Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2009;38:312–318
doi:10.1093/ije/dyn174

Childbearing, breastfeeding, other reproductive factors and the subsequent risk of hospitalization for gallbladder disease

Bette Liu,* Valerie Beral, Angela Balkwill, on behalf of the Million Women Study Collaborators

Accepted 28 July 2008

Background While parous women are known to be at an increased risk of gallbladder disease, little is known about the effects of other reproductive factors such as breastfeeding, age at menarche and age at menopause.

Methods The Million Women Study is a prospective cohort study of 1.3 million middle-aged women in England and Scotland recruited from 1996 to 2001. Participants were followed-up by record-linkage for a mean of 6.1 years for admissions to hospital. The adjusted relative risk of hospital admission for cholelithiasis, cholecystitis or cholecystectomy according to parity, breastfeeding, age at menarche and age at menopause was examined.

Results During follow-up of 1 289 029 eligible women, 25 111 were admitted to hospital for gallbladder disease, of whom 21 735 (87%) had a cholecystectomy. The hospital admission rate over 5 years for gallbladder disease was 1.6/100 women and for cholecystectomy was 1.4/100 women. The adjusted relative risk of gallbladder disease increased with increasing parity by 8% (95% CI 7–9%, $P < 0.0001$) for each birth. Among women of a given parity, breastfeeding reduced the risk of gallbladder disease, the relative risk decreasing by 7% (95% CI 5–10%, $P < 0.0001$) per year of breastfeeding. Women's age of menarche and age at menopause did not alter the risk of gallbladder disease ($P = 0.4$ and $P = 0.3$, respectively for linear trend).

Conclusion Hospitalization for gallbladder disease is common in middle-aged women. The risk increases the more children a woman has had, but decreases the longer she breastfeeds. The increased risk of gallbladder disease associated with having children can be offset by breastfeeding.

Keywords Gallbladder diseases, cholecystectomy, breastfeeding, parity, Million Women Study

Introduction

Symptomatic gallbladder disease is one of the commonest reasons for hospital admission among women in developed countries and incidence rates peak in middle age.[1] There is substantial evidence suggesting that oestrogens are involved in its aetiology.[2,3] Results from studies that have examined the effect of a

Cancer Epidemiology Unit, University of Oxford, Richard Doll Building, Roosevelt Drive, Oxford OX3 7LF, UK.
* Corresponding author. Cancer Epidemiology Unit, University of Oxford, Richard Doll Building, Roosevelt Drive, Oxford OX3 7LF, UK. E-mail: bette.liu@ceu.ox.ac.uk

woman's reproductive history on gallbladder disease are not always consistent.[4–10] The number of children that women have had is frequently reported as a risk factor for gallbladder disease[2,11] but some studies have found no association[8] and it is unclear whether the risk increases incrementally with each birth.[4–7,9] There is little evidence regarding the effect of other reproductive influences such as breastfeeding, the age at menarche and the age at menopause on gallbladder disease. We report here on the relationship between these reproductive factors and the risk of hospital admission for gallbladder disease in a large prospective cohort of middle-aged women.

Methods

Study population and definitions

The Million Women Study is a prospective study that recruited 1.3 million middle-aged women mostly aged 50–64 years-old through National Health Service (NHS) breast screening centres in England and Scotland during 1996–2001. Women completed a baseline questionnaire on entry to the study (available at www.millionwomenstudy.org). Sociodemographic details, anthropometric measurements, the use of exogenous hormones and a brief medical history were collected. As well, women were asked about their reproductive history including their age at menarche, age at menopause and number of births. A question on the duration of breastfeeding for each birth was added to the baseline questionnaire after the first 9% were recruited. All participants provided written consent to be included in the study and the Million Women Study has been approved by the Eastern Multi-centre Research Ethics Committee.

