

Hormonal contraceptives and asthma in women of reproductive age: analysis of data from serial national Scottish Health Surveys

Bright I Nwaru¹ and Aziz Sheikh^{1,2,3}

¹Asthma UK Centre for Applied Research, Centre for Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, EH8 9AG, UK

²Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, MA 02120, USA

³Department of Medicine, Harvard Medical School, Boston, MA 02115, USA

Corresponding author: Aziz Sheikh. Email: aziz.sheikh@ed.ac

Abstract

Objectives: Sex steroid hormones may explain known gender-related variations in asthma prevalence and clinical manifestation. We investigated the relationship between use of hormonal contraceptives and asthma in women, and assessed evidence of biological interaction between use of hormonal contraceptives and body mass index in this relationship.

Design: Population-based analysis using data from serial (i.e. 2003, 2008 and 2010) Scottish Health Surveys.

Setting: Random samples of the Scottish general population.

Participants: A total of 3257 non-pregnant, 16–45-year-old women.

Exposure: Current use of hormonal contraceptives.

Main outcome measures: Self-reported current physician-diagnosed asthma, current wheezing symptoms, wheezing attacks and treatment for asthma or wheeze.

Results: Women comprising 30.9% (95% confidence interval 29.3–32.5) were currently using any hormonal contraceptive and current physician-diagnosed asthma was present in 6.5% (95% confidence interval 5.7–7.4). Use of any hormonal contraceptive was associated with reduced risk of current physician-diagnosed asthma (odds ratio 0.68; 95% confidence interval 0.47–0.98) and receiving ≥ 3 asthma care episodes (odds ratio 0.45; 95% confidence interval 0.25–0.82), but the evidence was equivocal for wheezing attacks. Use of hormonal contraceptives among overweight or obese women was non-statistically significantly associated with asthma, but there was 42–135% increased risk in overweight and obese non-contraceptive using women.

Conclusions: Use of hormonal contraceptives may reduce asthma exacerbations and number of care episodes. Overweight and obese non-contraceptive-using women may be at increased risk of asthma. Prospective studies are now needed to confirm these findings. Both oestrogen and progesterone may stimulate smooth airway muscle function and inhibit the activities of TH2 responses. Future studies should investigate these underlying mechanisms.

Keywords

Asthma, hormonal contraceptives, oestrogen, progesterone, wheeze, women

Introduction

Asthma is more common in boys than in girls during early childhood, but during adulthood the prevalence, severity, healthcare utilisation and impact on health-related quality of life have been found to be considerably higher in women than in men.^{1–3} The specific mechanisms for these differences are unclear, but female sex hormones have been implicated.^{1,4,5} Menstrual-related changes are associated with a decline in pulmonary function, asthma exacerbations and hospitalisation.^{6,7} In contrast, hormone replacement therapy is associated with an increased risk of asthma and use of asthma medications in postmenopausal women,^{8–13} although contrary evidence also exists.¹⁴

Only a few studies have examined the impact of use of hormonal contraceptives on the risk of asthma. Some studies have reported no associations between use of any hormonal contraceptive or combined oral contraceptives and asthma and asthma symptoms;¹⁵ others have reported a decreased risk,^{16,17} yet others have observed an increased risk of asthma, wheeze and other allergies such as hay fever.^{17,18} Hormonal contraceptives come in two main formulations: combined oral contraceptives (i.e. containing both oestrogen and progesterone) and progesterone-only preparations. It is, however, unclear whether the hormonal contraceptive types may have differential effects on asthma. Only one study among reproductive age women studied the different hormonal contraceptive types, reporting no association with each type.¹⁵ Among postmenopausal women, oestrogen-only and oestrogen/progesterone hormone

replacement preparations have both been associated with an increased risk of asthma,^{11–13} as well as contrasting effects.¹¹

Given this uncertainty, we sought to investigate the relationship between current use of hormonal contraceptives and asthma in women of reproductive age. We hypothesised that the use of any hormonal contraceptive is associated with higher prevalence of asthma and poorer asthma outcomes, and if so we were interested in whether there is a difference in direction and/or size of effect in those using combined oral contraceptives and progesterone-only preparations. Our secondary aim was to investigate whether there is any evidence of biological interaction between use of hormonal contraceptives and body mass index in relation to the risk of asthma.¹⁸

Materials and methods

Ethical considerations

National Health Service South East Scotland Research Ethics Service assessed this study and decided that it did not require National Health Service ethical review since it involved utilisation of previously collected anonymised data.

