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Severe teenage acne and risk of endometriosis

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STUDY QUESTION: Is there a relationship between severe teenage acne and endometriosis?

SUMMARY ANSWER: Endometriosis is positively associated with severe teenage acne.

WHAT IS KNOWN ALREADY: No studies have specifically explored a possible association between severe acne in adolescence and risk of endometriosis.

STUDY DESIGN, SIZE, DURATION: This prospective cohort study used data collected from 88 623 female nurses from September 1989 to June 2009 as part of the Nurses' Health Study II (NHS II) cohort.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Regression models were used to calculate hazard ratios (HRs) and confidence intervals (CIs) for endometriosis among women with and without severe teenage acne. Multivariate models were adjusted for established risk factors of endometriosis.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 4 382 laparoscopically confirmed endometriosis cases were documented during 1 132 272 woman-years of follow-up. Compared with women without a history of severe teenage acne, women who had severe teenage acne had a 20% increased risk of endometriosis (HR = 1.20, 95% CI: 1.08–1.32). The association was not affected by adjusting for use of tetracycline or isotretinoin.

LIMITATIONS AND REASONS FOR CAUTION: The HR is likely to be underestimated since we only included endometriosis cases confirmed by laparoscopy. Although geographically diverse, the NHS II cohort is primarily Caucasian, which may limit generalization to more ethnically diverse populations.

WIDER IMPLICATIONS OF THE STUDY: The results of this study suggest that severe teenage acne is associated with an increased risk of endometriosis. As a visible and non-invasive clinical indicator, severe teenage acne may be useful for early detection of endometriosis. We bring this counter-intuitive association to the attention of clinicians for the benefit of the patient and an early diagnosis of endometriosis.

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Key words: acne / endometriosis / diagnosis / screening / epidemiology

Introduction

Endometriosis is a chronic disease that is defined by the presence of endometrial glands and stroma outside the uterine cavity. It affects ~10% of females and is the third leading cause of gynaecologic hospitalization in the USA (Eskenazi and Warner, 1997; Farquhar, 2007; Bulun, 2009). The consequences of endometriosis that disturb women of reproductive age include infertility, chronic pelvic pain and non-specific symptoms

(Missmer *et al.*, 2004). Many of these symptoms will not manifest until adolescence, and some patients remain asymptomatic. Owing to the need for an invasive test, the diagnosis and treatment of endometriosis is often delayed by 6–12 years from the onset of symptoms (Hadfield *et al.*, 1996; Arruda *et al.*, 2003; Husby *et al.*, 2003; Ballard *et al.*, 2006; Hudelist *et al.*, 2012).

Although the aetiology of endometriosis is not fully understood, several risk factors of the disease have been identified. Family history has been established as a strong risk factor (Stefansson *et al.*, 2002; Hansen and Eyster, 2010). Estrogen imbalance is another important factor contributing to the establishment and maintenance of endometriosis (Garai *et al.*, 2006). The growth of endometriotic tissue is stimulated by estrogen and can be suppressed by hormonal treatments such as androgens, aromatase inhibitors and antiprogestins (Attar and Bulun, 2006; Bulun, 2009). Additionally, an aberrant immunologic response is involved in endometriosis, although whether it is a cause or a consequence of the disease is unclear (Kennedy *et al.*, 2005). Other potential risk factors that have been associated with endometriosis to date include early menarche, short menstrual cycles, nulliparity and low body mass index (BMI) (Vitonis *et al.*, 2010; Kvaskoff *et al.*, 2013, 2014; Peterson *et al.*, 2013; Shah *et al.*, 2013).

Acne vulgaris is an inflammatory disorder resulting from impaction and distention of the pilosebaceous unit, due to excess sebum produced from the hyperplasia of sebaceous glands (James, 2005). Androgen may increase sebum production. Common treatments for acne include topical retinoids, topical and oral antimicrobials and isotretinoin. Hormonal therapy, including the use of estrogens, antiandrogens or agents decreasing endogenous androgen production may also be used for women with irregular menstrual cycles, severe seborrhea or hyperandrogenism (Thiboutot, 2001; Gollnick *et al.*, 2003; Ebede TL *et al.*, 2009).

Our hypothesis that severe teenage acne is associated with an increased risk of endometriosis was based on the biological mechanism that both the inheritable diseases have genetic traits closely located at chromosome 8q24. A novel discovery from a recent genome-wide association study reported that the single nucleotide polymorphism (SNP) rs4133274 on chromosome 8q24 was solely significantly associated with severe teenage acne [odds ratio = 4.01, 95% confidence interval (CI): 2.37–6.82] (Zhang *et al.*, 2014). In both eutopic and ectopic endometriotic tissues, previous immunohistological studies have consistently reported altered expression of c-myc, which is also located at chromosome 8q24 (Schenken *et al.*, 1991; Schneider *et al.*, 1998; Johnson *et al.*, 2005; Pellegrini *et al.*, 2012), and may be an important regulator of cell proliferation in endometriotic tissue. This differential expression of myc was also observed in genetic studies of endometriosis (Meola *et al.*, 2010; Khan *et al.*, 2012).