For outcome ascertainment, participants were followed-up through computerized databases of NHS hospital admissions, deaths and cancer registrations using their unique health care number (NHS number), date of birth and other identifying details. The NHS hospital episode statistics (HES) contain a record of all NHS hospital admissions from April 1997 in England[12] and the Scottish Morbidity Records contain similar information from January 1981 in Scotland.[13] Up to 14 clinical diagnoses and 12 procedures are coded according to respectively the International Classification of Diseases (ICD-10)[14] and the Office of Population Censuses and Survey Classification of Surgical Operations and Procedures (OPCS-4).[15] As it is symptomatic gallbladder disease that is of clinical importance, for the purposes of this study, a woman was defined as having gallbladder disease if she had a hospital admission with either a primary diagnosis of cholelithiasis or cholecystitis (ICD-10 code K80 or K81) or a procedural code for an excision of the gallbladder (OPCS-4 code J18) after joining the study. Analyses were conducted using any diagnosis of gallbladder disease as the outcome and then the main analyses were repeated using 'excision of the gallbladder/cholecystectomy' alone as the outcome.

Analysis

Women were excluded from analyses if they had a cancer (except non-melanoma skin cancer, ICD-10 code C44), an admission for gallbladder disease before recruitment or if parity was unknown. Cox regression analysis was used to estimate the relative risk of gallbladder disease in relation to parity (in the categories nulliparous, parous, 1, 2, 3, 4 and 5+ children, and as a continuous variable), age at menarche (<13, 13, 14, 15+ years), the age at menopause in postmenopausal women (⩽48, 49–51, 52+ years) and for women with information on breastfeeding, the total duration of breastfeeding (in the categories never, ever, <6, 6–11, 12+ months, and as a continuous variable). As the total duration of breastfeeding is associated with the number of births, the effect of breastfeeding was also examined as the duration per child who was breastfed within subgroups of individual parity. The duration of breastfeeding per child breastfed was calculated using a woman's total cumulative months of breastfeeding divided by the number of children the woman reported having breastfed.

Person–years were calculated from the date of a woman's recruitment into the study to the date of the first hospital admission for gallbladder disease, death, emigration or end of follow-up, whichever came first. The last date of follow-up corresponded to the date beyond which the hospital admission databases were incomplete at the time of linkage (in England this was March 31, 2005 and in Scotland December 31, 2003). For a small proportion of women (5%) who were recruited in England before hospital admission data was available, person–years were calculated from April 1, 1997.

All analyses were routinely adjusted for the potential confounders: age at recruitment (in 2-year categories), region of recruitment (10 regions), socioeconomic status (in quintiles using the Townsend deprivation index,[16] a score based on each participant's postcode of residence, which takes into account census information regarding employment, overcrowding, car and home ownership), body mass index (<22.5, 22.5–24.9, 25–27.4, 27.5–29.9, 30+ kg/m^2), smoking (never, ever), hysterectomy (yes, no), use of oral contraceptives (never, ever) and hormone replacement therapy (never, current, past). Adjustment for parity and breastfeeding was also made as appropriate. Additional adjustment for alcohol intake and past medical history was also tested. All analyses were conducted with the STATA 9.2 statistical software package. The effect of breastfeeding on rates of cholecystectomy in parous middle-aged women was estimated using the calculated relative risks and breastfeeding rates from the 1970s.

Results

There were 1 289 029 women (96% of the cohort) included in the analyses. At recruitment women had a mean age of 56 years, mean parity of 2.1 and parous women had last given birth an average of 28 years previously. Follow-up was for a mean of 6.1 years per woman and during this time 25 112 women had a first admission for gallbladder disease, an incidence rate of 1.6/100 over 5 years. Of the women who had an admission for gallbladder disease, 87% (21 735) also had a cholecystectomy on the first or a subsequent admission, giving an incidence rate for cholecystectomy of 1.4/100 over 5 years. Admissions occurred a mean of 3.4 years following recruitment. Table 1 shows baseline characteristics of the study participants according to parity. Body mass index (BMI) and the percentage of women with a hysterectomy appeared to increase with increasing parity while average alcohol intake decreased with increasing parity. There were no consistent trends for socioeconomic status, smoking status and use of exogenous hormones. Age at recruitment, age at menarche and age at menopause did not differ substantially by parity. Among parous women, the percentage of women who had breastfed and the mean duration of breastfeeding (both total duration and duration per child who was breastfed) increased with increasing numbers of births. Regarding the duration of breastfeeding, socioeconomic group was found to be somewhat higher in those who breastfed for longer. The percentage of women in the highest socioeconomic tertile was 31.3, 34.1, 36.8 and 37.9%, respectively, in women with a total duration of breastfeeding of, 0, 1–5, 6–11 and 12+ months.

