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2 **Does use of hormonal contraceptives impact on severe exacerbation in women with asthma? A 17-year**  
3 **population-based cohort study**  
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**ABSTRACT****Background**

Longitudinal studies investigating impact of exogenous sex steroids on clinical outcomes in women are lacking. We investigated the association between use of hormonal contraceptives and risk of severe asthma exacerbation in reproductive-age women with asthma.

**Methods**

We used the Optimum Patient Care Research Database, a population-based longitudinal anonymised primary care database in the UK, to construct 17-year (1/1/2000–31/12/2016) retrospective cohort of reproductive-age (16-45 years,  $N=83,084$ ) women with asthma. Using READ codes, we defined use, subtypes, and duration of use of hormonal contraceptives. Severe asthma exacerbation was defined according to recommendation of the European Respiratory Society/American Thoracic Society as asthma-related hospitalisation, accident and emergency department visits due to asthma and/or oral corticosteroid prescriptions. Analyses were done using multilevel mixed-effects Poisson regression with QR decomposition.

**Results**

The 17-year follow-up resulted in 456,803 person-years of follow-up time. At baseline, 34% of women were using any hormonal contraceptives, 25% combined (oestrogen/progestogen), and 9% progestogen-only contraceptives. Previous (incidence rate ratio [IRR] 0.94, 95%CI 0.92-0.97) and current (IRR 0.96, 95%CI 0.94-0.98) use of any, previous (IRR 0.92, 95%CI 0.87-0.97) and current use of combined (IRR 0.93, 95%CI 0.91-0.96), and longer duration of use (3-4 years: IRR 0.94; 95%CI 0.92-0.97; 5+ years: IRR 0.91; 95%CI 0.89-0.93) of hormonal contraceptives, but not progestogen-only contraceptives, were associated with reduced risk of severe asthma exacerbation compared to non-use.

**Conclusion**

Use of hormonal contraceptives may reduce the risk of severe asthma exacerbation in reproductive-age women. Mechanistic studies investigating the biological basis for influence of hormonal contraceptives on clinical outcomes of asthma in women are required.

**KEY MESSAGES**

- *What is the key question?*

Does the use of hormonal contraceptives have any impact on severe asthma exacerbation in reproductive-age?

- *What is the bottom line?*

Use of hormonal contraceptives was associated with a small protective effect on severe asthma exacerbations in reproductive-age women.

- *Why read on?*

This is the largest longitudinal study investigating the impact of hormonal contraceptives on a key clinical outcome of asthma in reproductive-age women with already established asthma.

## INTRODUCTION

The female sex steroid hormones are thought to partly explain the notable sex-related differences in incidence and manifestation of clinical outcomes of asthma.<sup>1,2</sup> Fluctuations of the levels of estradiol and progesterone during women's menstrual cycle have been linked to worsening of asthma symptoms in some women.<sup>3</sup> A predominance of T-helper (Th) cell 2 over Th cell 1-mediated immunity has also been observed during the premenstrual period.<sup>4,5</sup> It is estimated that up to 45% of women with asthma experience heightened exacerbation during the premenstrual period.<sup>6</sup> In some women, the use of exogenous hormonal contraceptives appears to improve asthma outcomes, including reduced Th2 responses, reduced asthma symptoms, and improved lung function.<sup>7-10</sup> In a previous exploratory analysis of data from serial national cross-sectional Scottish Health Surveys, we observed up to 32% (95% CI 2-53) reduction in asthma exacerbations and up to 55% (95% CI 18-75) reduction in asthma hospital episodes in reproductive age females using hormonal contraceptives compared to those not using exogenous sex hormones.<sup>11</sup>

Although the role of exogenous sex steroids in asthma in women has been the subject of intense investigations for several decades, findings remain conflicting and inconclusive. Our recent systematic review and meta-analysis highlighted the lack of prospective studies investigating the impact of use of hormonal contraceptives on clinical outcomes of asthma in women with established asthma.<sup>12</sup> In previous studies, the association of use of hormonal contraceptives with asthma outcomes has typically been studied by including women with and without asthma.<sup>12</sup> Such studies, the majority of which have been cross-sectional, are at high risk of bias, including self-selection bias, patient reporting bias, lack of objective measures of exposures and outcomes, and in particular confounding bias.<sup>12</sup> A more robust design is to undertake long-term follow-up of a cohort of women with already established asthma and investigate the influence of use of hormonal contraceptives on subsequent clinical outcomes. Deciphering the role of hormonal contraceptives on clinical outcomes of asthma is essential in resolving the current uncertainty in the underlying evidence. This is also essential in evaluating any potential benefit or harm of exogenous sex steroids in the management of asthma.

In the current study, we investigated the association of use of hormonal contraceptives, their subtypes and duration of use with severe asthma exacerbation in reproductive-age. We used the Optimum Patient Care Research Database (OPCRD),<sup>13,14</sup> a large population-based longitudinal anonymised primary care database in the UK, to construct a cohort of reproductive-age (16-45 years) women with asthma. We also assessed whether body mass index (BMI) and cigarette smoking modified these associations.

## METHODS

### Ethics approvals and permissions

The Anonymised Data Ethics and Protocol Transparency Committee, responsible for approval of research using the OPCRd database, gave approval for the current study (reference number: ADEPT1317). In addition, Optimum Patient Care has an existing ethics approval for the use of OPCRd for research purposed from the NHS Health Research Authority (REC Ref: 15/EM/150). All researchers involved in the analysis of the data completed required information governance courses.