Additionally, both diseases may be caused by small defects during embryogenesis. Sebaceous glands as an ectodermal organ originate from interactions between the epithelium and mesenchyme (Pispa and Thesleff, 2003). A recent analysis of 101 human female fetuses discovered that endometriosis may also be caused by dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis (Signorile *et al.*, 2012). To test our hypothesis, we conducted a prospective cohort analysis in the Nurses' Health Study II (NHS II).

Materials and Methods

Study population

The NHS II is a prospective cohort established in 1989, when 116 430 U.S. female nurses, 25–42 years of age, completed an initial questionnaire. Participants have been followed by biennially mailed questionnaires to update exposure information, lifestyle factors and ascertain non-fatal incident diseases. The women have also completed a semi-quantitative food frequency questionnaire (FFQ) every 2–4 years since 1991.

Exposure and covariates measurement

In 1989, participants in the NHS II were asked 'Have you ever had physician-diagnosed severe teenage acne?' Covariate information on adult weight, height, weight at age 18, number of nevi on lower legs (from knee to ankle on both legs), age of menarche, age at first birth, parity, alcohol drinking at ages 15–17 (collected by FFQ), ethnicity group, menstrual cycle length at ages 18–22, oral contraceptive use and smoking status were collected in the same baseline questionnaire. Among these, weight, parity, oral contraceptive use and smoking status were updated in the follow-up questionnaires every 2 years. We calculated adult BMI from current height and weight, and BMI at age 18 from weight at age 18 years and current height. Information on ibuprofen use was first collected in 1995 and then updated in the following questionnaire cycles. Tetracycline use was defined as >5 years use in 1993. Isotretinoin use was defined as ever use in 1993. Skin characteristics, including number of sunburns, childhood skin's reaction to sun (no reaction, some redness only, burn, painful burn and burn with blistering) and natural hair colour (red, blonde, light brown, dark brown and black), were asked at the baseline questionnaire or in the 1991 questionnaire. Self-reported infertility was validated in a study of 100 randomly selected women who reported ovulatory infertility; 95% of self-reports were confirmed through medical record review (Rich-Edwards *et al.*, 1994a,b).

Identification and analytic definition of endometriosis

To minimize outcome misclassification, analyses of incident endometriosis were restricted to women who reported laparoscopic confirmation of their diagnosis. In 1993, women were asked if they had 'ever had physician-diagnosed endometriosis'. If 'yes', they were asked to report the date of diagnosis and whether it had been confirmed by laparoscopy, the gold-standard for endometriosis diagnosis (Kennedy *et al.*, 2005). These questions were asked again in each subsequent questionnaire cycle. In March 1994, we conducted a validation study to assess the accuracy of self-reported endometriosis within the NHS II (Missmer *et al.*, 2004). A supplementary questionnaire was mailed to 200 women randomly selected from the 1766 cases who had then reported incident endometriosis diagnosis. Among those reporting laparoscopic confirmation and for whom records were received and reviewed ($n = 105$), a diagnosis of endometriosis was confirmed in 96% of cases.

Statistical analysis

We excluded participants who reported endometriosis diagnosis before baseline from our analysis. Additionally, we excluded women diagnosed with any cancer other than non-melanoma skin cancer, and we restricted the analysis to women who were premenopausal and had intact uteri, since the occurrence of endometriosis is rare after menopause or hysterectomy. Participants accrued person-time from the return of date of the 1989 questionnaire until the earliest of the following events: laparoscopically confirmed endometriosis diagnosis, hysterectomy, menopause onset, independently confirmed death or cancer diagnosis (except non-melanoma skin cancer) or date of end of follow-up (June 2009). Deaths were reported by family or postal authorities. We also searched for names of non-responders in the National Death Index (Stampfer *et al.*, 1984; Rich-Edwards *et al.*, 1994a,b). Our primary exposure variable was self-reported history of severe teenage acne collected at the baseline questionnaire in 1989.

We used Cox proportional hazards regression models, to calculate hazard ratios (HRs) and 95% CIs of laparoscopically confirmed endometriosis.

We handled time-varying covariates using the Anderson–Gill data structure (Therneau and Hamilton, 1997), with covariate values set at the time the questionnaire was returned. To control for confounding by age, calendar time and any two-way interactions, we stratified jointly by age at the start of each follow-up period and calendar year of each follow-up period. The time scale was in months since the return date for each follow-up period. To assess the proportional hazards assumption, we used time-dependent variables by creating an interaction term between the main predictor (acne) and a function of survival time. We compared the model with the interaction term to the model without, and obtained the *P*-value using a Wald statistic with 1 degree of freedom and a χ^2 distribution under the null.

In multivariate models, we adjusted for age, baseline BMI (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), BMI at age 18 (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), age of menarche (≤11, 12–13, 14+ year), parity (nulliparous, 1 pregnancies >6 months, 2 pregnancies >6 months, 3 pregnancies >6 months and 4+ pregnancies >6 months), menstrual cycle length at ages 18–22 (<21, 21–25, 26–31, 32–39 and 40+ day), oral contraceptive use (never, current and past), smoking status (never, past and current), height (<1.60, 1.60–1.65 and 1.70+ m), age at first birth (<25, 25–29 and 30+ year), ibuprofen use (yes, no), alcohol drinking at ages 15–17 (non-drinker, 1–3/month, 1/week, 2–4/week, 5–6/week and 7+/week) and ancestry (Caucasian, African American, Hispanic, Asian and others). Covariates were selected based on *a priori* criteria to include established risk factors for endometriosis in our cohort.