Table 2 shows the association between parity, age at menarche, age at menopause and the risk of gallbladder disease. Overall, parous women had a higher risk of hospital admission for gallbladder disease than nulliparous women (adjusted relative risk 1.24, 95% CI 1.19–1.30). Among parous women the risk increased with increasing parity (adjusted relative risk per birth 1.08, 95% CI 1.07–1.09). The risk estimates obtained for parity ranged from 1.07 to 1.08 when additional adjustments were made for alcohol intake and pre-existing medical illnesses (treatment for high blood pressure and a history of high cholesterol). Neither women's age at menarche nor their age at menopause appeared to be related to the risk of gallbladder disease admissions. Comparing women who had their menarche aged 15 years or older to those aged 12 years or younger the adjusted relative risk was 1.00 (95% CI 0.97–1.04). Comparing post-menopausal women aged 52+ years at menopause to those aged $\leqslant$48 years the relative risk was 0.97 (95% CI 0.90–1.03). *P*-values for the trends of association were $P = 0.4$ and $P = 0.3$ for the age of menarche and the age of menopause, respectively. For the outcome of cholecystectomy alone, the effects of parity, age of menarche and age of menopause were similar to the results for all gallbladder disease. The relative risk of cholecystectomy for parous women

Table 1 Baseline characteristics of study participants according to parity

	Parity					
Characteristic	Nulliparous	One	Two	Three	Four or more	All women
No. of women	140 240	182 140	542 523	277 909	146 217	1 289 029
Mean age at recruitment (years) (SD)	56.0 (4.8)	56.0 (4.8)	55.6 (4.6)	56.3 (4.6)	57.2 (4.7)	56.0 (4.7)
Mean body mass index (kg/m^2) (SD)	25.8 (4.8)	26.0 (4.7)	26.0 (4.4)	26.5 (4.7)	27.4 (5.1)	26.2 (4.7)
Mean alcohol intake (g/day) (SD)	7.0 (8.5)	6.1 (7.6)	6.5 (7.5)	6.1 (7.4)	5.0 (7.1)	6.2 (7.6)
Percentage in upper third socioeconomic group	34.0	32.8	37.5	32.0	21.7	33.5
Current smokers (percentage)	17.5	22.5	18.3	21.6	27.9	20.6
Ever used oral contraceptives (percentage)	45.9	58.1	64.2	61.5	55.8	59.8
Ever used hormone therapy (percentage)	46.3	50.2	51.6	51.6	48.6	50.5
Percentage with a hysterectomy	19.6	22.9	24.5	27.1	30.1	24.9
Age at menarche (years) (SD)	12.9 (1.6)	13.0 (1.6)	13.0 (1.6)	13.0 (1.6)	13.1 (1.7)	13.0 (1.6)
Age at menopause[a] (years) (SD)	49.5 (4.5)	49.6 (4.4)	50.2 (4.1)	50.1 (4.2)	49.8 (4.5)	49.9 (4.3)
Percentage who breastfed	–	52.1	67.0	74.5	78.1	59.7
Mean total duration of breastfeeding (months) (SD)	–	1.9 (3.5)	4.5 (6.3)	7.0 (9.2)	10.7 (14.7)	4.8 (8.2)
Mean duration breastfeeding per child (months) (SD)	–	1.9 (3.5)	2.5 (3.2)	2.8 (3.3)	3.0 (3.4)	2.2 (3.3)

[a]In post-menopausal women aged >52 years with a natural menopause who had never used hormone replacement therapy nor had a hysterectomy.

Percentages exclude women with missing values.

