNT2 and HUNT3 and 4652 participants from HUNT3 alone. For those who participated in both HUNT2 and HUNT3, we used baseline measurements from HUNT3 in order to include as much information as possible on reproductive history and eventual use of HRT. In this study we defined reproductive history as parity, age at menarche, years of menstruation and age at menopause. Hormonal therapies included use of OC and use of HRT. Height and weight were measured by trained personnel. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres. Bilateral oophorectomy in premenopausal women induces premature menopause[18], and women who undergo a hysterectomy with ovarian preservation may almost double their risk of premature menopause compared to women with intact uteri[19]. We therefore chose to exclude both of these groups at baseline (n = 3710). After also excluding 1183 participants with joint replacement before recruitment, 91 with missing date of operation, 436 with missing BMI and 1148 with missing information on smoking, the analyses included 30,289 women (Fig. 1).

For follow-up, we identified cases with a TKR or THR due to primary osteoarthritis, according to the operating surgeon, using information from the Norwegian Arthroplasty Register (NAR). This linkage was conducted using the 11-digit personal identification number that is unique to each Norwegian citizen. NAR contains a record of over 95% of all TKRs and THRs in Norway[20]. If a person had more than one arthroplasty, only the first procedure was considered as the event.

Cox proportional hazards models were used to estimate the hazard ratios (HRs) of TKR and THR according to parity (nulliparous, 1, 2, 3, 4+ births), age at menarche (≤11, 12, 13, 14, 15+ years), menopausal status (pre/peri- and postmenopausal), age at menopause (≤48, 49–51, 52+ years), years of menstruation (age at menopause minus age at menarche), oral contraceptive use (never or ever, and duration of use) and HRT use (never, past, current; local or systemic and duration of use). Age was used as the time scale in the analyses. Model 1 adjusted for BMI