### Protocol registration and publication

We registered the study protocol with the European Union electronic Register of Post-Authorization Studies (EUPAS22967), which was additionally published in a peer-reviewed journal prior to undertaking the analyses.<sup>15</sup>

### Study design and population

OPCRd is a longitudinal anonymised primary care database, comprising 630 primary care practices across the UK with over six million patients at the time of extracting data for the current study. The database is used to conduct epidemiological, clinical, and pharmaceutical studies ([www.http://optimumpatientcare.org/opcrd/](http://optimumpatientcare.org/opcrd/)).<sup>13,14</sup> We established an open retrospective cohort of reproductive-age women 16-45 years who had any asthma event (including diagnosis, hospitalisation, medication prescription) using previously established Read codes (Online Supplementary File 1) starting from baseline on 1<sup>st</sup> January 2000 or five years prior to this date. Participants entered the cohort from baseline or date of registration with a general practice or the year of turning age 16 years and were followed-up until 31<sup>st</sup> December 2016. Participants exited the cohort on the date of death, deregistration from a practice, year of turning 45 years, or 31<sup>st</sup> December 2016, whichever came first. Women were excluded in any year they were pregnant and included

1  
2 in the years they were not pregnant. In total, the study cohort comprised 83,084 women with a total of 456,803  
3 person-years of follow-up time over the 17-year period (Figure 1).  
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### 5 **Ascertainment of hormonal contraceptives**

6 We used the Read Clinical Classification System<sup>16</sup> (Read codes; Online Supplementary File 2) to extract  
7 information on prescription of hormonal contraceptives. Based on the extracted information, we defined the  
8 following exposures for the use of hormonal contraceptives for each year of follow-up:

- 9 1. Previous (anytime in the past) and current (during that year) use versus non-use
- 10 2. Previous and current use of subtypes of hormonal contraceptives (combined oestrogen/progestogen,  
11 progestogen-only versus non-use)
- 12 3. Duration of use: 1-2 years; 3-4 years; 5 years or more versus non-use.  
13

14 In each instance, we counted use of each of hormonal contraceptives only if it occurred before a record of  
15 severe asthma exacerbation.  
16

### 17 **Potential confounding variables**

18 We selected potential confounding variables for adjustment in the analysis based on evidence from the previous  
19 literature on the topic and on the basis of the evidence provided in our data. We used relevant Read codes  
20 (Online Supplementary File 3) to extract data from the database for the following variables: gravidity, BMI,  
21 smoking, Charlson Comorbidity Index,<sup>17</sup> gynaecological conditions (endometriosis, polycystic ovary  
22 syndrome, acne, bilateral salpingo-oophorectomy (BSO), hysterectomy with BSO, hysterectomy without  
23 BSO, fibroids, and menstrual bleeding complaints identified under coding terms: menorrhagia, metrorrhagia;  
24 menometrorrhagia),<sup>18</sup> and Index of Multiple Deprivation (IMD).<sup>19</sup> Age was derived using the date of birth. Our  
25 a priori plan was to carry out an analysis using propensity scores.<sup>15</sup> However, we were unable to design a  
26 suitable statistical model (within the context of time-varying multilevel mixed-effects negative binomial or  
27 Poisson regression models) and instead performed a conventional confounding adjustment.  
28  
29

### 30 **Study outcome**

31 The study outcome was severe asthma exacerbations (Read codes in Online Supplementary File 1), defined  
32 according to the recommendation of the European Respiratory Society/American Thoracic Society<sup>20</sup> as  
33 asthma-related hospitalisation, accident and emergency department visits due to asthma and/or prescription for  
34 oral corticosteroids. Any exacerbations occurring within a 14-day period were considered as one event. This  
35 definition has been validated and used in previous studies within the OPCR database.<sup>21</sup> Read codes used to  
36 define the study outcome are available in Online Supplementary File 1.  
37  
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### 39 **Statistical analyses**

40 The Pearson's Chi-square test and differences in means were used to describe the distribution of the baseline  
41 study characteristics in relation to the use of hormonal contraceptives and the study outcomes. We initially  
42 used multilevel mixed-effects negative binomial regression to study the associations between use of hormonal  
43 contraceptives and severe asthma exacerbations, but this resulted in non-convergence of some of the models,  
44 particularly the models for smoking-stratified analyses. To improve the convergence of the models, we used  
45 multilevel mixed effects Poisson regression with QR decomposition, which provides an alternative approach  
46 to fitting models for Poisson distribution data by using the QR decomposition of the variance-components  
47 matrix. The approach helps to improve the convergence of models when the variance components is close to  
48 the border of the parameter space.<sup>22</sup> The models accounted for variations across general practices and the  
49 longitudinal nature of the variables. We adjusted for the confounding variables described in the previous  
50 section and the variables were included in the models using the categories given in Table 1. All variables were  
51 treated as time-varying in the models, so that each variable was allowed to take different values at each year  
52 of follow-up. We evaluated interactions of BMI and smoking with hormonal contraceptives by including  
53 interaction terms in each adjusted model; the analyses were subsequently stratified by BMI or smoking only if  
54 the interaction terms achieved p-values of <0.20. As both BMI and smoking were analysed as time-varying  
55 variables, we assumed that their interactions with the use of hormonal contraceptives in relation to the risk of  
56 severe asthma exacerbations were constant over the study follow-up time. We evaluated the potential for  
57 residual confounding after the adjusted regression analyses by calculating the E-values for the observed  
58 estimates of association of use of hormonal contraceptives and severe asthma exacerbations.<sup>23</sup> The derived  
59 estimates of the E-value signify the minimum magnitude of association that an unmeasured confounder should  
60

1  
2 have both in relation to respective exposures and the outcome in order to negate the observed estimate of  
3 association between the exposures and the outcome.<sup>23</sup>  
4

5 Data management and editing were undertaken using R version 3.5.1 (R Foundation for Statistical Computing,  
6 Vienna, Austria). Statistical analyses were undertaken using and Stata 14 (Stata Statistical Software: Release  
7 14. College Station, TX: StataCorp LP).  
8

## 9 **Reporting**

10 This manuscript is reported following the recommendations of STROBE (Strengthening the Reporting of  
11 Observational Studies in Epidemiology)<sup>24</sup> and RECORD (Reporting of studies Conducted using Observational  
12 Routinely-collected Data).<sup>25</sup>  
13

## 14 **Results**

### 15 *Characteristics of the study populations*

16 Table 1 shows the characteristics of the study population. At baseline, 34% of the women were using any  
17 hormonal contraceptives: 25% combined (oestrogen/progestogen) and 9% progestogen-only. Women aged  
18 between 21-25 years were more likely to use any and combined hormonal contraceptives than women of other  
19 age groups, but after this age, the use of hormonal contraceptives decreased with increasing age. Those who  
20 had or currently smoking were less likely to use combined hormonal contraceptives, but more likely to use  
21 progestogen-only contraceptives. Use of any and combined hormonal contraceptives decreased with increasing  
22 BMI and number of previous pregnancies, but use of progestogen-only contraceptives increased with  
23 increasing BMI and number of previous pregnancies. Use of combined hormonal contraceptives was lower  
24 but use of progestogen-only contraceptives was higher in those with at least one gynaecological condition than  
25 in those without. Use of any combined hormonal contraceptives was lower, but use of progestogen-only  
26 contraceptives was higher in those with at least one Charlson Comorbidity Index score than in those with zero  
27 score. The proportion of women with severe asthma exacerbation at baseline increased with increasing age;  
28 higher in ever smokers than in non-smokers; increased with increasing BMI; increased with increasing number  
29 of previous pregnancies; higher in women with a prior gynecological condition than those without; higher in  
30 women with any co-morbidity than in women without any co-morbidity;; and relatively equally distributed  
31 between IMD quintiles (Table 1).  
32  
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### 34 *Association between use of hormonal contraceptives and asthma exacerbations*

