Relative weight at ages 10 and 16 years and risk of endometriosis: a case–control analysis

C.M. Nagle1,7, T.A. Bell1,2, D.M. Purdie3, S.A. Treloar1,4, C.M. Olsen1,5, S. Grover6, and A.C. Green1

1Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Herston, Brisbane 4006, Australia
2Faculty of Sciences, Engineering and Health, Central Queensland University, Bundaberg, Australia
3Genentech Inc., 1 DNA Way, South San Francisco, CA, USA
4Centre for Military and Veterans’ Health, The University of Queensland, Brisbane, Australia
5School of Population Health, University of Queensland, Brisbane, Australia
6Mercy Hospital for Women, Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia
7Corresponding author. E-mail: christina.nagle@qimr.edu.au

**BACKGROUND:** Although previous epidemiological studies have shown that women with endometriosis are more likely to be thinner and underweight, it is currently not clear whether this is a true characteristic of women who develop endometriosis or a consequence of their disease and its symptoms. The aim of this study was to investigate the relationship between endometriosis and relative weight in childhood and adolescence, prior to diagnosis.

**METHODS:** This case–control study included 268 Australian women with surgically confirmed moderate to severe endometriosis (cases) and 244 women without endometriosis (controls). Relative weight at ages 10 and 16 years, as recalled and classified ('underweight', 'average weight' and 'overweight') separately by the women themselves and their mothers, was analyzed.

**RESULTS:** Women who reported being overweight at 10 years had an increased risk of endometriosis (OR 2.8; 95% CI 1.1–7.5). Mothers' reports and concordant responses among mother–daughter pairs were consistent with this association. There was no clear evidence of an association between relative weight at 16 years and risk of endometriosis.

**CONCLUSIONS:** These data suggest that being overweight during late childhood is associated with the development of endometriosis; however, the results warrant confirmation in larger study populations.

**Key words:** endometriosis / relative weight / childhood / adolescence

**Introduction**

A number of characteristics of women’s menstrual patterns and reproductive histories, such as shorter menstrual cycle lengths and longer flow (Cramer et al., 1986), earlier age at menarche (Moen and Schei, 1997; Signorello et al., 1997) and parity (Missmer et al., 2004a), have been associated with endometriosis. Other personal and lifestyle characteristics, in addition to certain environmental factors such as dioxin-like compounds (Heilier et al., 2008), have also been implicated, but most of these remain equivocal as risk factors. Many epidemiological studies evaluating the effects of putative risk factors that change over time (i.e. menstrual cycle patterns, weight) have collected data as current exposures in women affected by endometriosis (Cramer and Missmer, 2002). This is problematic since current personal characteristics and habits are likely to be highly associated with disease symptoms and even a consequence of endometriosis rather than a preceding factor involved in its development. A more accurate approach to identifying factors that are causally related to endometriosis is to measure these factors in early life, prior to diagnosis, because they correctly reflect the temporal relationship between exposures and the subsequent development of endometriosis (Cramer and Missmer, 2002).

Previous studies have reported that women with endometriosis are more likely to be thinner and underweight (Darrow et al., 1993; McCann et al., 1993; Signorello et al., 1997; Hemmings et al., 2004; Missmer et al., 2004b; Ferrero et al., 2005; Hediger et al., 2005; Matalliotakis et al., 2008), but because these reports were based on current weight, it is difficult to determine whether this association is a true characteristic of women who develop endometriosis or a consequence of their disease symptoms. Although two recent studies (Missmer et al., 2004b; Hediger et al., 2005) have reported that women who were thinner and leaner in late...
adolescence have an increased risk of endometriosis, the potential role of relative weight in childhood and in early adolescence in the development of endometriosis remains an open question.

The aim of this novel study was to determine whether relative weight in early life, as reported by cases, controls and their mothers, is associated with subsequent diagnosis of endometriosis. The structured data collection of our study enabled analysis of associations in relation to specific time periods of exposure, including in childhood and in adolescence, prior to diagnosis. This methodological approach should be highly relevant to evaluating the etiological relationship between relative weight and the development of endometriosis (Missmer and Cramer, 2003). This approach is also particularly important in light of recent suggestions of the possible role of in utero and childhood environment in the causation of endometriosis (Missmer et al., 2004c; Buck Louis et al., 2007).