For sensitivity analyses, we additionally adjusted for infertility history (ever, never), natural hair colour (red, blonde, light brown, dark brown and black), number of blistering sunburns and childhood skin's reaction to sun (no reaction, some redness only, burn, painful burn and burn with blistering), since these skin and hair characteristics were reported to be associated with endometriosis (Missmer *et al.*, 2006; Kvaskoff *et al.*, 2009; Somigliana *et al.*, 2010). Tetracycline use >5 years in 1993 (yes, no) was additionally adjusted to reduce potential bias, as it was considered as a probable long-term treatment for endometriosis that could be an indicator of underlying disease severity of endometriosis. Isotretinoin use (ever, never) was additionally adjusted for as an indicator of acne severity. We also additionally adjusted for number of nevi (1–2, 3–4 and 5+), because associations between acne and number of nevi (Zhang *et al.*, under consideration for publication) and between number of nevi and endometriosis (Kvaskoff *et al.*, 2013, 2014) were found in the NHS II. Further, we conducted stratified analyses by infertility history (ever, never) and BMI (<25, ≥25). Owing to the incidental detection of asymptomatic endometriosis during the evaluation of infertility, risk factors for endometriosis with infertility may differ from those for endometriosis without infertility. The association may differ by BMI, since body mass is an endogenous source or repository for hormones. We obtained *P*-values for interaction using log-likelihood ratio tests. We estimated the difference in risk of endometriosis comparing women with acne to those without, using a multivariate model including the six most important risk factors: parity, ibuprofen, age at first birth, infertility, age of menarche and adult BMI. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and all analyses used two-sided *P*-values.

Ethics

The study was approved by the Institutional Review Board at Brigham and Women's Hospital and the Harvard School of Public Health.

Results

Of 88 623 women included in our study, 7.9% had a history of severe teenage acne. A total of 4 382 incident cases of laparoscopically confirmed endometriosis were reported over 1 132 272 person-years of follow-up. Table I compares the characteristics of study participants with and without a history of severe teenage acne. Women with a history of severe teenage acne were more likely to be nulliparous, and to use ibuprofen, isotretinoin, tetracycline and antibiotics. Women with acne had more sunburns and painful or blistering sunburns. Women without acne were more like to be smokers and have red hair. Other baseline characteristics were balanced between two groups.

A history of severe teenage acne was statistically significantly associated with an increased risk of endometriosis, with a multivariate-adjusted HR = 1.20 (95% CI: 1.08, 1.32) (Table II). These results were almost identical after additional adjustment for infertility, hair colour, number of blistering sunburns, childhood skin's reaction to the sun or number of nevi (Table II). Further adjustment for isotretinoin use and tetracycline use yielded a comparable HR = 1.18 (95% CI: 1.07–1.31). From the same model, the multivariate-adjusted HRs (95% CI) of isotretinoin use and tetracycline use were 0.96 (0.74–1.24) and 1.04 (0.82–1.31), respectively. When we excluded tetracycline and isotretinoin users, the HR (95% CI) of endometriosis for severe teenage acne was 1.18 (1.06–1.32). Further, the association was not statistically significantly modified by infertility history or BMI (<25, ≥25) (*P* for interaction = 0.53 and 0.90, respectively; Table III). The multivariate-adjusted risk difference

Table I Selected characteristics of NHS II study participants in 1989 by severe teenage acne status.

	Severe teenage acne	
	No (*n* = 81 666)	**Yes (*n* = 6957)**
Age[a], year	34.0 (4.7)	34.0 (4.5)
Age at menarche[a], year	12.4 (1.4)	12.3 (1.5)
Menstrual cycle length at ages 18–22, day	30.3 (6.1)	30.8 (6.7)
BMI, kg/m^2	24.0 (5.0)	24.0 (4.9)
BMI at age 18, kg/m^2	21.3 (3.3)	21.2 (3.2)
Height, m	1.65 (0.07)	1.65 (0.07)
Drink 7+/week at teenage, %	1.7	1.9
Alcohol consumption at ages 15–17, g/day	1.2 (3.9)	1.2 (4.2)
Current smokers, %	13.1	11.8
Infertility, %	15.6	16.7
Nulliparity, %	30.3	35.0
Ibuprofen user, %	18.3	24.7
Isotretinoin use, %	1.4	16.6
Tetracycline use, %	2.4	35.2
Current oral contraceptive user, %	14.1	14.0
White, %	93.2	93.6
More than five sunburns, %	9.4	10.8
Painful or blistering burn at childhood, %	23.0	26.4
Red hair, %	3.9	3.3

Values are means (SD) or percentages that are standardized to the age distribution of the study population.
[a]Not age adjusted.

between participants with acne compared with those without was 91 per 100 000 person-years. The corresponding crude incidence difference was 110 per 100 000 person-years.

Discussion

In this large prospective study of premenopausal women, we observed an increased risk of endometriosis among women with a history of severe teenage acne. To our knowledge, this is the first report on the relation between acne and endometriosis. The association was independent from previously identified risk factors for endometriosis, skin and hair characteristics, isotretinoin and tetracycline.