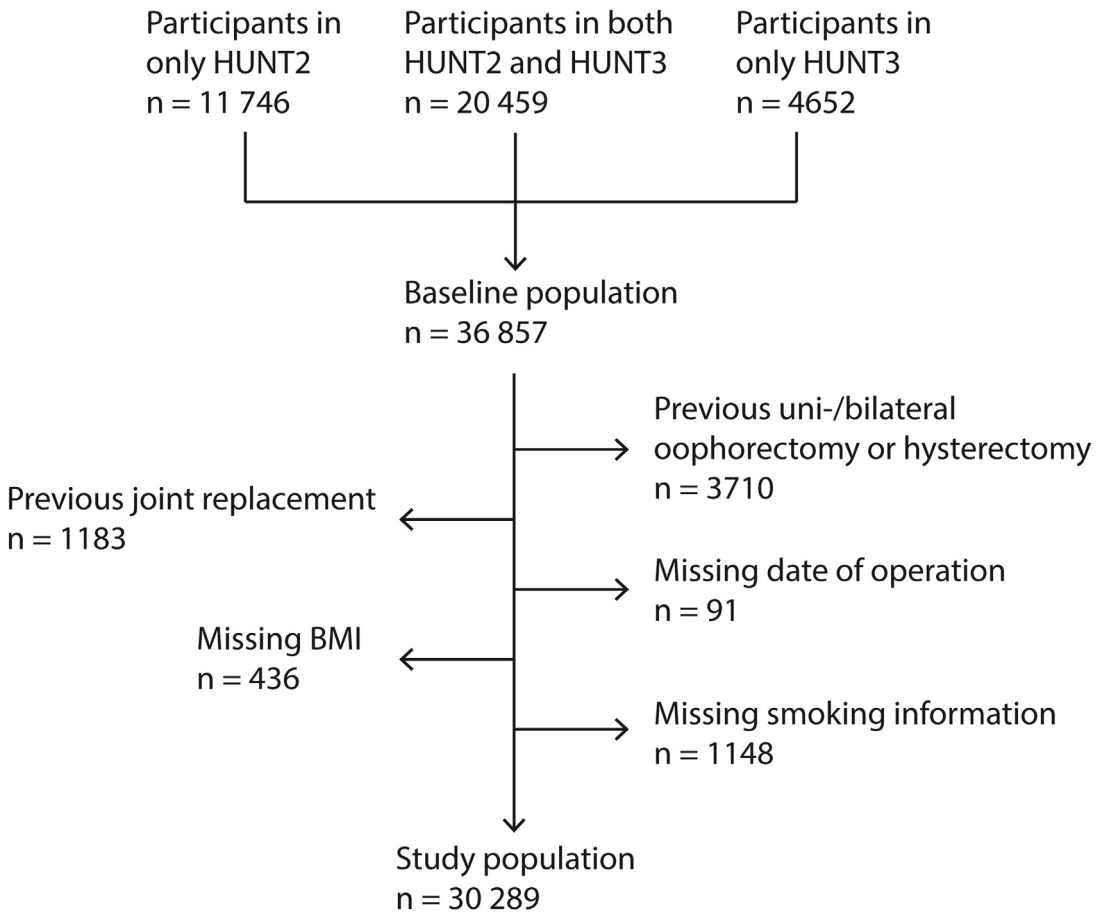

Fig. 1. Flowchart.

(continuous) and smoking (never, former or current). The fully adjusted model 2 also adjusted for physical activity (none, medium, hard) and other reproductive variables as appropriate for the individual exposures. Each exposure was analysed for its interrelationship with other potential hormone-related confounders in a direct acyclic graph (DAG), resulting in a slightly different set of confounders for each exposure (Table A, Appendix). In these DAG analyses, diabetes was only found to be a potential confounder to parity and age at menarche, and thus only adjusted for in these two analyses.

Information on education level was only available for 8745 participants from HUNT2, and an additional sensitivity analysis adjusting for education was performed on this group. Education level was evaluated to be a confounder to parity, oral contraceptive use and HRT (Tables B and C, Appendix), and was defined as the highest level of completed education (primary/vocational, secondary or post-secondary).

The analyses examining age at menopause were limited to postmenopausal women who had never used HRT. The tests for linear trends were based on the categorical variables scored as the mean of each category. All statistical analyses were two-sided with a significance level of $P < 0.05$. The analyses were performed using Stata 14.0/SE (StataCorp LP, College Station, TX, USA). Tests based on Cox regression methods showed no evidence that proportional hazard assumptions were violated.

Ethics

The participants signed written informed consent for participation in HUNT, NAR and linkage of data to national health registries. This study was approved by the Norwegian Regional Committee for Ethics in Medical Research (2013/151/REK Sør-Øst C).

Results

For the 30,289 women included in the study population, the mean age at baseline was 55.7 and mean follow-up time was 8.3 years (SD 4.5). In total, 430 participants had a primary TKR, and 675 had a THR, due to primary osteoarthritis.

Women who reported age at menarche of ≤11 years were older at baseline than those who reported menarche at ≥15 years (Table I). Never users of OC were older than ever users, and past or current users of HRT were older than never users. BMI slightly decreased with increasing age at menarche. A lower portion of the women with higher age at menarche smoked. There was a higher prevalence of diabetes in women who were never oral contraceptive users. Hard physical activity was more prevalent in premenopausal women and oral contraceptive users. Women that received a TKR or THR during follow-up were older, and there were a higher percentage of past or current HRT users than among those who did not get a joint replacement (Table II).

Increasing age at menarche was inversely associated with the risk of TKR (P-trend < 0.001) (Table III). Compared to women with early menarche, those with menarche at 14 years and ≥15 years had a significantly lower risk of TKR (HR 0.64, 95% confidence interval (CI) 0.43–0.95; and HR 0.52, 95% CI 0.34–0.80; respectively). The number of years of menstruation between menarche and menopause was not associated with TKR. Past users of HRT were at higher risk of TKR compared to never users (HR 1.42, 95% CI 1.06–1.90), but only those who used systemic HRT compared to local treatment (HR

Table I
Study population characteristics at baseline (OC: Oral contraceptives; HRT: Hormone replacement therapy)