Materials and Methods

Study population and sample

Cases included 268 Australian women aged between 18 and 55 years, with surgically confirmed endometriosis, recruited between 1996 and 2002 through the Australian component of the International Endogene Study (Trelloar et al., 2002). Cases were drawn from volunteer women, with no affected first-degree relative and no known family history of endometriosis, who had been diagnosed with moderate to severe endometriosis (revised American Fertility Society stage III/IV) (Holt and Weiss, 2000; Zondervan et al., 2002). Of 310 affected women who were eligible, two were residing overseas and seven were unable to be contacted. Among the remaining 301 eligible cases, 268 (89%) participated. Potential control participants were pairs of female twins enrolled with the Australian Twin Registry. One twin per pair was randomly selected and frequency-matched one-to-one with cases based on age (5-year groups) and geographic location (urban/rural). In all, 511 women were contacted. Of these, 40 were ineligible because they were either residing overseas (n = 11) or had a diagnosis of endometriosis (n = 29) and a further 39 were unable to be contacted. Of the remaining 432 eligible women, 244 (56%) agreed to participate. Permission was obtained from participating cases and controls to contact their mothers in order to invite them also to participate in the study. Among the 268 cases, 220 (82%) gave permission for their mothers to be contacted, and of these 196 (90%) mothers of cases participated. Among the control group of 244 women, 144 (59%) gave permission for their mother to be contacted and 132 mothers (93%) participated.

Data collection and exposures

Cases and controls completed a comprehensive health and lifestyle questionnaire, which included questions about their personal details, menstrual cycle patterns and habits such as smoking and alcohol use, as well as physical characteristics. Cases and controls were asked to report their relative weight at ages 10 and 16 years. These ages were thought to best represent relative weight pre- and post-menarche, respectively (Morabia and Costanza, 1998; Thomas et al., 2001). Relative weight was described in three pre-specified categories: ‘underweight’, ‘average weight’ and ‘overweight’. Participants were not asked to record weight in kilograms because of the potential biases of such data, particularly among women (Engstrom et al., 2003). The recall of childhood and adolescent relative weight has been shown in several studies to have reasonable validity (Must et al., 1993; Must et al., 2002). Mothers of cases and controls were also asked to classify their daughter’s relative weight at the same ages and in the same pre-defined categories.

Relative weights at 10 and 16 years were analyzed three ways: using participants’ reports of their own relative weight (self-report); each mother’s report of her daughter’s relative weight (mother’s report); and reports from both mother’s and daughter’s where the reports between the two sources were in agreement (concordant pairs).

Statistical analysis

Multivariable logistic regression was used to quantify associations and calculate odds ratios (OR) and 95% confidence intervals (CI). All analyses were adjusted for known confounding factors including state of residence, age at menarche and relative weight at 10 or 16 years (i.e. when relative weight at age 10 years was the variable of interest, it was adjusted for relative weight at age 16 years, and vice versa). Menstrual factors, smoking, alcohol consumption and other personal characteristics such as education were also considered as potential confounders but were not included in the final models as they did not materially alter the effect estimates. The level of concordance between the responses of the participants and their mothers was examined using a weighted kappa and its 95% CI. Discordant responses were weighted by the square of the deviation from exact agreement (Landis and Koch, 1977; Graham and Jackson, 1993). All analyses were performed using the Statistical Packages for Social Sciences for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA). Ethics approval for this study was received from the Queensland Institute of Medical Research, Bancroft Research Ethics Committee, the Australian Twin Registry, and the University of Queensland, Medical Research Ethics Committee.

Results

There were 268 women with moderate to severe endometriosis and 244 controls included in the study. There was no difference in the mean ages of cases and controls, but state of residence did differ between the case and control groups (P < 0.001), with more cases residing in Queensland, where the study was based, and more controls in Victoria, where the twin registry is based, and in nearby Tasmania (Table I). A significantly higher proportion of cases were born in Asia, Africa and Southern and Eastern Europe compared with controls (P = 0.04), whereas controls had more years of schooling than cases (P = 0.002). The average age at menarche for cases was 12.6 years [standard deviation (SD) ± 1.4 years] compared with 13.0 years (SD ± 1.4 years) for controls (P = 0.003), and 23% of cases experienced menarche before age 12 years compared with 13% of controls. Cases did not differ from controls with regard to marital status, religion, smoking status or alcohol consumption (Table I).