Study design

We drew on the Scottish Health Surveys, a serial population-based cross-sectional survey of randomly selected participants living in private households in Scotland (<http://www.scotland.gov.uk/Topics/Statistics/Browse/Health/scottish-health-survey>). It is designed to provide a comprehensive picture of the health of the Scottish population, covering issues related, but not limited to self-assessed health and disability, cardiovascular and respiratory disease, mental health, healthcare utilisation, smoking, and physical activity and anthropometric and biological measurements. Government departments, policy-makers and academic groups frequently use the data from these surveys in social and healthcare planning and research.

The survey started in 1995 and was then repeated in 1998, 2003 and 2008, after which it moved to an annual survey. A clustered sampling technique was used to select a representative sample of households and participants from across Scotland, involving a personal interview by a trained interviewer and a nurse interview and anthropometric and biological measurements. Questions on asthma and wheezing symptoms were included in the 1998, 2003, 2008, 2010 and 2012 surveys. We used data from the

2003, 2008 and 2010 surveys as these asked comparable questions in relation to use of hormonal contraceptives and asthma. A detailed study protocol was registered at ClinicalTrials.gov (number NCT02039102) prior to undertaking any analyses.

Study population

A total of 4538 (in 2003), 3623 (2008) and 4130 (2010) women aged ≥ 16 years were interviewed, with response rates of 63%, 57% and 59%, respectively. A random sub-sample of participants in 2008 and 2010 answered the questionnaire on asthma and respiratory symptoms. After selecting non-pregnant, 16–45-year-old women, the weighted study population for the present analysis was 3257 women who responded to the questionnaires on use of contraceptives and asthma symptoms.

Exposure assessment

The women were asked questions about their current contraception and type of contraceptives used. The exposure in the current analysis was current use of hormonal contraceptives, studied in three groups: (1) use of any hormonal contraceptive method (mini pill, combined oral contraceptives, unsure contraceptive pills, emergency pills, Mirena coil, injections and implant); (2) use of combined oral contraceptives; and (3) use of progesterone-only preparations (mini pill, Mirena coil, injections and implant). Unsure contraceptive and emergency pills were not included in the second and third groups since it was unclear the constituents of these groups of contraceptive pills and because emergency pills were not differentiated in the questionnaire and can come either as oestrogen-progestin or progesterone-only preparations.

Outcome assessment

Our primary outcome was current physician-diagnosed asthma, which we defined as ever having physician-diagnosed asthma and either an attack of asthma in the last 12 months or had asthma or wheeze care episodes in the last 12 months. Secondary outcomes were current wheezing attacks and number of asthma or wheeze care episodes. Current wheezing attack was defined as having ≥ 3 wheezing attacks in the last 12 months or having had one or more sleep disturbances per week in the last 12 months because of wheeze. Current care episodes for asthma was defined as having ≥ 3 asthma or wheeze care episodes in the last 12 months (Table S1).

Potential confounders

Based on previous literature,¹⁹ we selected the following potential confounding variables which were collected in the survey: age (16–20, 21–25, 26–30, 31–35, 36–40, >40 years), ethnicity (White, others), body mass index (<20, 20–24.9, 25–30, >30 kg/m²), current smoking status (never smoker, ex-smoker, current smoker), Scottish Index of Multiple Deprivation (in quintiles) (<http://www.scotland.gov.uk/Topics/Statistics/SIMD>) and highest educational qualification (degree or higher, higher national certificate/diploma or equivalent, higher grade or equivalent, standard grade or equivalent, others or no qualification).

Sample size determination

In the United Kingdom, oral contraceptives are used by approximately 35% of women aged 16–49 years.^{20,21} In the 2010 Scottish Health Survey, use of contraceptive pills was 20% among women ≥16 years, and this estimate was suggested to be higher among younger women than the older ones. These figures excluded the use of other progesterone-only contraceptives, such as Mirena coil, injections and implants. By assuming a conservative prevalence of current use of any hormonal contraceptives among women 16–45 years at 30% and a 20% prevalence of ever having physician-diagnosed asthma (as reported in the combined 2008 and 2010 Scottish Health Surveys), we estimated that we would need a sample size of 2494 to have 90% power to detect an odds ratio of 1.40 for the use of combined oral contraceptives.¹⁸

Statistical analyses

Simple frequencies, Pearson's chi-square and Fisher's exact tests were used for descriptive analyses; relevant sampling weights were applied to account for sampling methods and non-response. Logistic regression modelling was used to estimate the odds ratios for the associations between use of hormonal contraceptives and the risk of asthma and wheezing outcomes. Unadjusted models included survey year as a covariate. Adjusted models included the potential confounding factors and survey year. These analyses were also done separately by survey year. We performed biological interaction analyses to estimate the synergistic effect of hormonal contraceptives and body mass index in relation to each study outcome. We calculated the biological interaction measures separately for each group of hormonal contraceptives and overweight (body mass index ≥ 25 kg/m²) and hormonal contraceptive and

obesity (body mass index ≥ 30 kg/m²). We estimated the relative excess risk due to interaction and the attributable proportion due to interaction with their accompanying 95% confidence intervals following the methods proposed by Andersson et al.²² The interaction analyses were not undertaken by survey year because of lack of statistical power. Statistical significance for all analyses was taken as two-tailed $p < 0.05$. Statistical analyses were done using STATA SE/11.