35 The unadjusted and adjusted associations between use of hormonal contraceptives and severe asthma  
36 exacerbations are shown in Figure 1. In the adjusted models, previous and current use of any, combined, and  
37 longer duration of use were associated with a reduced risk of severe asthma exacerbations, compared to non-  
38 use. While women using hormonal contraceptives for 1-2 years had a null risk for asthma exacerbations, those  
39 using it for 3-4 years and those using for  $\geq 5$  years were at a reduced risk compared to non-users (Figure 2).  
40 When we stratified the analyses by BMI and smoking, the risk estimates did not substantially differ across  
41 BMI and smoking strata (Table 2). However, while the BMI-stratified results were statistically significant for  
42 combined oestrogen/progestogen contraceptives across the BMI strata, these were not the case for  
43 progestogen-only contraceptives (Table 2). We further separately analysed the category of very lean women  
44 (i.e., those with BMI less than 20 kg/m<sup>2</sup>), but we did not find the observed protection among these women,  
45 instead there was slight non-significant increased risk of severe asthma exacerbation (data not shown). The E-  
46 values for the association between hormonal contraceptives and asthma exacerbations ranged from 1.00 to  
47 1.39. These values signify the magnitude of risk estimates required by an unmeasured confounder, beyond the  
48 adjusted confounders, to negate the observed risk estimates. For example, an unmeasured confounder requires  
49 a minimum risk ratio of 1.00 and maximum of 1.39 in order to negate the observed association between  
50 hormonal contraceptives and asthma exacerbation after adjusting for all other confounding factors.  
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## 53 **DISCUSSION**

54 In this large population-based longitudinal cohort study of reproductive-age women followed for 17 years, we  
55 found that previous and current use of any, combined and longer duration of use were associated with a  
56 reduced, but small risk, of severe asthma exacerbations, compared to non-use. Sensitivity analyses evaluating  
57 the potential for residual confounding explaining these results indicate that we cannot exclude the impact of  
58 uncontrolled confounding factors from partly explaining our findings.  
59  
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1  
2 The OPCRD cohort is well characterised and largely representative of the UK primary care population. At the  
3 time of the current study, the database comprised 6.3 million patients from 630 general practices derived from  
4 across the UK. With large sample sizes, we could study the role of both duration and subtypes of hormonal  
5 contraceptives, thereby enabling good precision in estimates of effect sizes. The 17-year longitudinal follow-  
6 up provided sufficient time to study the associations of use of hormonal contraceptives with asthma  
7 exacerbations and allowed investigation of the time-dependence of the exposures. The use of the Read Clinical  
8 Classification System for assessment of all study variables ensured consistent recording of the study  
9 variables.<sup>15</sup> The UK national initiative, Quality and Outcomes Framework (QOF), which gave incentives to  
10 primary care to maintain a register of asthma patients, was established in 2004, leading to noticeable  
11 improvements in recording of clinical events of asthma. Thirteen of the 17 years of follow-up of our study  
12 occurred post-adoption of QOF, which should minimise bias resulting from under-diagnosis of asthma.<sup>26</sup> The  
13 definition of the study outcome, severe asthma exacerbation, followed recommended definition of the  
14 European Respiratory Society/American Thoracic Society<sup>20</sup> and has been validly ascertained within the  
15 OPCRD database.<sup>21</sup> To minimise the risk of confounding by indication, we exhaustively identified a list of  
16 conditions for which hormonal contraceptives are used as potential therapies and adjusted for them in our  
17 analyses.  
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19  
20 The definition of reproductive age women was based only on the age of the women, given that there was no  
21 additional information from the database to enhance these definitions. However, the chosen ages reflect the  
22 average age of reproductive age in the UK. Beyond this upper age limit of 45 years, women may use hormonal  
23 contraceptives for other indications, such as management of abnormal uterine bleeding, a symptom often  
24 reflecting ovulatory dysfunction as the menopause transition approaches. While we used information based  
25 only on prescription of hormonal contraceptives, it was not possible to determine whether this reflected actual  
26 use of the medications, as we did not have data on medication dispensation or actual use. We had planned to  
27 perform propensity score analysis as an adjustment strategy for potential confounding factors.<sup>15</sup> However, we  
28 were unable to do this as planned instead we performed conventional confounder adjustment by including the  
29 confounding factors in the statistical models, because we did not find an appropriate algorithm for propensity  
30 score analyses within the context of time-varying, multi-level modelling. Based on the values of the calculated  
31 E-values for residual confounding, it is possible that residual confounding may still remain after our  
32 confounder adjustment, thus may partly account for some of the observed risk estimates. We planned to study  
33 the role of routes of administration of hormonal contraceptives (oral, transdermal, subcutaneous,  
34 intramuscular, or local intrauterine), but this information was poorly and inconsistently recorded in the  
35 database, hence we did not undertake this aspect of the analysis. Registering and publishing the protocol before  
36 undertaking the analysis enhanced the transparency of our work.  
37