	n	%	Mean age	SD	BMI	SD	Current smokers (%)	Diabetes (%)	Hard physical activity (%)
All women								missing = 28	missing = 6253
Parity									
Nulliparous	1168	4.0	58.2	18.9	27.0	5.1	28.4	4.8	36.4
1	2966	10.3	53.6	16.2	26.9	5.2	33.4	3.9	44.2
2	10,649	36.8	52.7	14.2	26.6	4.6	29.9	3.3	49.3
3	8818	30.5	55.0	14.2	26.9	4.7	27.5	4.0	48.5
≥4	5322	18.4	63.6	14.1	27.9	4.9	25.8	7.0	39.3
Missing	1366		54.9	16.5	27.1	5.6	22.2	4.3	53.7
Age at menarche, years*									
≤11	2683	9.2	50.7	12.9	28.5	5.4	33.7	5.6	49.9
12	5502	18.9	52.2	14.1	27.6	5.0	29.7	4.4	47.2
13	7554	26.0	53.2	14.5	27.0	4.7	29.4	3.4	48.2
14	7227	24.8	57.2	15.2	26.6	4.6	27.8	4.2	47.0
≥15	6129	21.1	60.5	15.4	26.2	4.5	26.1	4.6	43.9
Missing/unknown	1194		64.4	16.6	27.1	4.9	20.8	5.2	34.4
Menopausal status†									
Pre/peri	10,336	40.9	41.9	6.9	26.5	4.9	32.1	1.4	50.5
Post	14,922	59.1	65.8	10.2	27.4	4.7	25.0	6.2	44.6
Missing/unknown	2855		63.2	16.7	27.0	5.0	31.5	6.6	32.6
Age at menopause, years‡									
≤48	4815	32.3	64.7	11.2	27.3	4.9	48.2	5.7	42.7
49–51	5090	34.1	66.6	10.4	27.3	4.6	31.6	6.3	44.1
≥52	5017	33.6	65.9	9.0	27.6	4.7	20.3	6.6	47.0
OC use§									
Never	6202	34.2	56.7	9.7	27.4	5.0	29.8	4.6	46.3
Ever	11,924	65.8	46.0	9.8	26.5	4.7	31.4	1.9	52.4
Missing	5733		50.1	11.1	26.9	5.0	37.7	3.1	42.1
HRT use									
Never	22,203	83.0	52.3	14.5	26.9	4.9	29.2	3.5	48.4
Past	2536	9.5	64.4	9.5	27.1	4.6	24.2	5.3	48.0
Current	2003	7.5	64.4	10.2	27.1	4.4	23.0	5.4	46.4
Missing	3547		65.5	16.5	27.1	4.9	29.8	7.6	30.9

* Asked of women who were between 19 and 55 years old in HUNT3, but asked of all women in HUNT2.
† Excluded those with amenorrhoea after surgery or radiotherapy ($n = 2176$).
‡ Only in postmenopausal women.
§ Only information in women ≤ 70 years.

Table II
Study population characteristics at baseline in all women, and those who received a total knee replacement (TKR) or total hip replacement (THR)

	All women $n = 30,289$	TKR $n = 430$	THR $n = 675$
Mean age, years (SD)	55.7 (15.2)	64.3 (10.6)	65.6 (10.5)
BMI, mean (SD)	27.0 (4.8)	30.8 (5.3)	28.7 (4.8)
Current smokers, *n* (%)	8613 (28.4)	83 (19.3)	159 (23.6)
Diabetes, *n* (%)	1293 (4.3)	23 (5.4)	33 (4.9)
Hard physical activity, n (%)	11,200 (37.0)	139 (39.8)	232 (42.3)
Parity, mean (SD)	2.6 (1.3)	2.9 (1.4)	2.9 (1.5)
Age at menarche, mean (SD)*	13.4 (1.5)	13.2 (1.5)	13.6 (2.0)
Years of menstruation, mean (SD)	36.0 (4.6)	36.6 (4.7)	36.2 (4.6)
Postmenopausal, *n* (%)†	14,922 (59.1)	341 (88.1)	515 (88.8)
Age at menopause, mean (SD)‡	49.6 (4.4)	49.8 (4.4)	49.9 (4.0)
Ever users of oral contraceptives, *n* (%)§	11,924 (65.8)	103 (44.2)	133 (40.8)
Past users of HRT, *n* (%)	2536 (9.5)	69 (18.7)	88 (15.3)
Current users of HRT, *n* (%)	2003 (7.5)	57 (15.5)	95 (16.6)

* Asked of the women who were between 19 and 55 years old in HUNT3, but asked of all women in HUNT2.
† Excluded those with amenorrhoea after surgery or radiotherapy ($n = 2176$).
‡ Only in postmenopausal women.
§ Only information in women $\leq$ 70 years.