Results

Characteristics of the study population

The combined 2003, 2008 and 2010 surveys gave us a total of 3257 women aged 16–45 years. Thirty-one per cent (95% confidence interval 29.3–32.5) were currently using any hormonal contraceptive and 13.5% (95% confidence interval 12.3–14.7) and 13.4% (95% confidence interval 12.3–14.6) were using combined oral contraceptives and progesterone-only preparations, respectively (Table 1). There were differences in the use of hormonal contraceptives with regard to age, ethnicity, body mass index, smoking, level of education and survey year (Table 1).

The prevalence of self-reported current physician-diagnosed asthma was 6.5% (95% confidence interval 5.7–7.4), ≥3 wheezing attacks 14.2% (95% confidence intervals 13.0–15.4) and ≥3 asthma or wheeze care episodes 3.3% (95% confidence interval 2.7–4.0) (Table 2). Asthma and wheezing outcomes differed according to ethnicity, body mass index, smoking and level of education (Table 2).

Hormonal contraceptives and asthma

Use of any hormonal contraceptive (odds ratio: 0.71, 95% confidence interval 0.50–1.01) was borderline significantly associated with a decreased risk of current physician-diagnosed asthma (Table 3). Use of combined oral contraceptives and progesterone-only preparations was also associated with reduced risk of current physician-diagnosed asthma, but with wide 95% confidence intervals (Table 3). Use of any hormonal contraceptive, combined oral contraceptives, and progesterone-only preparations was associated with reduced risk of having ≥3 wheezing attacks in the last 12 months, but with wide 95% confidence intervals (Table 3). Use of any hormonal contraceptive (odds ratio 0.46, 95% confidence interval 0.27–0.78) and combined oral contraceptives (odds ratio 0.33, 95% confidence interval 0.13–0.82) was associated with reductions in asthma or wheeze care episodes. Use of progesterone-only preparations was

Table 1. Background characteristics by current use of hormonal contraceptives: results from the Scottish Health Survey 2003, 2008 and 2010.

	Frequency N = 3257* n (%) ^a		Currently using any hormonal contraceptive [†] n = 1005		Currently using combined oral contraceptives n = 439		Currently using progesterone-only preparations [‡] n = 436	
	n (%) ^a	p value [§]	n (%) ^a	p value [§]	n (%) ^a	p value [§]	n (%) ^a	p value [§]
Age (years)		<0.001		<0.001		<0.001		<0.001
16–20	508 (15.6)		168 (33.1)		109 (21.5)		40 (7.9)	
21–25	463 (14.2)		208 (44.8)		105 (22.7)		91 (19.7)	
26–30	481 (14.7)		189 (39.4)		85 (17.7)		96 (20.0)	
31–35	565 (17.3)		167 (29.6)		76 (13.5)		79 (14.0)	
36–40	596 (17.3)		149 (25.0)		42 (7.1)		65 (10.9)	
>40	644 (19.8)		124 (19.2)		21 (3.3)		65 (10.1)	
Ethnicity		<0.001		<0.001		0.047		0.013
White	3132 (96.2)		990 (31.6)		431 (13.8)		429 (13.7)	
Others	110 (3.4)		14 (12.7)		8 (7.2)		6 (5.5)	
Missing information	15 (0.4)							
Body mass index (kg/m ²)		<0.001		<0.001		<0.001		0.024
<20	748 (23.0)		196 (26.2)		103 (13.8)		79 (10.6)	
20–25	1114 (34.2)		372 (33.4)		170 (15.3)		148 (13.3)	
>25–30	794 (24.4)		275 (34.6)		121 (15.2)		114 (14.4)	
>30	585 (18.0)		159 (27.2)		44 (7.5)		94 (16.1)	
Missing information	16 (0.5)							
Current smoking status		0.031		0.031		0.087		<0.001
Never smoked	1644 (50.5)		478 (29.1)		245 (14.9)		169 (10.3)	
Ex-smoker	595 (18.3)		190 (31.9)		72 (12.1)		92 (15.5)	
Current smoker	973 (29.9)		330 (33.9)		120 (12.3)		172 (17.7)	

(continued)

Table 1. Continued.