38  
39 All of the previous studies identified in our earlier systematic review investigating the role of hormonal  
40 contraceptives in clinical outcomes of asthma were cross-sectional studies and hence of inferior quality  
41 compared to the current study.<sup>12</sup> Furthermore, the previous studies were limited because assessment of use of  
42 hormonal contraceptives and/or asthma outcomes were based on self-reports and in most studies sample size  
43 was small. In the current study we have attempted to overcome these limitations and to clarify the underlying  
44 evidence. Overall, our study, by providing the clearest evidence on the role of use of hormonal contraceptives  
45 in clinical outcomes of asthma, indicate that previous, current, and long-term use of hormonal contraceptives  
46 and subtypes were associated with small, reduced clinical effects in reducing asthma exacerbations in women  
47 of reproductive age with established asthma.  
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49  
50 Oestrogen and progesterone exhibit varying immunological effects, including reported enhancement of Th2  
51 and Th17 responses and inhibition of the synthesis of Th1-, Th2-, and Th17-associated cytokines, potentially  
52 dependent on concentrations studied.<sup>27,28</sup> Th17 cytokines in particular are associated with severe asthma, and  
53 there is evidence that Th17 cells manifest more IL-17A and IL-23R in women with severe asthma than in  
54 men.<sup>27,28</sup> Increased IL-17A synthesis is linked to female gender, obesity and asthma severity.<sup>29,30</sup> Studies of the  
55 effects of hormonal contraceptives directly in patients, including on distinct Th17 subsets, antigen presenting  
56 cells and cytokines that influence IL-17A synthesis, and fatty acid metabolism may provide mechanistic  
57 insights beyond those derived from animal models and laboratory studies.<sup>31,32</sup> Menstruation is accompanied  
58 by fluctuations in the levels of oestradiol and progesterone, which seem to worsen asthma symptoms in some  
59 women.<sup>33</sup> It is believed that the use of hormonal contraceptives to suppress these hormonal fluctuations could  
60 confer protection from poor asthma outcomes. Both oestrogen and progesterone are known to influence smooth  
muscle functions, inflammation, and airway responsiveness.<sup>34</sup> While supporting this proposed protective role

1  
2 of hormonal contraceptives on clinical outcomes of asthma, our study demonstrates that the impact on asthma  
3 exacerbation may be rather small. Although our findings do not suggest any changes to current asthma  
4 management guidelines, they however indicate the need for further mechanistic studies to better understand  
5 how hormonal contraceptives influence clinical outcomes in women with established asthma.  
6

7 Stratification of our results by BMI and smoking status did not reveal any major differences across BMI and  
8 smoking categories. The impact of hormonal contraceptives on asthma may be modified by the BMI, given  
9 the close interplay between endogenous sex hormones and body fat mass.<sup>11,35</sup> In lean women, endogenous  
10 oestrogen is low, compared to higher levels in heavier women.<sup>36</sup> In a cross-sectional study of the association  
11 between use of oral contraceptive pills and asthma and allergy in women aged 25-44 years, Macsali and  
12 colleagues, by stratifying the results by BMI, found that use of oral contraceptive pills was associated with an  
13 increased risk of reported asthma attacks and allergy in normal weight and overweight women but not in lean  
14 women.<sup>35</sup> Beside being a cross-sectional study, contrasting the longitudinal design of the current study, these  
15 results observed by Macsali and colleagues<sup>35</sup> contrast the findings from the current study in which we found a  
16 protective effect of hormonal contraceptives on severe asthma exacerbations across all BMI categories. In our  
17 previous analysis of the serial cross-sectional Scottish Health Surveys, we found that while the risk of asthma  
18 care episodes was decreased in overweight or obese women who were using combined oral contraceptives, the  
19 risk was increased in overweight and obese women who were not using hormonal contraceptives.<sup>11</sup> In the  
20 current study, the results for combined oestrogen/progestogen contraceptives showed statistical significance  
21 across the BMI categories while the results for progestogen-only contraceptives were not. While this may  
22 reflect inadequate power to detect a statistical significance for progestogen-only contraceptives, the  
23 differences may also reflect the oestrogen effect, given the interplay observed between body mass and local  
24 oestrogen production.<sup>37</sup> Among post-menopausal women, use of menopausal hormone therapy has been  
25 linked to greater risk of asthma in lean than in overweight/obese women, and this has been attributed to  
26 oestrogen effect.<sup>38,39</sup> Regarding smoking, a potential effect-effect modification is possible, given the suggestion  
27 that smoking may alter the haemostasis profiles in oral contraceptive users.<sup>40,41</sup> While Macsali and colleagues  
28 found an increased risk of asthma similarly for women who were smoking and those not smoking,<sup>35</sup> the  
29 findings from the current study showed that use of hormonal contraceptives is associated with a decreased risk  
30 of severe asthma exacerbations similarly for non-smokers and ever smokers.  
31  
32

### 33 CONCLUSIONS

34 In conclusion, we observed that the use of hormonal contraceptives is associated with a small beneficial effect  
35 on severe asthma exacerbation. Further longitudinal studies are required to confirm these findings, as well as  
36 mechanistic studies investigating the underlying biological processes through which exogenous sex steroids  
37 influence the pathogenesis of asthma in women.  
38  
39

### 40 CONFLICT OF INTERESTS

41 Colin Simpson, Aziz Sheikh, and Catherine Hawrylowicz currently receive funding from Asthma UK and Aziz  
42 Sheikh also received funding from the Health Data Research UK BREATHE Hub. Susannah McLean was  
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44 research support for laboratory consumables and staff from Bayer AG and provides consultancy advice (but  
45 with no personal remuneration) for Bayer AG, PregLem SA, Gedeon Richter, Vifor Pharma UK Ltd, AbbVie  
46 Inc., Myovant Sciences GmbH. HODC receives royalties from UpToDate for article on abnormal uterine  
47 bleeding. David Price has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi,  
48 Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva  
49 Pharmaceuticals, Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim,  
50 Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance; grants  
51 and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic  
52 Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma,  
53 Novartis, Pfizer, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva  
54 Pharmaceuticals, Theravance, UK National Health Service; payment for lectures/speaking engagements from  
55 AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma,  
56 Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the development  
57 of educational materials from Mundipharma, Novartis; payment for travel/accommodation/meeting expenses  
58 from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis, Thermofisher; funding for  
59 patient enrolment or completion of research from Novartis; stock/stock options from AKL Research and  
60 Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient  
8



Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment. Other authors declare no conflict of interest related to this work.

#### AUTHORS' CONTRIBUTION

Conceived idea for the study (BN, AS); designed the study (BN, AS, CRS, CMH); data collection (BN, AS, RP, DP, INS, FA); data analyses (BN, RP, HT, AS, SAS); clinical/primary care expertise on asthma and OPCRd-related expertise (DR, DP); expertise on sex steroids (HC); drafted the manuscript (BN, AS); all authors critically revised the manuscript for intellectual content and approved the final version.