Table III
Reproductive history and use of hormonal medication, and risk of total knee replacement (TKR) (OC: Oral contraceptives; HRT: Hormone replacement therapy)

	Population at risk	Person years	Cases	Model 1*		Model 2†	
				HR	95% CI	HR	95% CI
Parity							
Nulliparous	1168	12,610	17	1	Ref	1	Ref
1	2966	26,173	27	0.79	(0.43–1.45)	0.57	(0.28–1.19)
2	10,649	86,907	127	1.20	(0.72–2.00)	0.91	(0.50–1.67)
3	8818	71,050	134	1.28	(0.77–2.12)	0.88	(0.48–1.61)
≥4	5322	44,731	111	1.04	(0.62–1.73)	0.7	(0.38–1.30)
P linear trend				0.55		0.55	
Age at menarche, years							
≤11	2683	21,502	48	1	Ref	1	Ref
12	5502	45,203	83	0.81	(0.56–1.15)	0.83	(0.56–1.23)
13	7554	62,328	105	0.77	(0.55–1.09)	0.70	(0.48–1.03)
14	7227	59,988	104	0.68	(0.48–0.96)	0.64	(0.43–0.95)
≥15	6129	50,698	78	0.58	(0.40–0.84)	0.52	(0.34–0.80)
P linear trend				0.002		0.001	
Menopausal status							
Pre/peri	10,336	91,247	46	1	Ref	1	Ref
Post	14,922	112,668	341	0.95	(0.63–1.44)	1.16	(0.72–1.87)
Age at menopause, years							
≤48	4815	37,504	111	1	Ref	1	Ref
49–51	5090	38,187	105	0.92	(0.70–1.20)	0.88	(0.64–1.21)
≥52	5017	36,976	125	0.99	(0.77–1.29)	0.98	(0.73–1.32)
Years of menstruation	14,386	250,254	430	1.01	(0.99–1.04)	1.02	(0.99–1.04)
OC use							
Never	6202	56,109	130	1	Ref	1	Ref
Ever	11,924	96,117	103	1.37	(1.03–1.84)	1.36	(1.00–1.86)
Years of OC use	11,488	90,646	94	0.99	(0.93–1.06)	1.01	(0.95–1.09)
HRT use							
Never	22,203	175,094	243	1	Ref	1	Ref
Past	2536	18,035	69	1.45	(1.10–1.90)	1.42	(1.06–1.90)
Current	2003	16,964	57	1.36	(1.02–1.82)	1.25	(0.90–1.73)
HRT use by site							
Never	22,203	175,094	243	1	Ref	1	Ref
Local	2197	16,539	62	1.33	(1.00–1.76)	1.23	(0.90–1.68)
Systemic	2342	18,460	64	1.49	(1.13–1.98)	1.40	(1.03–1.90)
Years of HRT use	3370	22,306	99	1.02	(0.99–1.05)	1.03	(1.00–1.06)

* Adjusted for age, BMI and smoking.
† Adjusted for age, BMI, smoking and physical activity in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

1.40, 95% CI 1.03–1.90). Ever users of OC had a higher risk of TKR (HR 1.38, 95% CI 1.03–1.84), but this association was only borderline significant in the fully adjusted model (HR 1.36, 95% CI 1.00–1.86).

No association was found between parity, age at menarche, postmenopausal status or oral contraceptive use and THR (Table IV). Current HRT users had increased risk of THR after adjustment for age, BMI and smoking, but this association was no longer significant in the fully adjusted model. There was, however, an increased risk of THR associated with years of HRT use (HR 1.04, 95% CI 1.01–1.07). The vast majority of past/current HRT users were postmenopausal women ($n = 4046$), compared to pre/perimenopausal women ($n = 329$) (data not shown).

Table IV
Reproductive history and use of hormonal medication, and risk of total hip replacement (THR) (OC: Oral contraceptives; HRT: Hormone replacement therapy).