Previous studies have found that women with a history of endometriosis may have an increased risk of cancers, infections and endocrine diseases (Rich-Edwards *et al.*, 1994). For skin diseases specifically, women with a personal history of endometriosis have been reported to have an increased risk of cutaneous melanoma (Somigliana *et al.*, 2006; Kvaskoff *et al.*, 2007). Positive relationships have been observed between risk of endometriosis and skin factors, including skin sensitivity to sun exposure, number of nevi and number of freckles (Kvaskoff *et al.*, 2009; Somigliana *et al.*, 2010). An association with red hair has also been observed in the NHS II (Missmer *et al.*, 2006). However, the association between acne and melanoma (Beral *et al.*, 1983; Elwood *et al.*, 1986; Cartwright *et al.*, 1988) is mostly null or negative, and the association with sun exposure has been controversial (Magin *et al.*, 2005; Bhate and Williams, 2013). It seems that other skin conditions do not provide an alternative explanation for the observed results.

Genetic factors may be the underlying mechanism for the observed association. The fact that acne and endometriosis both aggregate in families and have polygenic genetic predispositions (Bulun, 2009; Taylor *et al.*, 2011) suggests that a linkage disequilibrium between genetic predispositions of these two diseases may exist. The reported rs4133274 SNP on chromosome 8q24 from the recent GWAS study on severe teenage acne is located only 72 kb upstream of the myc gene (Zhang *et al.*, 2014). Besides its well-known associations with multiple types of cancer, myc has been reported to regulate androgenic effects and a myc consensus site was identified to up-regulate androgen receptor (Grad *et al.*, 1999). For endometriosis, several studies have shown differential expression of myc in eutopic and ectopic endometrial tissue (Meola *et al.*, 2010; Khan *et al.*, 2012; Pellegrini *et al.*, 2012). Thus, a linkage disequilibrium most likely exists between the rs4133274 SNP and the myc gene nearby.

Androgens are related to both acne and endometriosis, but they are unlikely to be the underlying mechanism. Acne results from hyperplasia of the sebaceous glands, and the seborrhea is heavily influenced by androgens (Tasoula *et al.*, 2012). Androgens are involved in the pathogenesis of acne through androgenic hormone triggers, sebum

Table II History of severe teenage acne and risk of laparoscopically confirmed endometriosis in the NHS II cohort, 1989–2009.

	No acne	Acne
Number of cases/ person-year	3951/1 044 018	431/88 254
Age-adjusted RR	1.00	1.29 (1.17–1.42)
MV RR[a]	1.00	1.20 (1.08–1.32)
MV1: MV plus infertility	1.00	1.20 (1.08, 1.33)
MV2: MV1 plus skin and hair characteristics[b]	1.00	1.19 (1.08, 1.32)
MV3: MV2 plus selected medications[c]	1.00	1.18 (1.07, 1.31)

[a]Adjusted by age, BMI (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), BMI at age 18 (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), age of menarche (≤11, 12–13 and 14+ years), parity (nulliparous, 1 pregnancies >6 months, 2 pregnancies >6 months, 3 pregnancies >6 months and 4+ pregnancies >6 months), menstrual cycle length at ages 18–22 (<21, 21–25, 26–31, 32–39 and 40+ days), oral contraceptive use (never, current and past), smoking status (never, past and current), height (<1.60, 1.60–1.65 and 1.70+), age at first birth (<25, 25–29 and 30+), ibuprofen use (yes, no), alcohol drinking at ages 15–17 (non-drinker, 1–3/month, 1/week, 2–4/week, 5–6/week and 7+/week) and ancestry (Caucasian, African American, Hispanic, Asian and others).
[b]Number of sunburns, childhood skin's reaction to sun (no reaction, some redness only, burn, painful burn, burn with blistering), and natural hair colour (red, blonde, light brown, dark brown, and black).
[c]Tetracycline use for >5 years (collected in 1993), isotretinoin use (never, ever).

Table III History of severe teenage acne and risk of laparoscopically confirmed endometriosis in the NHS II cohort, stratified by infertility history and BMI (<25, ≥25 kg/m^2), 1989–2009.

	Never infertile		Ever infertile		
	No acne	Acne	No acne	Acne	
Number of cases/person-year	3136/986 301	331/82 842	815/57 519	100/5396	*P* inter
RR[a]	1.00	1.17 (1.04, 1.31)	1.00	1.28 (1.03, 1.60)	0.53
	BMI < 25		BMI ≥ 25		
	No acne	Acne	No acne	Acne	
Number of cases/person-year	2326/582 468	246/48 693	1413/414 253	158/35 544	*P* inter
RR[a]	1.00	1.14 (1.00, 1.30)	1.00	1.22 (1.03, 1.44)	0.90