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## FIGURE LEGENDS

**Figure 1.** Flowchart of study cohort and baseline severe asthma exacerbations and use of hormonal contraceptives

**Figure 2.** Unadjusted (panel A) and adjusted (panel B) associations between use of hormonal contraceptives and severe asthma exacerbations rates in reproductive age women

**Table 1.** Baseline characteristics by use of hormonal contraceptives in reproductive age (16-45 years) with asthma and mean number of severe asthma exacerbations

Background characteristics	Frequency <i>N</i> = 83,084 <i>n</i> (%)	Used any hormonal contraceptives <i>n</i> = 28,575 (34%) % (95% CI) <sup>2</sup>	Used combined hormonal contraceptives <i>n</i> = 20,629 (25%) % (95% CI) <sup>2</sup>	Used progesterone-only hormonal contraceptives <i>n</i> = 7,946 (9%) % (95% CI) <sup>2</sup>	Severe asthma exacerbations at baseline <i>n</i> = 8,024 (10%) % (95% CI) <sup>2</sup>
Age, years					
16-20	24,504 (29.5)	42.6 (41.9-43.2)	35.3 (34.7-35.9)	7.2 (6.9-7.5)	8.3 (8.0-8.7)
21-25	11,754 (14.1)	47.4 (46.5-48.3)	36.7 (35.8-37.6)	10.7 (10.2-11.3)	9.1 (8.6-9.6)
26-30	13,870 (16.7)	38.5 (37.7-39.3)	26.9 (26.2-27.7)	11.5 (11.0-12.1)	10.0 (9.5-10.5)
31-35	14,985 (18.0)	28.0 (27.3-28.7)	16.7 (16.1-17.3)	11.3 (10.8-11.8)	10.3 (9.8-10.8)
36-40	12,456 (15.0)	18.8 (18.2-19.5)	9.3 (8.8-9.8)	9.6 (9.1-10.1)	10.6 (10.0-11.1)
41-45	5,515 (6.6)	12.5 (11.7-13.4)	4.7 (4.2-5.3)	7.8 (7.1-8.6)	12.1 (11.2-13.0)
Smoking status					
Non-smokers	39,982 (48.1)	34.6 (34.1-35.1)	26.2 (25.7-26.6)	8.4 (8.1-8.7)	8.0 (7.8-8.3)
Ever smokers	43,102 (51.9)	34.2 (33.7-34.6)	23.6 (23.2-24.0)	10.6 (10.3-10.9)	11.1 (10.9-11.4)
Body mass index, kg/m <sup>2</sup>					
<25	40,018 (48.2)	37.8 (37.3-38.3)	29.9 (29.5-30.3)	7.9 (7.6-8.1)	8.0 (7.7-8.3)
25.29.9	21,555 (25.9)	35.1 (34.4-35.7)	25.5 (24.9-26.0)	9.6 (9.2-10.0)	9.5 (9.2-10.0)
≥30	21,511 (25.9)	27.4 (26.8-28.0)	14.7 (14.2-15.2)	12.7 (12.2-13.1)	12.8 (12.4-13.3)
Gravidity					
None	50,772 (61.1)	34.9 (34.5-35.3)	27.7 (27.3-28.1)	7.2 (7.0-7.4)	8.7 (8.4-8.9)
One	15,319 (18.4)	36.5 (35.7-37.2)	24.7 (24.0-25.4)	11.8 (11.3-12.3)	10.1 (9.6-10.6)
Two	9,560 (11.5)	33.2 (32.2-34.1)	18.7 (18.0-19.5)	14.4 (13.7-15.2)	11.3 (10.7-12.0)
Three or more	7,433 (9.0)	28.2 (27.2-29.2)	13.5 (12.8-14.3)	14.7 (13.9-15.5)	13.1 (12.4-13.9)
Any gynaecological condition <sup>1</sup>					
No	62,729 (75.5)	34.0 (33.7-34.4)	25.5 (25.1-25.8)	8.5 (8.3-8.8)	8.6 (8.4-8.9)
Yes	20,355 (24.5)	35.5 (34.8-36.1)	22.8 (22.2-23.4)	12.7 (12.2-13.1)	12.7 (12.3-13.2)
Charlson Comorbidity Index					
0	78,749 (94.8)	34.8 (34.5-35.1)	25.3 (25.0-25.6)	9.4 (9.3-9.7)	9.3 (9.1-9.5)
1+	4,335 (5.2)	26.8 (25.5-28.2)	15.8 (14.7-16.9)	11.0 (10.1-12.0)	15.7 (14.6-16.8)
Index of Multiple Deprivation quintiles					
1 <sup>st</sup> quintile (least deprived)	16,968 (20.4)	28.8 (28.1-29.5)	21.0 (20.4-21.6)	7.7 (7.3-8.1)	9.1 (8.7-9.6)
2 <sup>nd</sup> quintile	15,732 (18.9)	34.0 (33.2-34.7)	24.7 (24.1-25.4)	9.2 (8.8-9.7)	10.6 (10.2-11.1)
3 <sup>rd</sup> quintile	16,554 (19.9)	36.6 (35.9-37.4)	26.2 (25.5-26.9)	10.4 (9.9-10.9)	9.0 (8.6-9.5)

4 <sup>th</sup> quintile	17,004 (20.5)	35.2 (34.5-35.9)	25.3 (24.6-26.0)	9.9 (9.5-10.4)	10.5 (10.1-11.0)
5 <sup>th</sup> quintile (most deprived)	16,826 (20.2)	37.4 (36.7-38.1)	26.8 (26.2-27.5)	10.5 (10.1-11.0)	9.0 (8.6-9.4)

<sup>1</sup>Defined as having any of the following conditions: endometriosis, polycystic ovary syndrome, menorrhagia, acne, metrorrhagia, bilateral salpingo-oophorectomy (BSO), hysterectomy BSO, hysterectomy, fibroids, and menometrorrhagia

<sup>2</sup>Difference between groups of background variables were statistically significant ( $P < 0.001$ )

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**Table 2.** Association between use of hormonal contraceptives and severe asthma exacerbation rates in reproductive age women and by BMI and smoking<sup>1</sup>