	Frequency N = 3257* n (%) [*]	Currently using any hormonal contraceptive [†] n = 1005		Currently using combined oral contraceptives n = 439		Currently using progesterone-only preparations [‡] n = 436	
		n (%) [*]	p value [§]	n (%) [*]	p value [§]	n (%) [*]	p value [§]
Missing information	45 (1.4)						
Scottish index of multiple deprivation			0.625		0.977		0.562
1st quintile (least deprived)	669 (20.5)	195 (29.1)		88 (13.2)		80 (12.0)	
2nd quintile	685 (21.0)	218 (31.8)		95 (13.9)		90 (13.1)	
3rd quintile	624 (19.1)	190 (30.5)		84 (13.5)		81 (13.0)	
4th quintile	635 (19.5)	190 (29.9)		82 (12.9)		88 (13.9)	
5th quintile (most deprived)	644 (19.8)	211 (32.8)		90 (14.0)		97 (15.1)	
Highest education qualification			<0.001		<0.001		0.003
Degree or higher	941 (28.9)	303 (32.2)		119 (12.6)		151 (16.0)	
HNC/D or equivalent	584 (17.9)	193 (33.0)		98 (16.8)		86 (14.7)	
Higher grade or equivalent	457 (14.0)	169 (37.0)		75 (16.4)		65 (14.2)	
Standard grade or equivalent	846 (26.0)	248 (29.3)		117 (13.8)		92 (10.9)	
Others or no qualification	414 (12.7)	89 (21.5)		30 (7.2)		40 (9.7)	
Missing information	15 (0.5)						
Survey year			0.001		<0.001		0.255
2003	2109 (64.8)	607 (28.8)		333 (15.8)		274 (13.0)	
2008	567 (17.4)	204 (36.0)		51 (9.0)		72 (12.7)	
2010	581 (17.8)	195 (33.6)		55 (9.5)		90 (15.5)	

*All proportions are weighted; N and n are unweighted total study sample and frequencies, respectively.

[†]Includes use of combined contraceptive pill, other contraceptive pills but unknown by respondent, emergency contraceptive and progesterone-only preparations (mini pill, Mirena, implant and injection).

[‡]Included mini pill, Mirena, implant and injection.

[§]p values based on the Pearson's Chi-square test or Fisher's exact test when the cells are smaller than five cases.

Table 2. Background characteristics by prevalence of current asthma and wheeze: Results from the Scottish Health Survey 2003, 2008 and 2010.

	Frequency N = 3257	Current physician-diagnosed asthma [†] n = 213		≥3 current wheezing attacks n = 461		≥3 current asthma/wheeze care episodes [‡] n = 107	
		n (%) [*]	p value [§]	n (%) [*]	p value [§]	n (%) [*]	p value [§]
Age, years			0.637		0.138		0.027
16–20	508 (15.6)	28 (5.5)		52 (10.2)		7 (1.4)	
21–25	463 (14.2)	30 (6.5)		69 (14.9)		20 (4.3)	
26–30	481 (14.7)	27 (5.6)		68 (14.2)		11 (2.3)	
31–35	565 (17.3)	44 (7.8)		89 (15.8)		17 (3.0)	
36–40	596 (17.3)	38 (6.4)		89 (14.9)		23 (3.9)	
>40	644 (19.8)	46 (7.1)		95 (14.7)		29 (4.5)	
Ethnicity			0.046		0.032		0.153
White	3132 (96.2)	210 (6.7)		452 (14.4)		105 (3.4)	
Others	110 (3.4)	2 (1.8)		8 (7.2)		1 (0.9)	
Missing information	15 (0.4)						
Body mass index, kg/m ²			0.004		0.001		<0.001
<20	748 (23.0)	37 (4.9)		101 (13.5)		18 (2.4)	
20–25	1114 (34.2)	66 (5.9)		129 (11.6)		21 (1.9)	
>25–30	794 (24.4)	53 (6.7)		120 (15.1)		30 (3.8)	
>30	585 (18.0)	57 (9.7)		110 (18.8)		38 (6.5)	
Missing information	16 (0.5)						
Current smoking status			0.007		<0.001		<0.001
Never smoked	1644 (50.5)	92 (5.6)		163 (9.9)		43 (2.6)	
Ex-smoker	595 (18.3)	34 (5.7)		60 (10.1)		10 (1.7)	

(continued)

Table 2. Continued.