[a]Adjusted by age, BMI (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), BMI at age 18 (<18.5, 18.5–22.4, 22.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9 and 40+), age of menarche (≤11 years, 12–13 years, 14+ years), parity (nulliparous, 1 pregnancies >6 months, 2 pregnancies >6 months, 3 pregnancies >6 months and 4+ pregnancies >6 months), menstrual cycle length at ages 18–22 (<21 days, 21–25 days, 26–31 days, 32–39 days and 40+ days), oral contraceptive use (never, current and past), smoking status (never, past and current), height (<1.60, 1.60–1.65 and 1.70+), age at first birth (<25, 25–29 and 30+), ibuprofen use (yes, no), alcohol drinking at ages 15–17 (non-drinker, 1–3/month, 1/week, 2–4/week, 5–6/week and 7+/week) and ancestry (Caucasian, African American, Hispanic, Asian and others).

hypersecretion, follicular hyperkeratosis, *Propionibacterium acnes* proliferation and their resultant inflammatory response (Wu *et al.*, 1988). Endometriosis is associated with excessive production of prostaglandin and the development of progesterone resistance (Missmer and Cramer, 2003). Androgen may serve as a precursor for estrogens via aromatase conversion in ectopic-implanted endometriosis tissue. However, we believe this may be a consequence of disease as opposed to a causal factor, since androgens are also effective treatments for endometriosis to induce regression of the lesions.

Other sex hormones including estrogens may be a potential mechanism underlying the observed association. First, acne development is influenced by estrogens, as acne occurrence in women reaches a peak at puberty, when rising levels of estradiol are the highest (Tasoula *et al.*, 2012). Fluctuation of sebum production that is related with acne development is also observed in women during the menstrual cycle (Farage *et al.*, 2009). Sufficient dose of oral contraceptives can suppress sebum production and reduce acne lesions (van Vloten *et al.*, 2002). In addition, estrogen receptors including alpha and beta isotypes are expressed in sebocytes and other skin cells (Zouboulis, 2009). Endometriosis is an estrogen-dependent disease. The growth of endometrial tissue is regulated by estrogens and is greatly influenced by reproductive events (Bulun, 2009). Nevertheless, not all ectopic endometriosis is characterized by increased aromatase expression and high concentrations of estrogens (Huhtinen *et al.*, 2012). This raises the possibility that the strength of the association documented in this report may be stronger for some types of endometriosis (endometriomas) than for others (peritoneal and deep infiltrating). If true, then we may need to consider endometriosis as a complex disease and give consideration to the surgical diagnosis of endometriosis as opposed to viewing endometriosis more simplistically in a dichotomous light, as suggested by others (Toor *et al.*, 2014).

Finally, immune malfunction may be another common mechanism between the two diseases. Acne is characterized as an inflammatory lesion on the skin, which is often accompanied with papules, pimples, nodules or cysts. Symptoms include redness, swelling and irritation of the skin. Oral antibiotics and topical benzoyl peroxide are common treatments for acne. For endometriosis, inflammation and abnormalities in immune response may increase the chance of implantation and growth of ectopic endometrial tissue (Garai *et al.*, 2006). Macrophages, tumour necrosis factor-α and interleukin-6 concentrations are often elevated in the abdominal fluid of women with endometriosis (Bulun, 2009). Both diseases are related to a decreased ability of the immune system to clear infections.

For alternative explanations, the observed positive association is unlikely to be confounded by androgenic treatments. Some endometriosis treatments for pelvic pain relief have androgenic effects including acne development; in the past these have included (derivatives of the synthetic steroid ethisterone). They were rarely used by our study population, and we did not include these drugs in our questionnaires. These drugs are not initial treatments for endometriosis, due to their masculinizing side-effects and have limited usage in pregnant or breastfeeding women (Schrager, *et al.*, 2013). In addition, the observed association is not confounded by androgenic medications, since these medications would be inversely associated with endometriosis but positively associated with acne. If such confounding by androgenic treatments exists, it should induce a negative association instead of the positive association that we observed.

Nutritional factors could likewise be confounding factors of the observed positive association, most likely through hormonal effects. However, to be a major confounding factor contributing to the positive association, it has to be strongly associated with both diseases in the same direction. Studies have reported an inverse association between dairy food intake and risk of endometriosis (Trabert *et al.*, 2011; Harris *et al.*, 2013). Certain dairy products have been positively associated with acne (Melnik 2011; Veith and Silverberg, 2011; Burris *et al.*, 2014), including our cohort (Adebamowo *et al.*, 2005). Thus, dairy food alone would induce an inverse association between acne and endometriosis instead of the observed positive one, which suggests that dairy food is unlikely to be an explanation. For other nutritional factors, they are less likely to be associated with both diseases and limited data are available for endometriosis.

The temporal relation between occurrence of acne and endometriosis development is complex, because the exact timing of endometriosis onset is unknown (Missmer *et al.*, 2004). The distribution of age at endometriosis diagnosis among our study population ranged from 24 to 54 years old, with the majority younger than 40 years old. While, generally the average age at an office-based physician visit for acne is 24 years, with 10% of visits happening when individuals are between 35 and 44 years old, many visits are between 15 and 19 years old (James, 2005). The significant overlap of age distributions suggests that acne and endometriosis have the potential to develop during the teenage years after menarche with changes in endogenous hormone levels. But due to the difficulty of studying natural history of endometriosis because of delayed diagnosis and spontaneous resolve of endometriosis tissue, their temporal relationship becomes uncertain (Farquhar, 2007).