Hormonal contraceptives (HC) use	Stratified analyses by BMI Incidence Rate Ratio (95% CI) <sup>2,3</sup>			Stratified analyses by smoking status Hazard Ratio (95% CI) <sup>2,4</sup>	
	<25 kg/m <sup>2</sup>	25-29.9 kg/m <sup>2</sup>	≥30 kg/m <sup>2</sup>	Non-smokers	Ever smokers
Any HC during any previous or current year					
None	1	1	1	1	1
Yes	<b>0.92 (0.88-0.96)</b>	<b>0.93 (0.88-0.98)</b>	0.96 (0.92-1.01)	<b>0.92 (0.88-0.96)</b>	<b>0.96 (0.93-1.00)</b>
Any HC during current year of asthma exacerbation					
None	1	1	1	1	1
Yes	<b>0.96 (0.93-0.99)</b>	0.98 (0.95-1.02)	<b>0.94 (0.91-0.96)</b>	0.99 (0.96-1.02)	<b>0.94 (0.92-0.96)</b>
Type of HC during any previous or current year					
None	1	1	1	1	1
Progestogen-only	0.91 (0.79-1.04)	0.95 (0.81-1.10)	1.16 (1.00-1.33)	<b>1.17 (1.02-1.35)</b>	0.91 (0.82-1.01)
Combined oestrogen/progestogen	<b>0.87 (0.80-0.95)</b>	<b>0.85 (0.76-0.95)</b>	1.09 (0.98-1.21)	1.01 (0.91-1.11)	<b>0.87 (0.81-0.93)</b>
Type of HC during current year of asthma exacerbation					
None	1	1	1	1	1
Progestogen only	0.98 (0.93-1.02)	1.02 (0.97-1.07)	0.97 (0.94-1.01)	0.98 (0.94-1.03)	1
Combined oestrogen/progestogen	<b>0.96 (0.92-0.99)</b>	<b>0.95 (0.91-1.00)</b>	<b>0.87 (0.83-0.91)</b>	0.99 (0.96-1.03)	0.98 (0.96-1.01) <b>0.89 (0.87-0.92)</b>
Duration of use of any hormonal contraceptives, years					
None	1	1	1	1	1
1-2	1.03 (0.99-1.07)	0.96 (0.92-1.00)	1.03 (0.99-1.06)	0.99 (0.96-1.03)	1.02 (0.99-1.05)
3-4	<b>0.92 (0.88-0.97)</b>	1.00 (0.95-1.05)	<b>0.92 (0.88-0.96)</b>	<b>0.95 (0.90-0.99)</b>	<b>0.93 (0.90-0.97)</b>
5+	<b>0.93 (0.89-0.97)</b>	<b>0.92 (0.87-0.96)</b>	<b>0.89 (0.86-0.93)</b>	<b>0.98 (0.94-1.02)</b>	<b>0.87 (0.84-0.90)</b>

<sup>1</sup>All analysis were based on multilevel mixed-effects Poisson regression that accounted for clustering of patients within GP practices

<sup>2</sup>Adjusted for follow-up time, level of adherence to asthma medication, age, smoking, Charlson co-morbidity index, BMI, gravidity, any gynaecological condition, and index of multiple deprivation

<sup>3</sup>Stratified analyses performed after interaction term between use of HC and BMI gave: *p*=0.023 for any HC and BMI; *p*=0.000 for HC types and BMI; and *p*=0.113 for duration of HC and BMI

<sup>4</sup>Stratified analyses performed after interaction term between use of HC and smoking gave: *p*=0.048 for any HC and smoking; *p*=0.107 for HC types and smoking; and *p*=0.000 for duration of HC and smoking

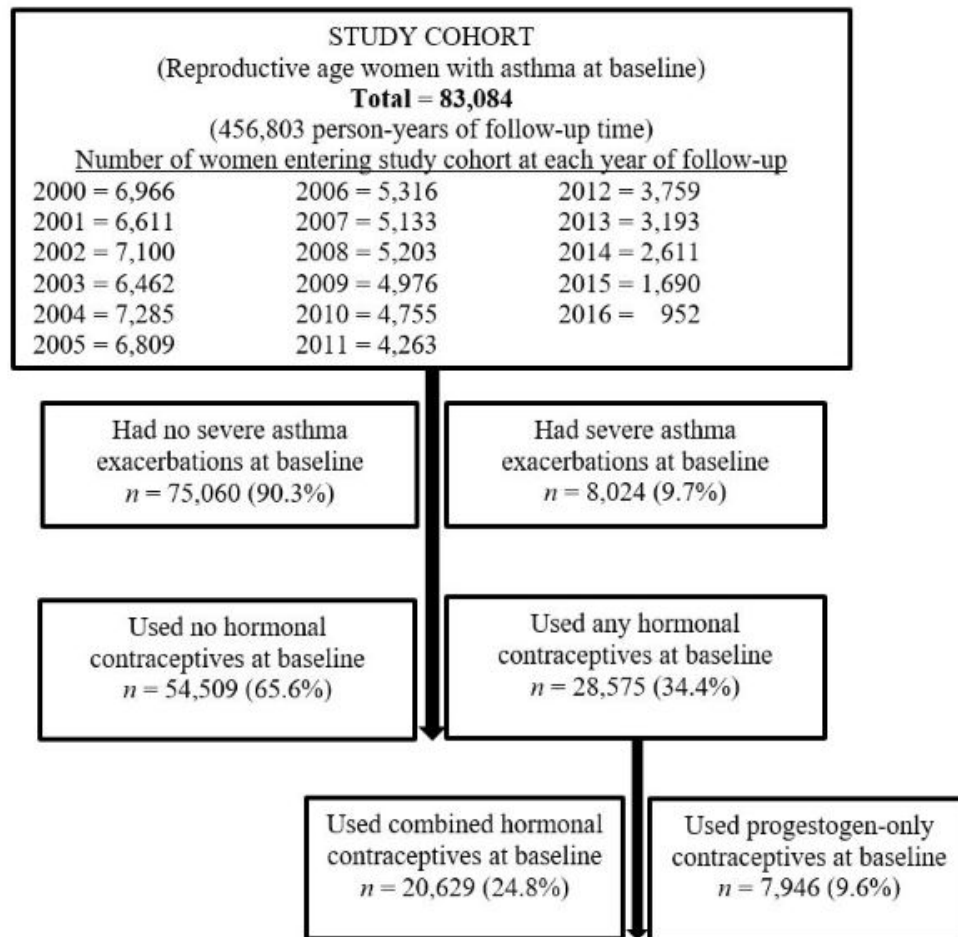


Figure 1. Flowchart of study cohort and baseline severe asthma exacerbations and use of hormonal contraceptives