	Frequency N = 3257 n (%) [*]	Current physician-diagnosed asthma [†] n = 213		≥3 current wheezing attacks n = 461		≥3 current asthma/wheeze care episodes [‡] n = 107	
		n (%) [*]	p value [§]	n (%) [*]	p value [§]	n (%) [*]	p value [§]
Current smoker	973 (29.9)	84 (8.6)		235 (24.2)		52 (5.3)	
Missing information	45 (1.4)						
Scottish index of multiple deprivation			0.696		0.093		0.371
1 st quintile (least deprived)	669 (20.5)	43 (6.4)		98 (14.6)		21 (3.1)	
2 nd quintile	685 (21.0)	47 (6.9)		86 (12.6)		23 (3.4)	
3 rd quintile	624 (19.1)	33 (5.3)		78 (12.5)		13 (2.1)	
4 th quintile	635 (19.5)	45 (7.1)		89 (14.0)		23 (3.6)	
5 th quintile (most deprived)	644 (19.8)	45 (7.0)		111 (17.2)		26 (4.0)	
Highest education qualification			0.033		<0.001		<0.001
Degree or higher	941 (28.9)	54 (5.7)		111 (11.8)		20 (2.1)	
HNC/D or equivalent	584 (17.9)	35 (6.0)		76 (13.0)		19 (3.3)	
Higher grade or equivalent	457 (14.0)	30 (6.6)		66 (14.4)		14 (3.1)	
Standard grade or equivalent	846 (26.0)	51 (6.0)		108 (12.8)		21 (2.5)	
Others or no qualification	414 (12.7)	42 (10.2)		99 (24.0)		33 (8.0)	
Missing information	15 (0.5)						
Survey year			0.645		0.636		0.651
2003	2109 (64.8)	134 (6.4)		307 (14.6)		68 (3.2)	
2008	567 (17.4)	36 (6.3)		78 (13.8)		16 (2.8)	
2010	581 (17.8)	43 (7.4)		76 (13.1)		22 (3.8)	

*All proportions are weighted; N and n are unweighted total study sample and frequencies, respectively.

[†]Current physician-diagnosed asthma defined as ever physician-diagnosed asthma PLUS either an attack of asthma in the last 12 months or received treatment for asthma/wheeze in the last 12 months.

[‡]Current wheeze defined as having had wheezing or whistling in the chest in the last 12 months.

[§]p values based on the Pearson's Chi-square test or Fisher's exact test in cells smaller than five cases.

Table 3. Unadjusted and adjusted associations between current use of hormonal contraceptives and wheeze among Scottish women in 2003, 2008 and 2010: Odds ratios (odds ratio and 95% confidence intervals).

Current use of hormonal contraceptives	Current physician-diagnosed asthma Odds ratio (95% confidence interval)		≥ 3 current wheezing attacks Odds ratio (95% confidence interval)		≥ 3 current asthma or wheeze care episodes Odds ratio (95% confidence interval)	
	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†	Unadjusted*	Adjusted†
Any contraceptive p value	0.71 (0.50–1.01) 0.059	0.68 (0.47–0.98) 0.039	0.86 (0.67–1.11) 0.241	0.82 (0.63–1.06) 0.130	0.46 (0.27–0.78) 0.004	0.45 (0.25–0.82) 0.008
Combined oral contraceptives p value	0.69 (0.41–1.16) 0.160	0.71 (0.41–1.23) 0.219	0.88 (0.60–1.28) 0.495	0.96 (0.65–1.42) 0.841	0.33 (0.13–0.82) 0.017	0.40 (0.16–1.05) 0.063
Progestosterone-only preparations p value	0.83 (0.52–1.30) 0.410	0.76 (0.47–1.22) 0.256	0.93 (0.68–1.27) 0.635	0.81 (0.59–1.13) 0.223	0.66 (0.33–1.30) 0.229	0.58 (0.28–1.23) 0.157

*Adjusted for survey year.

†Adjusted for year of survey, age, ethnicity, body mass index, smoking, Scottish index of multiple deprivation and highest educational qualification.

associated with reduction in asthma or wheeze care episodes, but the estimates were imprecise (Table 3).

After adjusting for confounders, use of any hormonal contraceptive was associated with decreased risk of current physician-diagnosed asthma (odds ratio 0.68, 95% confidence interval 0.47–0.98) and reduction in asthma or wheeze care episodes (odds ratio 0.45, 95% confidence interval 0.25–0.82) (Table 3). Use of any hormonal contraceptive was similarly associated with decreased risk of having ≥ 3 wheezing attacks but with wide 95% confidence intervals (Table 3). Use of combined oral contraceptives and progesterone-only preparations was associated with decreased risk of each outcome, but with wide 95% confidence intervals (Table 3). The results by survey year were comparable to each other and similar to the estimates from the combination of all survey years, except for wide 95% confidence intervals (Tables S2–S4).

Biological interactions between use of hormonal contraceptives and body mass index in relation to current asthma

We did not observe any statistically significant association in overweight or obese women who were using any hormonal contraception in relation to current physician-diagnosed asthma (Tables 4 and 5). These results were similar for the use of combined oral contraceptives and progesterone-only preparations (Tables 4 and 5). However, in overweight and obese women who were not using any hormonal contraceptives, combined oral contraceptives and progesterone-only preparations, the risk of current, physician-diagnosed asthma and other outcomes increased between 42% and 135% (Tables 4 and 5).