Strengths of our study include the prospective study design, large sample size, long time of follow-up, measurement on acne treatments, endometriosis risk factors, including infertility and many lifestyle factors. Confounding by other lifestyle factors is unlikely, since we have adjusted for BMI, oral contraceptive use, cigarette smoking and alcohol drinking, and the association did not change materially. In addition, since the majority of our study participants were white nurses, there was relatively small variation in their socioeconomic characteristics. Another advantage is the accurate outcome identification, as our validation study has showed laparoscopically confirmed endometriosis diagnosis could be confirmed in 96% of women.

A limitation of our study is that validity information on acne was not available in our cohort. Since teenage acne was self-reported, there is potential for misclassification. However, we expect such misclassification to be non-differential with regard to endometriosis and when existing, it would bias the association toward the null. To our knowledge, there were validation studies conducted on self-reported acne, showing an overall moderate sensitivity and specificity regardless of severity, among college students and adolescent males who registered for military service (Menon *et al.*, 2008; de Almeida *et al.*, 2013). However, these studies also showed that with a greater intensity of the acne lesions, the chance of error was lower. Since we used severe acne as our exposure measurement, we expect reasonable sensitivity and specificity in our study. Because severe acne has been shown to be a traumatizing teenage experience, self-report of severe teenage acne may also carry less potential for recall bias (Wu *et al.*, 1988; Murray and Rhodes, 2005; Tasoula *et al.*, 2012). In addition, beliefs about acne play an important role in help-seeking behaviours and whether the acne is confirmed by a physician (Cheng *et al.*, 2010). The healthcare professional background of our cohort members distinguishes us from studies conducted on general population and probably helps to obtain more accurate acne status.

For the outcome, since we only included endometriosis cases confirmed by laparoscopy, it is conceivable that the HR was underestimated, because women with severe acne but without a diagnosis of endometriosis may in fact have minimal to mild unrecognized disease owing to lack of pain and location of implants (atypical locations such as umbilicus or cutaneous lesions that are only found incidentally at the time of surgery). Another limitation is that although geographically diverse, the NHS II cohort is primarily Caucasian, which may limit generalization to more ethnically diverse populations.

The social function and lifestyle of patients with a delayed diagnosis of endometriosis are adversely affected. If the disease could be diagnosed by a reliable and non-invasive method at an early stage, further treatment would prevent its progression. Many resources have been invested on identifying innovative biomarkers to reduce commonly delayed diagnosis of endometriosis (Fassbender *et al.*, 2013). However, until now there is no clinical prediagnostic test available. Patients with undiagnosed endometriosis that causes symptoms including chronic abdominal and pelvic pain are often misdiagnosed as appendicitis, ectopic pregnancy, ovarian cysts, bowel obstruction, pelvic inflammatory disease and many others.

Incorporating query or examination of acne or history of severe acne may be helpful for clinical practice to identify patients with undiagnosed endometriosis. If confirmed in other populations, severe teenage acne may be added to a biomarker panel to improve prediction ability for endometriosis early detection, diagnosis or prevention. It can be incorporated into an endometriosis screening tool, together with questions, including pelvic pain and heavy bleeding. Compared with a laparoscopy surgical procedure, it has non-invasive, visible and low-cost characteristics.

In conclusion, our findings in a well-established, long-term prospective cohort study suggest a positive association between severe teenage acne and endometriosis risk. Our study suggests there may be an intrinsic link between severe acne and endometriosis and two diseases probably develop at the same age. In addition, the magnitude of observed association was probably underestimated in our study. However, we admit our study is an observational study with intriguing findings that need replication. Further studies are needed to explore the mechanisms.

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Authors' roles

J.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.X. drafted the article and all the other authors revised it critically for important intellectual content. All the authors approved the final version for publication.

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Conflict of interest

The authors state no conflict of interest.

References

Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol* 2005;**52**:207–214.

Arruda MS, Petta CA, Abrão MS, Benetti-Pinto CL. Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of Brazilian women. *Hum Reprod* 2003;**18**:756–759.

Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? *Fertil Steril* 2006;**85**:1307–1318.

Ballard K, Lowton K, Wright J. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. *Fertil Steril* 2006;**86**:1296–1301.

Beral V, Evans S, Shaw H, Milton G. Cutaneous factors related to the risk of malignant melanoma. *Br J Dermatol* 1983;**109**:165–172.

Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013;**168**:474–485.

Bulun SE. Endometriosis. *N Engl J Med* 2009;**360**:268–279.

Burris J, Rietkerk W, Woolf K. Relationships of self-reported dietary factors and perceived acne severity in a cohort of New York young adults. *J Acad Nutr Diet* 2014;**114**:384–392.

Cartwright R, Hughes B, Cunliffe W. Malignant melanoma, benzoyl peroxide and acne: a pilot epidemiological case–control investigation. *Br J Dermatol* 1988;**118**:239–242.

Cheng CE, Irwin B, Mauriello D, Liang L, Pappert A, Kimball AB. Self-reported acne severity, treatment, and belief patterns across multiple racial and ethnic groups in adolescent students. *Pediatr Dermatol* 2010;**27**:446–452.

de Almeida H, Cecconi J, Duquia RP, Souza PR, Breunig J. Sensitivity and specificity of self-reported acne in 18-year-old adolescent males. *Int J Dermatol* 2013;**52**:946–948.