	Population at risk	Person years	Cases	Model 1*		Model 2†	
				HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	1168	12,610	25	1	Ref	1	Ref
1	2966	26,173	55	1.17	(0.73–1.88)	1.12	(0.58–2.18)
2	10,649	86,907	209	1.43	(0.94–2.17)	1.56	(0.86–2.81)
3	8818	71,050	186	1.30	(0.85–1.97)	1.42	(0.79–2.57)
≥4	5322	44,731	184	1.29	(0.85–1.97)	1.34	(0.74–2.44)
P linear trend				0.57		0.61	
Age at menarche, years							
≤11	2683	21,502	49	1	Ref	1	Ref
12	5502	45,203	118	1.04	(0.75–1.45)	1.15	(0.78–1.71)
13	7554	62,328	155	0.96	(0.70–1.33)	1.00	(0.68–1.47)
14	7227	59,988	177	0.93	(0.67–1.28)	1.04	(0.71–1.53)
≥15	6129	50,698	163	0.92	(0.67–1.28)	1.07	(0.73–1.58)
P linear trend				0.352		0.968	
Menopausal status							
Pre/peri	10,336	91,247	65	1	Ref	1	Ref
Post	14,922	112,668	515	0.99	(0.70–1.41)	0.97	(0.67–1.40)
Age at menopause, years							
≤48	4815	37,504	156	1	Ref	1	Ref
49–51	5090	38,187	185	1.13	(0.92–1.40)	1.14	(0.89–1.45)
≥52	5017	36,976	174	1.04	(0.83–1.29)	1.03	(0.80–1.32)
Years of menstruation	14,386	236,732	667	1.01	(0.99–1.03)	1	(0.98–1.03)
OC use							
Never	6202	56,109	193	1	Ref	1	Ref
Ever	11,924	96,117	133	1.11	(0.87–1.42)	1.03	(0.79–1.35)
Years of OC use	11,488	90,646	120	0.94	(0.87–1.01)	0.96	(0.89–1.04)
HRT use							
Never	22,203	175,094	391	1	Ref	1	Ref
Past	2536	18,035	88	1.12	(0.88–1.41)	1.03	(0.80–1.33)
Current	2003	16,964	95	1.32	(1.05–1.66)	1.19	(0.92–1.53)
HRT use by site							
Never	22,203	175,094	391	1	Ref	1	Ref
Local	2197	16,539	100	1.26	(1.01–1.58)	1.16	(0.90–1.48)
Systemic	2342	18,460	83	1.16	(0.91–1.48)	1.05	(0.80–1.36)
Years of HRT use	3370	22,306	116	1.04	(1.01–1.07)	1.04	(1.01–1.07)

* Adjusted for age, BMI and smoking.
† Adjusted for age, BMI, smoking and physical activity in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

In a sensitivity analysis of 8745 participants from HUNT2 on parity, oral contraceptive use, and HRT use, adjusted for education level, we found a reduced risk of TKR in women reporting 1 birth (HR 0.15, 95% CI 0.09–0.78) or ≥ 4 births (HR 0.18, 95% CI 0.22–0.97) compared to nulliparous women, but there was no significant trend across the categories ($P = 0.37$) (Table B, Appendix). Years of HRT use slightly increased the risk of THR, but past or current use of HRT was not associated with THR (Table C, Appendix).

Discussion

This prospective cohort study of over 30,000 women found that older age at menarche was associated with decreased risk of TKR. We also found an association between past and systemic HRT use and increased risk of TKR. Parity did not increase the risk of TKR or THR.

The observation that increasing age at menarche was inversely related to the risk of TKR has also been reported in a large prospective study of 1.3 million middle-aged women by Liu *et al.*[4]. The mechanisms underlying these associations are unclear, but there could be several possible explanatory factors. A recent cross-sectional study found an association between early age at menarche and chronic widespread musculoskeletal complaints later in life[21]. One may therefore speculate that an increased level of pain from knee osteoarthritis in this group could lead to a higher incidence of TKR. Early onset of menarche has also been linked to other conditions of ageing such as elevated blood pressure and glucose intolerance, independent of body composition[22]. A cross-sectional study by Kalichman *et al.* demonstrated a negative association between age at menarche and radiological hand osteoarthritis. They proposed that one possible explanation could be that early menarche was associated with an increased rate of the general ageing process[23]. Yet another explanation could be that younger age at menarche may be a marker of other factors such as higher BMI when young[4]; weight gain at a young age has been shown to be a significant risk factor for TKR and THR due to osteoarthritis later in life[24,25].

Systemic use of HRT increased the risk of TKR, and although we did not find any association between current use of HRT and joint replacement, our finding of increased risk of TKR in women with past use of HRT is in agreement with the results by Liu *et al.*[4]. They reported that past or current use of postmenopausal hormone therapy was associated with a significant increase in the incidence of THR and TKR. However, clinical and epidemiological studies have shown conflicting results, and a systematic review found no clear association between HRT and osteoarthritis[26]. Heterogeneity between the hormones used and outcome measurements also made statistical data pooling impossible. They concluded that the relationship was, perhaps, too complex, or that other factors play a role in the increased incidence of osteoarthritis in women aged >50.