Table 2 Adjusted relative risk for gallbladder disease according to parity, age at menarche and age at menopause

	Cases/population	Minimally adjusted[a] RR	Fully adjusted[b] RR (95% CI)
All women	25 112/1 289 029	–	–
Parity			
Nulliparous	2 058/140 240	1.00	1.00
Parous	23 054/1 148 789	1.36	1.24 (1.19–1.30)
By number of children			
One	3 345/182 140	1.24	1.18 (1.11–1.24)
Two	9 882/542 523	1.23	1.18 (1.12–1.23)
Three	5 939/277 909	1.44	1.29 (1.22–1.36)
Four	2 569/100 142	1.72	1.44 (1.36–1.53)
Five or more	1 319/46 075	1.91	1.47 (1.37–1.58)
P-value (linear trend)			$P < 0.0001$
Age at menarche (years)			
⩽12	10 100/481 843	1.00	1.00
13	5 596/307 520	0.86	0.96 (0.92–0.99)
14	4 802/259 120	0.88	0.97 (0.94–1.01)
15+	4 084/213 986	0.90	1.00 (0.97–1.04)
P-value (linear trend)			$P = 0.4$
Age at menopause (years)[c]			
⩽48	1 629/103 052	1.00	1.00
49–51	1 566/103 559	0.97	0.98 (0.92–1.06)
52+	2 150/143 006	0.97	0.97 (0.90–1.03)
P-value (linear trend)			$P = 0.3$

[a]Adjusted for age, region of recruitment.
[b]Adjusted for age, region of recruitment, socioeconomic status, smoking, BMI, hysterectomy, use of hormone replacement therapy and oral contraceptives. For age at menarche and menopause relative risks additionally adjusted for parity and breastfeeding.
[c]In post-menopausal women aged >52 years with a natural menopause who had never used hormone replacement therapy nor had a hysterectomy.

compared with nulliparous women was 1.25 (95% CI 1.19–1.31) with a relative risk of 1.08 (95% CI 1.07–1.09) per birth, i.e. an increase in risk of 8% (95% CI 7–9%) per birth. There was no association with the age of menarche nor the age at menopause.

Table 3 shows the relationship between hospital admissions for gallbladder disease and breastfeeding in analyses restricted to parous women and adjusted by parity (1, 2, 3, 4 and 5+) in addition to the other factors. Breastfeeding was associated with a reduced risk of gallbladder disease (adjusted relative risk for ever breastfeeding compared with never 0.92, 95% CI 0.90–0.96) and there was a decrease in the risk with increasing total duration of breastfeeding ($P < 0.0001$ for linear trend). For every year of breastfeeding the adjusted relative risk of gallbladder disease was 0.93 (95% CI 0.90–0.95), i.e. a reduction in risk of 7% (95% CI 5–10%). When we examined the effect of breastfeeding with additional adjustment for alcohol intake and other medical illnesses the calculated risks did not alter appreciably. Similarly stratifying our analyses by parity did not alter the results. The relationships were also similar for the outcome of cholecystectomy alone. The adjusted relative risk of cholecystectomy in women classified as ever breastfeeding compared to never breastfeeding was 0.94 (95% CI 0.91–0.97) and a total of 12 months of breastfeeding resulted in a reduction in the risk of cholecystectomy by 7% (95% CI 5–10%).

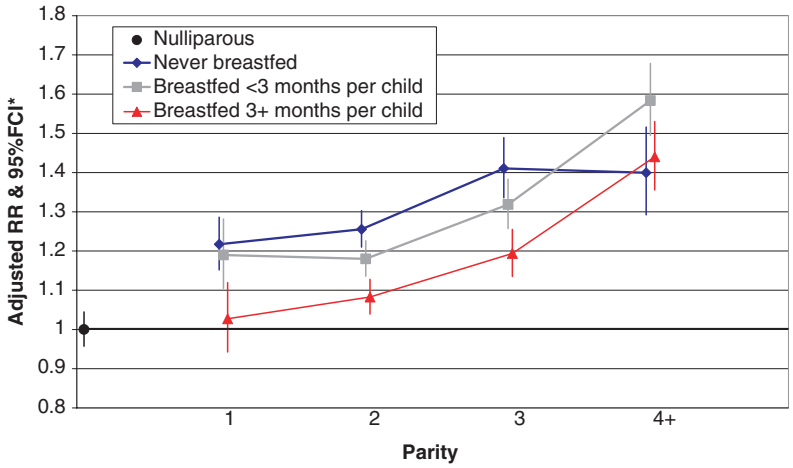
As the number of births in parous women is related to the likelihood of breastfeeding and the duration of breastfeeding (Table 1), we compared the effect of the duration of breastfeeding per child breastfed on the risk of admission for gallbladder disease in fine subdivisions of parity. Figure 1 shows the effect of breastfeeding in women with parity 1, 2, 3 and 4+, compared with nulliparous women. Within every category of parity, an increase in the duration of breastfeeding per child breastfed reduced the relative risk of gallbladder disease compared with those who had never breastfed. The magnitude of the reduction in risk was similar across all groups except in the small proportion of women with 4+ children who never breastfed, but this may be a chance finding.