Overall, judging by relative excess risk due to interaction and attributable proportion due to interaction, being overweight or obese and at the same time using any hormonal contraceptive, combined oral contraceptives, or progesterone-only preparations appeared to reduce the risk of asthma and outcomes, although the relative excess risk due to interaction and attributable proportion due to interaction measures were not precise, except for the relative excess risk due to interaction for the use of combined oral contraceptives among obese women in relation to current physician-diagnosed asthma and having ≥ 3 wheezing attacks (Tables 4 and 5).

Discussion

The use of any hormonal contraceptive was associated with substantial reductions in current physician-diagnosed asthma and number of asthma care

Table 4. Estimates of the biological interactions between use of hormonal contraceptives and body mass index in relation to current asthma and wheezing attacks among Scottish women in 2003, 2008 and 2010.

Current physician-diagnosed asthma		≥3 current wheezing attacks			
		Estimates of interaction		Estimates of interaction	
Interactions between use of hormonal contraceptives and body mass index	Odds ratio (95% confidence interval)*	Relative excess risk due to interaction (95% confidence interval)*	Attributable proportion due to interaction (95% confidence interval)*	Odds ratio (95% confidence interval)*	Relative excess risk due to interaction (95% confidence interval)*
<i>Use of hormonal contraceptives and overweight†</i>					
<i>Any hormonal contraceptive</i>					
User and overweight	0.89 (0.53–1.50)	–0.36 (–1.09 to 0.38)	–0.40 (–1.30 to 0.50)	1.00 (0.67–1.49)	–0.46 (–1.06 to 0.13)
User and not overweight	0.76 (0.46–1.25)			0.94 (0.66–1.33)	
Non-user and overweight	1.49 (1.03–2.15)			1.53 (1.17–2.00)	
<i>Combined oral contraceptives</i>					
User and overweight	0.88 (0.382.02)	–0.31 (–1.30 to 0.67)	–0.36 (–1.69 to 0.97)	1.11 (0.57–2.14)	–0.38 (–1.30 to 0.55)
User and not overweight	0.77 (0.37–1.59)			1.06 (0.64–1.75)	
Non-user and overweight	1.42 (1.02–1.98)			1.43 (1.12–1.82)	
<i>Progestrone-only preparations</i>					
User and overweight	1.09 (0.57–2.06)	–0.07 (–0.99 to 0.86)	–0.06 (–0.93 to 0.81)	1.00 (0.63–1.60)	–0.34 (–1.01 to 0.34)
User and not overweight	0.76 (0.38–1.49)			0.91 (0.58–1.43)	
Non-user and overweight	1.40 (0.99–1.96)			1.43 (1.11–1.84)	
<i>Use of hormonal contraceptives and obesity‡</i>					
<i>Any hormonal contraceptive</i>					
User and obese	0.84 (0.40–1.77)			0.93 (0.54–1.59)	

(continued)

Table 4. Continued.

	Current physician-diagnosed asthma		≥3 current wheezing attacks		
	Estimates of interaction		Estimates of interaction		
	Odds ratio (95% confidence interval)*	Relative excess risk due to interaction (95% confidence interval)*	Attributable proportion due to interaction (95% confidence interval)*	Odds ratio (95% confidence interval)*	Relative excess risk due to interaction (95% confidence interval)*
Interactions between use of hormonal contraceptives and body mass index					
User and not obese	0.75 (0.50–1.13)	–0.67 (–1.65 to 0.32)	–0.80 (–2.36 to 0.76)	0.88 (0.66–1.17)	–0.52 (–1.23 to 0.20)
Non-user and obese	1.76 (1.15–2.67)			1.57 (1.15–2.14)	
Combined oral contraceptives					
User and obese	0.38 (0.05–2.85)	–1.15 (–2.26 to 0.04)	–3.03 (–11.33 to 5.28)	0.61 (0.18–2.14)	–0.99 (–1.97 to 0.01)
User and not obese	0.83 (0.47–1.48)			1.07 (0.71–1.63)	
Non-user and obese	1.69 (1.16–2.47)			1.53 (1.16–2.02)	
Progestrone-only preparations					
User and obese	1.16 (0.50–2.71)	–0.24 (–1.47 to 0.99)	–0.21 (–1.40 to 0.99)	0.94 (0.48–1.83)	–0.42 (–1.22 to 0.39)
User and not obese	0.76 (0.43–1.33)			0.86 (0.59–1.24)	
Non-user and obese	1.64 (1.10–2.45)			1.50 (1.12–2.01)	

*Adjusted for year of survey, age, ethnicity, body mass index, smoking, Scottish index of multiple deprivation and highest educational qualification.

†Overweight defined as body mass index ≥25 kg/m².‡Obesity defined as body mass index ≥30 kg/m².