Relative weight at age 10 years was reported by 503 participants and 324 mothers, whereas relative weight at 16 years was reported by 504 participants and 322 mothers. Relative weight at ages 10 and 16 years were available for 318 daughter–mother pairs. There was moderate concordance between daughters’ and mothers’ reports of relative weight at age 10 years (weighted kappa = 0.4, 95% CI 0.3–0.5), with cases and their mothers attaining a better level of agreement (weighted kappa = 0.5) than controls and their mothers (weighted kappa = 0.3) (Table II). Similarly, there was moderate concordance between self-reports and mothers’ reports of relative weight at 16 years (weighted kappa = 0.4, 95% CI 0.3–0.5), and again there was a better level of agreement between cases and their mothers.
The associations between relative weight at 10 and 16 years and endometriosis are shown in Table III. In multivariate analysis adjusting for potential confounding variables, self-report of being overweight at age 10 years was associated with subsequent development of endometriosis; the odds ratio for being overweight at 10 years compared with being average weight was 2.8 (95% CI 1.1–7.5). Analysis of

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mothers’ reports and concordant responses among mother–daughter pairs were also suggestive of a positive association between being overweight at 10 years and endometriosis, but these results did not reach statistical significance. Being underweight at 10 years (as reported by self, mothers and concordant mother–daughter pairs) was not associated with a subsequent diagnosis of endometriosis.

There was no association between self-report of being underweight at age 16 years and endometriosis (OR 1.4, 95% CI 0.7–2.7). Similar results were noted when we restricted the analysis by the age of onset of first symptoms to exclude women who reported first symptoms before the age 16 years. However, there was a suggestion of a positive association between mothers and concordant mother–daughter pair reports of being overweight at 16 years and endometriosis. We found no significant association between a reported history of being overweight at 10 years (as reported by self, mothers and concordant mother–daughter pairs) and endometriosis.

**Discussion**

We have presented novel data from a case–control analysis of the associations between relative weight in childhood and in adolescence (before diagnosis) and subsequent development of endometriosis. We found that women who reported being overweight in childhood at age 10 years were more likely to be diagnosed with endometriosis. We found no clear evidence of an association between relative weight at 16 years (under- or over-weight) and endometriosis.

There are few published data pertaining to the association between body size or weight in adolescence and development of endometriosis (Missmer et al., 2004b; Hedger et al., 2005). One large prospective study found that women with a low body mass index (BMI) (<19) at 18 years had a higher rate of endometriosis than other women (Missmer et al., 2004b). Likewise, a recent study of 84 women (32 cases and 52 controls) found that women diagnosed with endometriosis reported a significantly leaner body shape and size during adolescence (15–19 years) and young adulthood (20–24 years) (Hedger et al., 2005). We found no significant association between relative weight at 16 years and endometriosis.

Our principal finding of an increased risk of endometriosis among women who are overweight at 10 years is consistent with current etiological hypotheses. A single hypothesis to explain the pathogenesis of endometriosis has not yet been elucidated, despite extensive research. Theories of retrograde menstruation and implantation of endometrial cells, probably through errors in the immune response, remain dominant, although evidence also shows that estradiol plays an important role in stimulating the development of endometriosis (Cramer and Missmer, 2002; Batt and Mitwally, 2003; Baldi et al., 2008). We can speculate on reasons for the observed positive relationship between being overweight at 10 years and endometriosis. Plump girls on average reach menarche earlier than their thin peers (Kaplowitz et al., 2001; Blell et al., 2008), so childhood body fatness could be assumed to increase exposure to menstrual flow and subsequently increase the risk of endometriosis. Furthermore, increased levels of bioavailable estradiol, which may result from increased production of estrogen by aromatase in adipose tissue could also explain the link between overweight in early life and endometriosis.