In UK the reported breastfeeding rate in the 1970s was about 50%.[17] Using the relative risk for hospitalization for gallbladder disease in parous women who

Table 3 Adjusted relative risk for gallbladder disease according to breastfeeding in parous women only

	Cases/population	Minimally adjusted[a] RR	Fully adjusted[b] RR (95% CI)
All parous women	23 054/1 148 789	–	–
Breastfeeding			
No	6 073/292 675	1.00	1.00
Yes	11 736/615 773	0.91	0.92 (0.90–0.96)
By total duration (months)			
<6	6 549/322 897	0.96	0.97 (0.93–1.00)
6–11	2 605/142 768	0.87	0.89 (0.85–0.94)
12+	2 582/150 074	0.83	0.85 (0.81–0.89)
P-value (linear trend)			<0.0001

[a]Adjusted for age, region of recruitment.
[b]Adjusted for age, region of recruitment, socioeconomic status, smoking, BMI, hysterectomy, use of hormone replacement therapy and oral contraceptives, parity.
Numbers of cases and population do not sum to totals because of missing values and women who were not asked about breastfeeding at recruitment (see Methods section).



*To permit valid comparisons between each group the relative risks and their confidence intervals were treated as floating absolute risks and 95% floating confidence intervals. [26] This approach does not alter the value of the relative risk but reduces the variances attributed to them and allows valid comparisons to be made between any two groups and tests of trend. Floated relative risks adjusted for age, region, socioeconomic status, BMI, hysterectomy, oral contraceptive and HRT use.

Figure 1 Adjusted relative risk of gallbladder disease according to duration of breastfeeding per child and a woman's parity

breastfed compared with those who did not and the rate of breastfeeding in the 1970s, we can estimate that among middle-aged women who had children in the 1970s, not having breastfed accounts for about 4% of admissions for gallbladder disease in this population today.

Discussion

Gallbladder disease is common in middle-aged women with 1.6 out of any 100 in this cohort admitted to hospital for the condition and 1.4/100 having a cholecystectomy over a 5-year period. We found that the number of children a woman has increases her risk of gallbladder disease and that compared with nulliparous women, the risk rises incrementally by 8% (95% CI 7–9%) with each additional birth. We also found that after accounting for the number of children, 12 months of breastfeeding reduces the risk of gallbladder disease in parous women by 7% (95% CI 5–10%). Other factors such as the age of menarche and the age at menopause have little if any, influence on the risk of gallbladder disease.

With respect to parity, three prospective studies have reported similar findings to ours, that is, that the risk of gallbladder disease or cholecystectomy increases with increasing number of children.[4–6] One study found no significant trend although women who had four or more children were at an increased risk[7] and another study reported no association with parity.[8]

Only one case-control study examined the effect of breastfeeding on the risk of gallbladder disease, and reported no association once parity was taken into account.[9] However that study involved only 200 cases compared with over 20 000 here, and as the number of births and breastfeeding patterns are closely interrelated, the study had limited scope to make within-parity comparisons.

We found that the risk of gallbladder disease increased with each subsequent birth and that this risk, despite what others have suggested,[10] appears to be present in women many years following their last birth. Oestrogens increase biliary cholesterol saturation[11] and ultrasound studies show increases in biliary sludge and stones in pregnant women.[18] Hence our findings could be explained by the fact that with each pregnancy, there is a repeated exposure to high oestrogen levels, resulting in a cumulative increase in the likelihood of development of gallstones or the enlargement of pre-existing gallstones and therefore an increased potential for symptomatic gallbladder disease later in life.[11] Childbearing is also known to induce long-term changes to a woman's hormonal balance[19,20] and this influence may also play a role in the increased risk of gallbladder disease that we found in women many years after they last gave birth.