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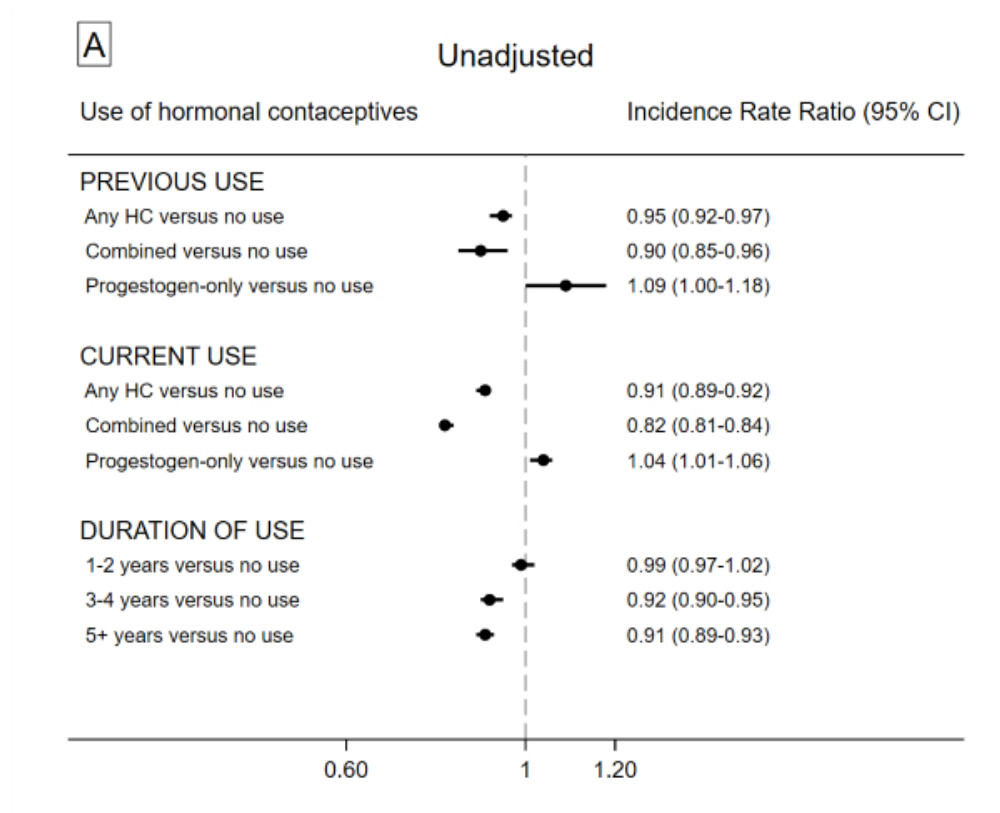


Figure 2. Unadjusted (panel A) and adjusted (panel B) associations between use of hormonal contraceptives and severe asthma exacerbations rates in reproductive age women



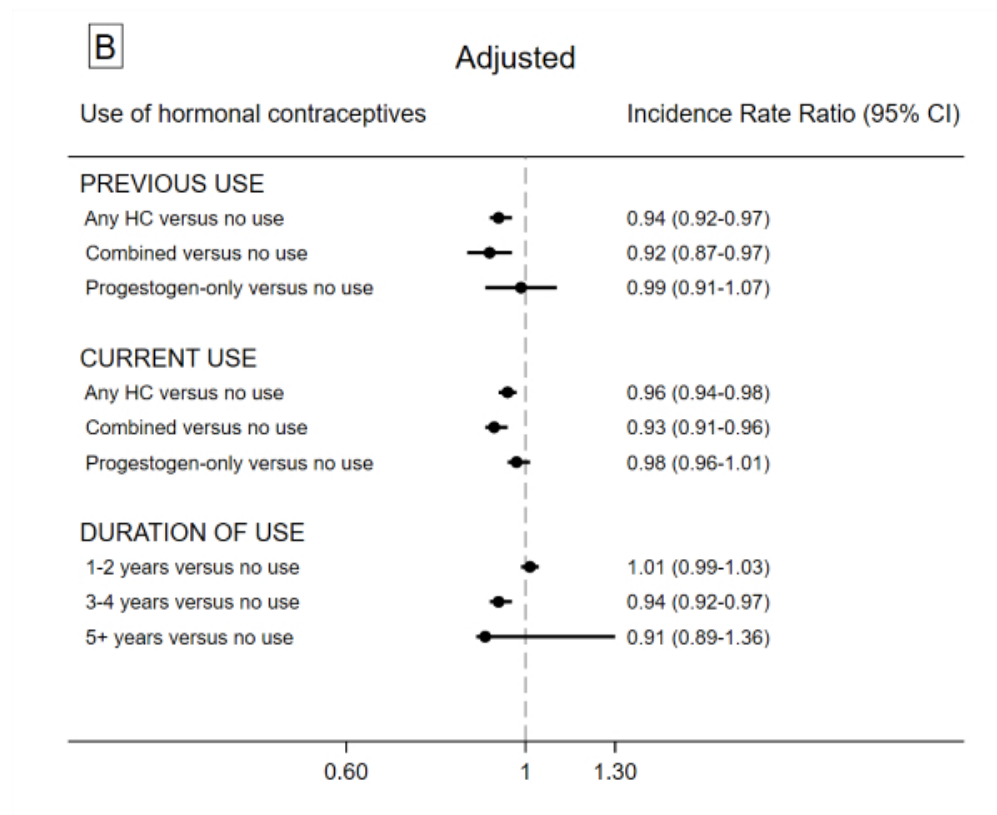


Figure 2. Unadjusted (panel A) and adjusted (panel B) associations between use of hormonal contraceptives and severe asthma exacerbations rates in reproductive age women

# ONLINE SUPPLEMENTARY INFORMATION

## READ CODES LISTS USED TO DEFINE AN ASTHMA EVENT

### Asthma Diagnosis

"H33.", "H330.", "H3300", "H3301", "H330z", "H331.", "H3310", "H3311", "H331z", "H332.", "H333.", "H334.", "H33z.", "H33z0", "H33z1", "H33z2", "H33zz".