Accumulating evidence supports a role of overweight/obesity in the etiology of many chronic diseases including inflammatory and immune-mediated disorders (Calle and Kaaks, 2004; Wellen and Hotamisligil, 2005; Mannino et al., 2006). The distinct possibility exists that overweight/obesity may be linked to endometriosis through altered adipocytokine secretion and circulating levels, in particular adiponectin and leptin. These adipocytokines are known to have inflammatory and angiogenic actions (Tilg and Moschen, 2006), factors widely believed to be central to the development of endometriosis (Agic et al., 2006; May and Becker, 2008). Several other lines of evidence indicate a potential role for adiponectin and leptin in the pathogenesis of endometriosis (Takemura et al., 2005; Milewski et al., 2008; Styer et al., 2008).

One of the strengths of this study was the use of time period data collection points [i.e. relative weight data collected before menarche (age 10 years) and after menarche (age 16 years)] which methodologically aimed to capture the timing of any causal relationship between relative weight and endometriosis. We found that the mean age at menarche was significantly later in controls than cases and to ensure that our results did not simply reflect an association between age of menarche and relative weight, all multivariate analyses were adjusted for age at menarche. Our models for childhood relative weight were also adjusted for relative weight at 16 years (and vice versa) because these two variables are correlated. Given that a large proportion of women with endometriosis have symptoms that begin during early adolescence (Greene et al., 2009), we repeated the analysis for relative weight at 16 years restricted to women with no symptoms at this age, and effect estimates were unchanged.

The findings do, however, require cautious interpretation. As with all studies of endometriosis, the choice of control group is likely to influence the value of the study findings. Our control group comprised single-sex twins who had volunteered to participate in Australian Twin Registry. Although we know that the childhood weight of twins is similar to that of singletons by age 9 years (Leon, 2001), it is possible that some volunteer bias remains. Another potential limitation was the relatively low participation rate among controls (56%). To assess the possible effect of this, we compared the distribution of key variables in our participating control group with data from the non-participating controls. We found that the distributions of key exposures (age, state of residence, education, age at menarche, smoking status and alcohol consumption) among participating and non-participating control women were not notably different. Unfortunately no exposure information (childhood/adolescent weight) was available for the non-participating controls, so the role of selection bias may explain the observed association between being overweight at 10 years and endometriosis. Even though our controls were women who reported no past history of endometriosis, it is possible that women with undiagnosed disease may have been included in our control group. However, as the community prevalence of more severe stages of endometriosis is less than 2% (Zondervan et al., 2002), an estimated maximum of five women with undiagnosed (more severe stage) disease may have been inadvertently included in our control group. These would be highly unlikely to influence our effect estimates.

Although the response rate for cases was high (89%), 33 eligible cases did not participate. Of these women, three actively refused to participate, whereas the remaining 30 women did not return questionnaires despite initial agreement in some cases. Comparison of socio-demographic factors (age, state, residential area) showed no significant differences between participating and non-participating
cases. Another potential source of bias in this study results from the fact that cases were volunteers. Although we know that individuals who self-select into studies often differ in key ways from the target or source population, we have attempted to account for the potential biases of ‘volunteers’ by choosing a comparison ‘volunteer’ control group.

Misclassification of exposure, as reported by mothers and mother–daughter pairs, is also a potential source of bias since fewer controls than cases gave permission to contact their mothers. Although such misclassification is likely to be non-differential, the focus of our interpretation rests with the results from the primary source, namely self-reports of relative weight, rather than mothers and mother–daughter pairs. Study data on relative weight at 10 and 16 years were self-reported, and although the correlation between cases’, controls’ and mothers’ reports of relative weight at these ages offers some support to the validity of these measures, we are aware that data of this type are subject to recall error whereby women with higher BMI are more likely to underestimate body size at young ages, whereas underweight women are more likely to over-estimate body size (Troy et al., 1995; Tehard et al., 2002; Nyholm et al., 2007). This might have led to non-differential misclassification that could have attenuated the true association between relative weight and endometriosis. Finally, the extent to which we have adequately addressed confounding factors is unknown, but every effort was made to measure and adjust for all factors currently thought to be related to the development of endometriosis.

In summary, we have provided new evidence that high relative weight in childhood is associated with the subsequent development of endometriosis. Confirmation of these findings and understanding the biological relations underpinning these observations is paramount.

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