Breastfeeding was found to reduce the risk of gallbladder disease in parous women. As oestrogen levels are known to fall during lactation[21] it is possible that the protective effect of breastfeeding could be mediated through oestrogen, although there are other hormonal changes that occur with lactation that may also have an effect. It is unclear as to why the age of menarche and menopause did not appear to affect gallbladder disease risk as they do mark significant periods of change in a woman's circulating oestrogen levels, albeit much less dramatic than those induced by pregnancy.

The strengths of this study lie in the large study population which allowed us to characterize the effects of parity on hospitalizations for gallbladder disease more precisely than previously. We were also able to examine the effects of breastfeeding on gallbladder disease in strata of individual parity, thereby excluding confounding by this factor. Our findings showed a generally consistent relationship between an increased duration of breastfeeding and a reduction in the risk of gallbladder disease at every parity (Fig. 1).

As all women in the study were registered with the NHS at recruitment and we used linked NHS hospital admission records for outcome ascertainment, we would expect to have close to complete ascertainment of hospital admissions for gallbladder disease for all study participants. The hospital admission records are routinely collected and coded independently of the study investigators therefore minimizing differential recording of outcome. As the NHS hospital admission databases contain only some of the privately funded admissions there would be some under-ascertainment of cases. However, the independent and private hospital sector is relatively small in UK[22] and we have previously demonstrated that in this cohort, that was recruited from the NHS breast screening program, few self-reported cholecystectomy cases are not found in the linked NHS hospital records suggesting that any missed cases would be minimal.[23]

Information on exposures were prospectively collected and although they were self-reported, we would expect that the number of children, the age at menarche in the categories examined[24] and age at menopause[25] to be relatively accurately recalled. Recall of the duration of breastfeeding may be less precise and we did not ask women for how long they exclusively breastfed. As this was a prospective study, any misclassification of the duration of breastfeeding should not differ according to whether a woman had an admission for gallbladder disease or not and therefore this misclassification would tend to dilute the estimated risk reduction attributable to a defined period of breastfeeding. Furthermore as participants were no longer of child-bearing age, the main exposures of interest would not change during follow-up.

The difference between the fully adjusted and minimally adjusted relative risks for gallbladder disease were found to increase with increasing parity but not for breastfeeding (Table 2 and 3). This was principally due to the addition of body mass index as an adjustment factor. This indicates that the confounders that we adjusted for, in particular body mass index are important for the effect of parity on gallbladder disease but less so for the effect of breastfeeding. The relationship between parity, duration of breastfeeding and socioeconomic group is inconsistent (Table 1) and all our analyses adjusted for socioeconomic status. If breastfeeding is influenced by unmeasured social factors and if such factors were also to influence the risk of gallbladder disease, then some residual confounding may still exist.

The findings from this study are limited to middle-aged women and hospitalizations for symptomatic gallbladder disease. However from a public health view point it is women of this age who are responsible for the greatest proportion of the burden of gallbladder disease[1] and it is symptomatic gallbladder disease which results in hospitalization that is of clinical importance. While our study showed every birth results in about an 8% increase in the risk of gallbladder disease, breastfeeding for 12 months reduces the risk by about the same amount. Breastfeeding is already known to protect against breast cancer in the long term[26] and our findings suggest that it can also provide a means to offset the impact of parity on the risk of gallbladder disease in later life.

Funding

Cancer Research UK; National Health Service Breast Screening Programme; Medical Research Council.

Acknowledgements

We thank all the women who participated in the Million Women Study, the study steering committee as well as ISD Scotland, the Information Centre for Health and Social Care and Northgate Solutions for the linkage of the hospital records.

Conflict of interest: None declared.

KEY MESSAGES

- Gallbladder disease is common in middle-aged women.
- Each birth results in about an 8% increase in the relative risk of gallbladder disease and breastfeeding for 12 months reduces the relative risk by about the same amount.
- Breastfeeding can offset some of the adverse effects of childbearing on the risk of developing gallbladder disease.

References

[1] Kang J-Y, Ellis C, Majeed A *et al*. Gallstones – an increasing problem: a study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther* 2003;**17:**561–69.