Table 5. Estimates of the biological interactions between use of hormonal contraceptives and body mass index in relation to number of asthma/wheeze care episodes among Scottish women in 2003, 2008 and 2010.

Interactions between use of hormonal contraceptives and body mass index	≥3 current asthma or wheeze care episodes		
	Odds ratio (95% confidence interval)*	Estimates of interaction	
		Relative excess risk due to interaction (95% confidence interval)*	Attributable proportion due to interaction (95% confidence interval)*
Use of hormonal contraceptives and overweight[†]			
Any hormonal contraceptive			
User and overweight	0.97 (0.46–2.03)	–0.71 (–1.97 to 0.54)	–0.74 (–2.24 to 0.77)
User and not overweight	0.45 (0.18–1.10)		
Non-user and overweight	2.23 (1.33–3.74)		
Combined oral contraceptives			
User and overweight	0.93 (0.27–3.16)	–0.57 (–2.06 to 0.91)	–0.62 (–2.77 to 1.54)
User and not overweight	0.33 (0.08–1.44)		
Non-user and overweight	2.17 (1.36–3.46)		
Progesterone-only preparations			
User and overweight	1.24 (0.49–3.14)	–0.061 (–2.23 to 1.02)	–0.49 (–2.07 to 1.09)
User and not overweight	0.62 (0.18–2.08)		
Non-user and overweight	2.23 (1.36–3.63)		
Use of hormonal contraceptives and obesity[‡]			
Any hormonal contraceptive			
User and obese	1.09 (0.42–2.81)	–0.52 (–2.04 to 1.00)	–0.48 (–2.16 to 1.21)
User and not obese	0.42 (0.21–0.85)		
Non-user and obese	2.19 (1.28–3.75)		
Combined oral contraceptives			
User and obese	0.79 (0.10–6.26)	–0.94 (–2.92 to 1.05)	–1.18 (–5.86 to 3.49)
User and not obese	0.44 (0.15–1.28)		
Non-user and obese	2.28 (1.41–3.71)		
Progesterone-only preparations			
User and obese	1.15 (0.31–4.19)	–0.76 (–2.71 to 1.19)	–0.66 (–3.05 to 1.73)
User and not obese	0.56 (0.21–1.44)		
Non-user and obese	2.35 (1.41–3.92)		

*Adjusted for year of survey, age, ethnicity, body mass index, smoking, Scottish index of multiple deprivation, and highest educational qualification.

[†]Overweight defined as body mass index ≥ 25 kg/m².[‡]Obesity defined as body mass index ≥ 30 kg/m².

episodes, while combined oral contraceptives and progesterone-only preparations were imprecisely associated with decreased asthma or wheezing attacks. Furthermore, the use of hormonal contraceptives among overweight or obese women was associated with reduced risks of asthma exacerbations and wheezing attacks; in contrast, overweight and obese women who were not using hormonal contraceptives were at increased risk. *A priori* we hypothesised that use of any hormonal contraceptive may increase the risk of current asthma and that the role of combined oral contraceptives may differ from progesterone-only preparations. We did not confirm these hypotheses.

The Scottish Health Survey is an important source of data to assess the health status of the Scottish population across a number of health indicators, including respiratory and cardiovascular diseases.^{23,24} The survey processes have followed well-designed and rigorous methodologies of data collection and management, employing well-accepted measurement tools for gathering valid responses. The surveys are random samples of the general Scottish population; hence, our findings are likely to be generalisable to the wider population of Scottish women aged 16–45 years. As a cross-sectional study, we cannot, however, rule out the possibility of reverse causation, although we think that this is unlikely: while it is possible that women might have been prescribed contraceptives because of their asthma,²⁵ differentially promoting prescription of hormonal contraceptives in those with well-controlled asthma is rationally unlikely. The absence of any recommendation for prescribing hormonal contraceptives for treating asthma in major guidelines in the United Kingdom indicates that it is unlikely to be used on any large scale by generalists.

Detailed data on use of contraceptives enabled us to examine the independent associations between the two main types of hormonal contraceptives (combined oral contraceptives and progesterone-only preparations) and asthma. However, grouping of the contraceptives could result in an overlap so that some women may at the same time fall into different contraceptive groups. Information on asthma symptoms were also collected in detail so that we could examine different definitions of asthma. Although we could not validate the responses to the questions on contraceptives and asthma, the proportion of women using hormonal contraceptives and the prevalence of current asthma are comparable to other United Kingdom estimates.^{20,21} We could not undertake the analyses by ethnicity because non-White ethnic groups were small.