Our study did not observe any association between parity and joint replacement. Previous studies on the association between parity and knee osteoarthritis have shown conflicting results[3–5].

However, the absolute numbers of joint replacements in the nulliparous group in our study were low ($n = 25$ and $n = 17$ for THR and TKR, respectively), which calls the power of this analysis into question. We cannot exclude the possibility that this may have weakened any association. Since both parity and joint replacement are associated with education level, we did a sub-analysis with additional adjustment for education in 8745 participants with data on education level; we revealed a reduced risk of TKR in women with 1 birth or ≥4 births, but there was no significant trend across the categories ($P = 0.37$). This could indicate a complex relationship between parity and TKR/THR that we were unable to clarify further in our study.

The healthcare system in Norway is publicly funded and free of charge for patients. Although socioeconomic status would not affect access to surgery, it could lead to a difference in those seeking surgery. In 2009, Statistics Norway reported that amongst women with musculoskeletal diseases, those with a higher level of education (university/college level) were more likely to contact specialist health services than those with lower levels of education (high school or lower)[27]. A negative association between the level of education and the waiting time for THR in Norway has been reported[28], although the income variable was insignificant.

Ever use of OC did not significantly increase the risk of TKR or THR in the fully adjusted model, although the point estimate of the *P* value was borderline significant for TKR, $P = 0.053$ (HR 1.36, 95% CI 1.00–1.86). Menopausal status and age at menopause were not associated with THR or TKR.

Strengths and limitations

Major strengths of this study were the large sample size, prospective population-based design, objective measurements and nearly complete registration of TKR and THR.

Our study used objective measurements of height and weight by trained personnel, and thus avoided potential information bias. The study by Liu *et al.*[4] used self-reported BMI. Self-reported BMI may be biased, and a recent study showed limited agreement with actual height and weight in overweight and obese individuals with clinical osteoarthritis[29].

At the time between HUNT2 (1995–1997) and HUNT3 (2006–2008) studies reported an association between HRT and coronary heart disease[30,31], and HRT and breast/gynaecological cancers[32–34]. The proportion of women using HRT could therefore have been lower in the HUNT3 study. In our data-set we found that 19% of participants in HUNT2 were past or current HRT users, compared to 16.3% in HUNT3. Therefore, HRT prescription did not differ substantially between the two surveys, and should not have greatly affected our results.

The design of this study is prospective since the baseline information was recorded prior to an eventual joint replacement. However, we cannot exclude the possibility that recall bias might have influenced some of the covariates, especially age at menarche. Table I shows a mean age difference of almost 10 years between the women that reported age at menarche ≤11 years, and those reporting age at menarche ≥15. As well, a Danish study from 2009 showed significantly earlier breast development among girls born more recently during a 15-year period[35]. This could indicate that the age at menarche may have decreased over time in our study population, thus creating a cohort effect. Adjusting for age may then be insufficient for correcting an eventual systematic information bias and a cohort effect bias.

At baseline, the mean age of our study population was 55.7, and 62.1% of the women in our study were postmenopausal. However, since our lower cut-off for age at inclusion was 30 years, the information on reproductive history and use of HRT or OC could have changed for some participants after baseline. This is especially relevant when it comes to parity, oral contraceptive use and HRT, and could have led to non-differential misclassification and thus weakened any associations. To increase the information on lifetime reproductive history and eventual use of HRT, we chose to use baseline measurements from HUNT3 for those that participated in both HUNT2 and HUNT3, even if this reduced follow-up time after baseline; the 9468 participants with baseline measurements from HUNT2 had a mean follow-up time of 13.0 years compared to 6.1 years for the 20,821 participants with baseline measurement from HUNT3. Lower incidences of TKR (1.2 %) and THR (1.8%) in the HUNT3 group, compared to TKR (1.8%) and THR (3.2%) in the HUNT2 group, might contribute to lower precision and underestimation of any associations.

A previous study from the HUNT2 material reported that women who had undergone unilateral oophorectomy entered menopause around 1 year earlier than women with two intact ovaries[36] (Separation between uni- vs bilateral oophorectomy was only available from HUNT2, as the HUNT3 questionnaire only asked about bilateral oophorectomy). We chose not to exclude participants that had had only one ovary surgically removed ($n = 776$), and additional adjustment for unilateral oophorectomy when analysing age at menarche did not change the results (data not shown).