[2] Portincasa P, Moschetta A, Palasciano G. Cholesterol gallstone disease. *Lancet* 2006;**368:**230–39.

[3] Cirillo DJ, Wallace RB, Rodabough RJ *et al*. Effect of estrogen therapy on gallbladder disease. *JAMA* 2005;**293:**330–39.

[4] Layde P, Vessey M, Yeates D. Risk factors for gall-bladder disease: a cohort study of young women attending family planning clinics. *J Epidemiol Community Health* 1982; **36:**274–78.

[5] Murray F, Logan R, Hannaford P, Kay C. Cigarette smoking and parity as risk factors for the development of symptomatic gall bladder disease in women: results of the Royal College of General Practitioners' oral contraception study. *Gut* 1994;**35:**107–11.

[6] Kritz-Silverstein D, Barrett-Connor E, Wingard D. The relationship between reproductive history and cholecystectomy in older women. *J Clin Epidemiol* 1990;**43:**687–92.

[7] Grodstein F, Colditz GA, Hunter D, Manson J, Willet W, Stampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. *Obstet Gynecol* 1994;**84:**207–14.

[8] Maclure K, Hayes K, Colditz GA, Stampfer MJ, Speizer F, Willet W. Weight, diet and the risk of symptomatic gallstones in middle-aged women. *N Engl J Med* 1989; **321:**563–69.

[9] Scragg R, McMichael A, Seamark R. Oral contraceptives, pregnancy, and endogenous oestrogen in gall stone disease - a case-control study. *Br Med J* 1984;**288:**1795–99.

[10] Thijs C, Knipschild P, Leffers P. Pregnancy and gallstone disease: an empiric demonstration of the importance of specification of risk periods. *Am J Epidemiol* 1991;**134:**186–95.

[11] Sanders G, Kingsnorth A. Gallstones. *Br Med J* 2007; **335:**295–99.

[12] The Information Centre. Hospital Episode Statistics. Available at: www.hesonline.nhs.uk.

[13] Kendrick S, Clarke J. The Scottish Record Linkage System. *Health Bull (Edinb)* 1993;**51**:72–79.

[14] World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. Tenth revision edn. Geneva: World Health Organization, 1992.

[15] Office of population censuses and surveys. *Classification of Surgical Operations and Procedures – Fourth Revision*. London: Crown copyright, 2000.

[16] Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. London: Croom Helm, 1988.

[17] Clark B, Laing S. Infant feeding: a review of breast- and formula-feeding practices. *J Hum Nutr Diet* 1990;**3:**1–9.

[18] Ko CW, Beresford SA, Schulte SJ, Matsumoto AM, Lee SP. Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. *Hepatology* 2005;**41:**359–65.

[19] Dorgan J, Reichman M, Judd J *et al*. Relationships of age and reproductive characteristics with plasma estrogens and androgens in premenopausal women. *Cancer Epidemiol Biomarkers Prev* 1995;**4:**381–86.

[20] Key T, Pike M, Wang D, Moore J. Long term effects of a first pregnancy on serum concentrations of dehydroepiandrosterone sulfate and dehydroepiandrosterone. *J Clin Endocrinol Metab* 1990;**70:**1651–53.

[21] Petrakis N, Wrensch M, Ernster V *et al*. Influence of pregnancy and lactation on serum and breast fluid estrogen levels: implications for breast cancer risk. *Int J Cancer* 1987;**40:**587–91.

[22] Williams B, Whatmough P, McGill J, Rushton L. Patients and procedures in short-stay independent hospitals in England and Wales, 1997-1998. *J Public Health Med* 2000;**22:**68–73.

[23] Liu B, Sweetland S, Beral V, Green J, Balkwill A, Casabonne D. Self-reported information on joint replacement and cholecystectomy agrees well with that in medical records. *J Clin Epidemiol* 2007;**60:**1190–94.

[24] Cooper R, Blell M, Hardy R *et al*. Validity of age at menarche self-reported in adulthood. *J Epidemiol Community Health* 2006;**60:**993–97.

[25] Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas* 1997;**27:**117–23.

[26] Collaborative group on hormonal factors in breast cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. *Lancet* 2002;**360**:187–95.