Ebede TL, Arch EL, Berson D. Hormonal treatment of acne in women. *J Clin Aesthet Dermatol* 2009;**2**:16–22.

Elwood J, Gallagher R, Stapleton P. No association between malignant melanoma and acne or psoriasis: results from the Western Canada Melanoma Study. *Br J Dermatol* 1986;**115**:573–576.

Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;**24**:235–258.

Farage M, Neill S, MacLean A. Physiological changes associated with the menstrual cycle: a review. *Obstet Gynecol Surv* 2009;**64**:58–72.

Farquhar C. Endometriosis. *Br Med J* 2007;**334**:249–253.

Fassbender A, Vodolazkaia A, Saunders P, Lebovic D, Waelkens E, De Moor B, D'Hooghe T. Biomarkers of endometriosis. *Fertil Steril* 2013;**99**:1135–1145.

Garai J, Molnar V, Varga T, Koppan M, Torok A, Bodis J. Endometriosis: harmful survival of an ectopic tissue. *Front Biosci* 2006;**11**:595–619.

Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, Shalita AR, Thiboutot D. Management of acne: a report from a global alliance to improve outcomes in acne. *J Am Acade Dermatol* 2003;**49**:S1–S37.

Grad JM, Le Dai J, Wu S, Burnstein KL. Multiple androgen response elements and a Myc consensus site in the androgen receptor (AR) coding region are involved in androgen-mediated up-regulation of AR messenger RNA. *Mol Endocrinol* 1999;**13**:1896–1911.

Hadfield R, Mardon H, Barlow D, Kennedy S. Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. *Hum Reprod* 1996;**11**:878–880.

Hansen K, Eyster K. Genetics and Genomics of Endometriosis. *Clin Obstet Gynecol* 2010;**53**:403–412. 410.1097/GRF.1090b1013e3181db1097ca1091.

Harris HR, Chavarro JE, Malspeis S, Willett WC, Missmer SA. Dairy-food, calcium, magnesium, and vitamin d intake and endometriosis: a prospective cohort study. *Am J Epidemiol* 2013;**177**:420–430.

Hudelist G, Fritzer N, Thomas A, Niehues C, Oppelt P, Haas D, Tammaa A, Salzer H. Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. *Hum Reprod* 2012;**27**:3412–3416.

Huhtinen K, Desai R, Stahle M, Salminen A, Handelsman D, Perheentupa A, Poutanen M. Endometrial and endometriotic concentrations of estrone and estradiol are determined by local metabolism rather than circulating levels. *J Clin Endocrinol Metab* 2012;**97**:4228–4235.

Husby GK, Haugen RS, Moen MH. Diagnostic delay in women with pain and endometriosis. *Acta Obstet Gynecol Scand* 2003;**82**:649–653.

James WD. Acne. *N Engl J Med* 2005;**352**:1463–1472.

Johnson MC, Torres M, Alves A, Bacallao K, Fuentes A, Vega M, Boric MA. Augmented cell survival in eutopic endometrium from women with endometriosis: expression of c-myc, TGF-beta1 and bax genes. *Reprod Biol Endocrinol* 2005;**3**:45.

Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E, Endometriosis obotESIGf *et al.* ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005;**20**:2698–2704.

Khan M, Sengupta J, Mittal S, Ghosh D. Genome-wide expressions in autologous eutopic and ectopic endometrium of fertile women with endometriosis. *Reprod Biol Endocrinol* 2012;**10**:84.

Kvaskoff M, Mesrine S, Fournier A, Boutron-Ruault M, Clavel-Chapelon F. Personal history of endometriosis and risk of cutaneous melanoma in a large prospective cohort of French women. *Arch Intern Med* 2007;**167**:2061–2065.

Kvaskoff M, Mesrine S, Clavel-Chapelon F, Boutron-Ruault M-C. Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: the French E3N cohort. *Int JEpidemiol* 2009;**38**:1143–1153.

Kvaskoff M, Bijon A, Clavel-Chapelon F, Mesrine S, Boutron-Ruault M-C. Childhood and adolescent exposures and the risk of endometriosis. *Epidemiology* 2013;**24**:261–269. 210.1097/EDE.1090b1013e3182806445.

Kvaskoff M, Han J, Qureshi AA, Missmer SA. Pigmentary traits, family history of melanoma and the risk of endometriosis: a cohort study of US women. *Int J Epidemiol* 2014;**43**:255–263.

Magin P, Pond D, Smith W, Watson A. A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight. *Fam Prac* 2005;**22**:62–70.

Melnik B. Evidence for acne-promoting effects of milk and other insulinotropic dairy products. *Nestle Nutr Workshop Ser Pediatr Program* 2011;**67**:131–145.

Menon C, Gipson K, Bowe WP, Hoffstad OJ, Margolis DJ. Validity of subject self-report for acne. *Dermatology* 2008;**217**:164–168.

Meola J, Rosa e Silva JC, Dentillo DB, da Silva WA Jr, Veiga-Castelli LC, de Souza Bernardes LA, Ferriani RA, de Paz CCP, Giuliatti S, Martelli L. Differentially expressed genes in eutopic and ectopic endometrium of women with endometriosis. *Fertil Steril* 2010;**93**:1750–1773.