In HUNT2 we had information on type of HRT medication in 2601 participants. Of these participants, 1456 (56%) used a combination of oestrogen and progesterone, and 1145 used oestrogen without progesterone. HUNT3 did not have information about the precise type of HRT used by each individual. A previous publication on HRT from HUNT3 reported that data from the Norwegian Prescription Database showed that during the time frame and region of the HUNT3 study, 83.5% of HRT users were prescribed a combination of oestradiol and/or oestriol and progesterone, 9.0% either oestradiol or oestriol without progesterone and 7.5% used the synthetic oestrogen tibolone[37,38].

Although there was a 10-year period between HUNT2 and HUNT3, they both used the same source population: All inhabitants ≥20 years of age in the county of Nord-Trøndelag in Norway. But there could be several reasons why HUNT2 and HUNT3 did not have all the same participants:

- The participation rate in HUNT3 was lower than in HUNT2 (58.7% and 75.5%, respectively). Some of the responders in HUNT2 could therefore have been non-responders in HUNT3.
- We would expect some of the older participants in HUNT2 to have died before HUNT3. And people that were too young to participate in HUNT2 could be part of the study population in HUNT3.

The population in Nord-Trøndelag is relatively homogeneous, with less than 3% non-Caucasian, and is relatively stable, with few people moving in or out of the county[39]. So despite the limitations that arise from using the participants from two consecutive waves of the HUNT health survey, we would argue that the two surveys represent one source population.

The osteoarthrosis diagnoses from the NAR have not been validated[40]. However, the Danish Hip Arthroplasty Registry has reported a positive predictive value of 85% regarding primary hip osteoarthritis diagnosis[41], and it is likely that these results are comparable to the NAR.

Previous injuries increase the risk of osteoarthritis, especially in the knee[42,43]. However, the operating surgeon reports whether each joint replacement is due to primary/idiopathic osteoarthritis, or due to other specified causes. We only included joint replacement due to primary/idiopathic osteoarthritis.

We used joint replacement as an indicator of severe osteoarthritis. Joint replacement is the most definitive treatment for osteoarthritis in the hip or knee, and has the advantage of being a strong indicator of severe clinical disease compared to other definitions of osteoarthritis[44]. Using total joint replacement as an endpoint also helps to identify the burden of severe disease, and is therefore relevant for health economics[45]. The decision to do a total arthroplasty does, however, rely on several factors: the severity of pain, radiographic findings, comorbidities and the patient's motivation for undergoing surgery. Subjects who wish to maintain an active lifestyle may be more motivated to have surgery than less active persons[46], even if they have less severe osteoarthritis. This potential healthy patient bias could lead to an underestimation of the effect of reproductive and hormonal therapies on osteoarthritis.

We found that increasing age at menarche reduced the risk of TKR. Past users and users of systemic HRT were at higher risk of TKR compared to never users. Parity did not increase the risk of TKR or THR.

Contributors

AIH participated in the study concept and design, obtained funding, performed the analysis, interpreted the data and drafted the manuscript. LN, MBJ, AL, GBF, OF, KS and JAZ were involved in the conception and design of the study. OF was also involved in the collection of THR and TKR data. AMF contributed with statistical expertise. All the authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

Conflict of interest

None.

Funding

This study was supported by research grants from the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU) (2014/23166), the Dr. Egil Kjeldaas Foundation (Lege Egil Kjeldaas legat), the Norwegian Orthopaedic Association and Levanger Hospital, Nord-Trøndelag Hospital Trust. The funding sources had no involvement in the study design, the collection, analysis or interpretation of data, writing the paper or the decision to submit the paper for publication.

Acknowledgements

The Nord-Trøndelag Health Study is a collaborative effort of the Faculty of Medicine at the Norwegian University of Science and Technology, the Norwegian Institute of Public Health and the Nord-Trøndelag County Council. The Norwegian Arthroplasty Register is owned by the Norwegian Orthopedic Association and administered by the Orthopedic Department at Haukeland University Hospital, Bergen, Norway.