Previous studies have been contradictory: in the Copenhagen City Health Study use of oral

contraceptive pills was not associated with the prevalence of self-reported asthma, wheeze and use of asthma medication.⁹ Use of combined oral contraceptives was, however, associated with a decreased risk of current asthma in our study although with imprecise estimates, and as well it was borderline associated with reduction in asthma care episodes. Use of any hormonal contraceptive or sub-types was not associated with asthma severity in a study from England,¹⁵ contrary to our observation. The women in that study were only aged 20–30 years compared to 16–45 years in our study, which may explain the differences in findings. Salam et al.¹⁷ in a cohort study of girls/women aged 13–28 years found that use of oral contraceptive pills was associated with an increased risk of current wheeze among women without asthma, but associated with a reduced risk of current wheeze in women with a history of asthma. The authors indicated that their findings may imply that the airways of women with and without a history of asthma may respond differently to exogenous sex hormones.¹⁷ We could not study whether there are differences in women with allergic asthma. However, in an Australian study of 29–32 year-old women, while use of combined oral contraceptives was associated with a decreased risk of current asthma in all women, combined oral contraceptives use did not predict asthma among women who had asthma or wheeze by the age of 7 years.¹⁶

Macsali et al.¹⁸ reported that the use of oral contraceptive pills was associated with an increased risk of asthma, wheeze and hay fever in women aged 25–44 years. By stratifying the analyses by body mass index, the increased risk of asthma and allergy was specific to normal weight and overweight women but not in lean women.¹⁸ Both the independent associations between use of oral contraceptive pills and its interaction with body mass index as observed in Macsali et al. study are contrary to our observations. Overall, the use of combined oral contraceptives was equivocally associated with reductions in asthma care episodes in our study. In addition, the synergistic effect of use of combined oral contraceptives and body mass index showed that while use of combined oral contraceptives appears to reduce the risk of asthma in overweight or obese women, the risk was increased in overweight and obese women who were not using combined oral contraceptives, any hormonal contraceptives or progesterone-only preparations.

The study by Macsali et al.,¹⁸ however, examined only statistical interaction contrary to biological interaction investigated in our study. Other previous studies did not take into account the interaction between hormonal contraceptives and body mass index. Considering the biologically plausible synergy

between body mass index and endogenous or exogenous sex steroid hormones,²⁶ a formal investigation of this potential synergistic effect should be based on biological interaction rather than statistical interaction.^{22,27} While statistical interaction focuses on including a product term between two factors (which in themselves may not conceptually have any evidence of synergistic effect) in a model, it has been recommended that reliably uncovering possible biological interaction or synergy between two factors would require formal evaluation using additive models.²⁷ Future studies in this evidence base should therefore undertake these steps.

The immunological properties of hormonal contraceptives may include influence on smooth muscle function, inflammation and modification of airway responsiveness.^{4,28,29} Both oestrogen and progesterone are believed to independently possess these properties, but evidence is conflicting as both pro- and anti-inflammatory effects have also been observed for these hormones.^{4,28,29} For example, while both hormones have been thought to relax the bronchial smooth muscle and reduce contractile responses, thereby improving lung function,⁴ oestrogen may also stimulate the endothelial nitric oxide synthase in bronchiolar epithelial cells,^{28,29} while progesterone is associated with reduced diurnal peak expiratory flow rate variability during pregnancy.^{17,28,29}

There is some evidence that endogenous steroid hormones fluctuate during the menstrual cycle and such fluctuations may increase asthma exacerbations in women.^{30,31} A predominance of T-helper cell 2 over T-helper cell 1-mediated immunity has also been observed during the premenstrual period, indicating that exogenous sex hormones may inhibit T-helper cell 2 immune responses.³² Case studies and case series indicate that intake of exogenous sex hormonal preparations may reduce the need for asthma medications and improve lung function.^{17,25} The conflicting findings from few existing population-based studies, however, mean that the putative effect of hormonal contraceptives on asthma is inconclusive.

Conclusions

We have shown that use of any hormonal contraceptive is associated with substantial reductions in current asthma. Analysis of data by contraceptive type also suggested reductions in risk, but these were imprecisely estimated. It is therefore unclear whether this represents an oestrogen, progesterone, or a combination of oestrogen and progesterone effects. In overweight and obese women, use of any type of hormonal contraceptives may reduce asthma

exacerbations, but may increase the risk in overweight and obese non-contraceptive using women. Prospective population-based studies, particularly with a long-term follow-up of women from puberty to pre-menopause with careful longitudinal assessments of use of hormonal contraceptives and asthma, are now required to understand the mechanism through which exogenous hormonal preparations may impact on asthma. Future studies should also consider the role of different types of hormonal contraceptives and the possible biological interaction with body mass index.

Declarations

Competing interests: AS has served as an advisor to the Scottish Health Survey. BN declares no conflicts of interest. The views presented here are those of the author and not necessarily those of The Commonwealth Fund, its directors, officers, or staff.

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