Missmer SA, Cramer DW. The epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 2003;**30**:1–19.

Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004;**160**:784–796.

Missmer SA, Spiegelman D, Hankinson SE, Malspeis S, Barbieri RL, Hunter DJ. Natural hair color and the incidence of endometriosis. *Fertil Steril* 2006;**85**:866–870.

Murray C, Rhodes K. 'Nobody likes damaged goods': the experience of adult visible acne. *Br J Health Psychol* 2005;**10**:183–202.

Pellegrini C, Gori I, Achtari C, Hornung D, Chardonnens E, Wunder D, Fiche M, Canny GO. The expression of estrogen receptors as well as GREB1, c-MYC, and cyclin D1, estrogen-regulated genes implicated in proliferation, is increased in peritoneal endometriosis. *Fertil Steril* 2012;**98**:1200–1208.

Peterson CM, Johnstone EB, Hammoud AO, Stanford JB, Varner MW, Kennedy A, Chen Z, Sun L, Fujimoto VY, Hediger ML *et al.* Risk factors associated with endometriosis: importance of study population for characterizing disease in the ENDO Study. *Am J Obstet Gynecol* 2013;**208**:451.e451–451.e411.

Pispa J, Thesleff I. Mechanisms of ectodermal organogenesis. *Dev Biol* 2003;**262**:195–205.

Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the national death index and Equifax nationwide death search. *Am J Epidemiol* 1994a;**140**:1016–1019.

Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, Manson JE. Adolescent body mass index and infertility caused by ovulatory disorder. *Am J Obstet Gynecol* 1994b;**171**:171–177.

Schenken R, Johnson J, Riehl R. c-myc proto-oncogene polypeptide expression in endometriosis. *Am J Obstet Gynecol* 1991;**164**:1031–1036.

Schneider J, Jimenez E, Rodriguez F, del Tanago J. c-myc, c-erb-B2, nm23 and p53 expression in human endometriosis. *Oncol Rep* 1998;**5**:49–52.

Schrager S, Falleroni J, Edgoose J. Evaluation and treatment of endometriosis. *Am Fam Physician* 2013;**87**:107–113.

Shah DK, Correia KF, Vitonis AF, Missmer SA. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. *Hum Reprod* 2013;**28**:1783–1792.

Signorile PG, Baldi F, Bussani R, Viceconte R, Bulzomi P, D'Armiento M, D'Avino A, Baldi A. Embryologic origin of endometriosis: Analysis of 101 human female fetuses. *J Cell Physiol* 2012;**227**:1653–1656.

Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. *Gynecol Oncol* 2006;**101**:331–341.

Somigliana E, Viganò P, Abbiati A, Gentilini D, Parazzini F, Benaglia L, Vercellini P, Fedele L. 'Here comes the sun': pigmentary traits and sun habits in women with endometriosis. *Hum Reprod* 2010;**25**:728–733.

Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, CH H. Test of the national death index. *Am J Epidemiol* 1984;**119**:837–839.

Stefansson H, Geirsson RT, Steinthorsdottir V, Jonsson H, Manolescu A, Kong A, Ingadottir G, Gulcher J, Stefansson K. Genetic factors contribute to the risk of developing endometriosis. *Hum Reprod* 2002;**17**:555–559.

Tasoula E, Gregoriou S, Chalikias J, Lazarou D, Danopoulou I, Katsambas A, Rigopoulos D. The impact of acne vulgaris on quality of life and psychic health in young adolescents in Greece. Results of a population survey. *An Bras Dermatol* 2012;**87**:862–869.

Taylor M, Gonzalez M, Porter R. Pathways to inflammation: acne pathophysiology. *Eur J Dermatol* 2011;**21**:323–333.

Therneau TM, Hamilton SA. rhDNase as an example of recurrent event analysis. *Stat Med* 1997;**16**:2029–2047.

Thiboutot DM. Endocrinological evaluation and hormonal therapy for women with difficult acne. *J Eur Acad Dermatol Venereol* 2001;**15**:57–61.

Toor K, Wessels JM, Agarwal SK, Leyland N, Foster WG. Clinical markers of endometriosis: have we been too quick to judge? *Med Hypotheses* 2014;**82**:493–501.

Trabert B, Peters U, De Roos A, Scholes D, Holt V. Diet and risk of endometriosis in a population-based case–control study. *Br J Nutr* 2011;**105**:459–467.

van Vloten W, van Haselen C, van Zuuren E, Gerlinger C, Heithecker R. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. *Cutis* 2002;**69**:2–15.

Veith W, Silverberg N. The association of acne vulgaris with diet. *Cutis* 2011; **88**:84–91.

Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. *Hum Reprod* 2010;**25**:1325–1334.

Wu S, Kinder B, Trunnell T, Fulton J. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. *J Am Acad Dermatol* 1988;**18**:325–333.

Zhang M, Qureshi A, Hunter D, Han J. A genome-wide association study of severe teenage acne in European Americans. *Hum Genet* 2014; **133**:259–264.

Zouboulis CC. Sebaceous gland receptors. *Dermato-Endocrinology* 2009; **1**:77–80.