Appendix

Table A
Covariates adjusted for in Model 1 and Model 2 (BMI: Body Mass Index; HRT: Hormone replacement therapy)

Exposure variable	Covariates adjusted for in Model 1	Additional covariates adjusted for in Model 2
Parity	Age, BMI, smoking	Diabetes, physical activity, age at menarche, menopausal status, HRT
Age at menarche	Age, BMI, smoking	Diabetes, physical activity, parity, menopausal status
Years of menstruation	Age, BMI, smoking	Diabetes, physical activity, parity
Menopausal status	Age, BMI, smoking	Physical activity, parity, age at menarche, HRT
Age at menopause	Age, BMI, smoking	Physical activity, parity, age at menarche, HRT
Use of oral contraceptives	Age, BMI, smoking	Physical activity, parity, age at menarche, menopausal status
Use of HRT	Age, BMI, smoking	Physical activity, parity, menopausal status

Table B
Parity, oral contraceptives (OC), hormone replacement therapy (HRT) and risk of total knee replacement (TKR); sensitivity analysis with additional adjustment for education

	Population at risk	Person years	Cases	HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	797	9743	14	1	Ref	1	Ref
1	961	13,486	10	0.52	(0.23–1.18)	0.15	(0.09–0.78)
2	2602	36,701	40	0.83	(0.45–1.53)	0.20	(0.27–1.12)
3	2131	29,165	40	0.87	(0.47–1.60)	0.20	(0.26–1.11)
≥4	1913	22,874	46	0.77	(0.42–1.41)	0.18	(0.22–0.97)
P linear trend				0.97		0.37	
OC use							
Never	2119	30,002	59	1	Ref	1	Ref
Ever	2176	35,524	21	0.92	(0.52–1.62)	0.95	(0.50–1.78)
Years of OC use	1883	30,955	16	1.04	(0.95–1.13)	1.05	(0.95–1.16)
HRT use							
Never	4897	67,037	81	1	Ref	1	Ref
Past	414	5172	10	1.05	(0.54–2.03)	1.06	(0.50–2.23)
Current	704	8760	22	1.38	(0.86–2.24)	1.36	(0.79–2.36)
HRT use by site							
Never	4897	67,037	81	1	Ref	1	Ref
Local	544	6269	20	1.50	(0.91–2.48)	1.56	(0.88–2.76)
Systemic	574	7662	12	0.99	(0.54–1.83)	0.93	(0.46–1.89)
Years of HRT use	319	3740	16	0.96	(0.81–1.14)	0.96	(0.80–1.14)

* Adjusted for age, BMI, smoking and education level.
† Adjusted for age, BMI, smoking, physical activity and education level in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

Table C
Parity, oral contraceptives (OC), hormone replacement therapy (HRT) and risk of total hip replacement (THR); sensitivity analysis with additional adjustment for education

	Population at risk	Person years	Cases	HR*	95% CI	HR†	95% CI
Parity							
Nulliparous	797	9743	21	1	Ref	1	Ref
1	961	13,486	21	0.83	(0.45–1.53)	1.02	(0.44–2.33)
2	2602	36,701	77	1.16	(0.72–1.89)	1.53	(0.77–3.02)
3	2131	29,165	61	0.97	(0.59–1.59)	1.17	(0.58–2.36)
≥4	1913	22,874	81	1.03	(0.64–1.67)	1.1	(0.55–2.23)
P linear trend				0.87		0.88	
OC use							
Never	2119	30,002	91	1	Ref	1	Ref
Ever	2176	35,524	33	0.97	(0.62–1.52)	1.01	(0.63–1.62)
Years of OC use	1883	30,955	25	0.96	(0.87–1.05)	0.95	(0.86–1.04)
HRT use							
Never	4897	67,037	144	1	Ref	1	Ref
Past	414	5172	14	0.77	(0.45–1.34)	0.85	(0.47–1.51)
Current	704	8760	35	1.04	(0.72–1.52)	1.03	(0.68–1.57)
HRT use by site							
Never	4897	67,037	144	1	Ref	1	Ref
Local	544	6269	26	0.98	(0.64–1.49)	1.07	(0.67–1.71)
Systemic	574	7662	23	0.92	(0.59–1.43)	0.86	(0.53–1.41)
Years of HRT use	319	3740	17	1.13	(1.03–1.25)	1.18	(1.05–1.33)

* Adjusted for age, BMI, smoking and education level.
† Adjusted for age, BMI, smoking, physical activity and education level in all analyses. Additional adjustment for diabetes, parity, menarche, menopausal status, oral contraceptives and hormone replacement therapy as appropriate in each DAG analysis.

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