### Asthma Medications

#### SABA Codes:

"x01Cq", "x01Cr", "c14r.", "c141.", "c14a.", "c14y.", "c149.", "c14c.", "c14z.", "c142.", "c14b.", "x006b", "c14t.", "c144.", "c14u.", "c145.", "c14v.", "c146.", "c14j.", "c14f.", "c14w.", "c147.", "c14x.", "c14i.", "c14g.", "x01Cs", "c14s.", "c143.", "c14h.", "c14e.", "c14.", "c14k.", "c148.", "x00Af", "x05Fg", "c11x.", "c111.", "c113.", "c115.", "c11e.", "c118.", "c11v.", "c112.", "c114.", "c116.", "c11y.", "c11k.", "c11a.", "c11d.", "c11n.", "c11p.", "c11o.", "c11q.", "c11w.", "c117.", "c11z.", "c11m.", "c11D.", "c11g.", "c11h.", "c11b.", "x05Fi", "c13v.", "c13a.", "c131.", "c132.", "c13p.", "c13H.", "c133.", "c13h.", "c13i.", "c134.", "c13J.", "c13L.", "c13Z.", "c13Y.", "c13T.", "c13R.", "c1E7.", "c13N.", "c13P.", "c13G.", "x00CE", "c13c.", "c131.", "c13n.", "c13K.", "c13O.", "c13U.", "c13V.", "c1E1.", "c13S.", "c13Q.", "c13L.", "c1E8.", "c1E2.", "c13M.", "c13x.", "c13q.", "c136.", "c13y.", "c13r.", "c137.", "c13C.", "x025g", "c13d.", "c1E3.", "c13D.", "x025h", "c13e.", "c1E4.", "c13E.", "x025i", "c13f.", "c1E5.", "c13F.", "x025j", "c13g.", "c1E6.", "c13w.", "c13W.", "c13A.", "c135.", "c13o.", "c13X.", "c13B.", "c13m.", "c13z.", "c139.", "c13j.", "x05Fh", "c12x.", "c124.", "c121.", "c12y.", "c125.", "c122.", "c12z.", "c126.", "c123.", "c12w.", "c1E9.", "c1EA.", "c1EB.", "c1EC.", "c1ED.", "c1EE.", "c11.", "c11A.", "c11B.", "c11C.", "c13.", "c138.", "c13b.", "c13s.", "c12.", "c1E.", "c51H.", "c51B.", "c51x.", "x0100", "x00zz", "c51v.", "c51w.", "c51C.", "c51D.", "c51F.", "c51E.", "c531.", "c51A.", "c51i."

#### LAB codes:

"c1C.", "c1C1.", "c1C2.", "c1C3.", "c1C4.", "c1C5.", "c1C6.", "c1C7.", "c1C8.", "c1Cy.", "c1Cz.", "c19.", "c191.", "c192.", "c193.", "c194.", "c195.", "c196.", "c197.", "c198.", "c199.", "c19A.", "c19B.", "c19z.", "c1b.", "c1b1.", "c1b2.", "c1b3.", "c1b4.", "c1d.", "c1d1.", "c1d2."

#### SAMA codes:

"x01Db", "c31.", "c31x.", "c311.", "c31z.", "c313.", "c31t.", "c31G.", "c31u.", "c315.", "c31A.", "c318.", "c31B.", "c319.", "c31v.", "c314.", "c31C.", "c316.", "c31E.", "c31w.", "c312.", "c31D.", "c317.", "c31F.", "c31y.", "186.", "c51A.", "c51i.", "c51B.", "c51x.", "x0100", "x00zz", "c51v.", "c51w.", "c51C.", "c51D.", "c51F.", "c51E.", "c531."

#### Methylxanthine codes:

"c43.", "c431.", "c432.", "c433.", "c434.", "c435.", "c436.", "c437.", "c438.", "c439.", "c43A.", "c43B.", "c43a.", "c43b.", "c43c.", "c43d.", "c43e.", "c43f.", "c43g.", "c43h.", "c43i.", "c43j.", "c43k.", "c43m.", "c43n.", "c43o.", "c43p.", "c43q.", "c43r.", "c43s.", "c43t.", "c43u.", "c43v.", "c43w.", "c43x.", "c43y.", "c43z.", "c41.", "c411.", "c412.", "c413.", "c414.", "c415.", "c416.", "c417.", "c418.", "c419.", "c41A.", "c41B.", "c41C.", "c41a.", "c41b.", "c41c.", "c41d.", "c41e.", "c41f.", "c41g.", "c41h.", "c41i.", "c41j.", "c41k.", "c41m.", "c42.", "c42w.", "c421.", "c42x.", "c422.", "c42z.", "c424.", "c42y.", "c423.", "x01Ej", "x01Ek"

#### SABA+SAMA codes:

"c51A.", "c51B.", "c51C.", "c51D.", "c51E.", "c51F.", "c51G.", "c51H.", "c51v.", "c51w.", "c51x.", "c531.", "c51i.", "x0100", "x00zz"

#### ICS codes:

"c61.", "c611.", "c612.", "c613.", "c614.", "c615.", "c616.", "c617.", "c619.", "c61A.", "c61a.", "c61B.", "c61b.", "c61C.", "c61c.", "c61D.", "c61d.", "c61E.", "c61e.", "c61F.", "c61f.", "c61G.", "c61g.", "c61H.", "c61h.", "c61i.", "c61J.", "c61j.", "c61K.", "c61k.", "c61L.", "c61l.", "c61M.", "c61m.", "c61N.", "c61n.", "c61O.", "c61P.", "c61p.", "c61Q.", "c61q.", "c61R.", "c61r.", "c61S.", "c61s.", "c61T.", "c61t.", "c61U.", "c61u.", "c61V.", "c61v.", "c61W.", "c61w.", "c61X.", "c61x.", "c61Y.", "c61y.", "c61Z.", "c61z.", "c64.", "c641.", "c642.", "c643.", "c644.", "c645.", "c647.", "c648.", "c649.", "c64A.", "c64a.", "c64B.", "c64b.", "c64C.", "c64c.", "c64D.", "c64d.", "c64E.", "c64e.", "c64F.", "c64G.", "c64g.", "c64H.", "c64h.", "c64I.", "c64i.", "c64J.", "c64j.", "c64K.", "c64k.", "c64L.", "c64l.", "c64M.", "c64m.", "c64N.", "c64n.", "c64o.", "c64p.", "c64u.", "c64v.", "c64w.", "c64x.", "c64y.", "c64z.", "c65.", "c651.", "c652.", "c653.", "c654.", "c655.", "c656.", "c657.", "c658.", "c659.", "c65A.", "c65a.", "c65B.", "c65b.", "c65C.", "c65c.", "c65D.", "c65d."

"c65E.", "c65e.", "c65F.", "c65f.", "c65G.", "c65g.", "c65H.", "c65I.", "c65J.", "c65K.", "c65L.", "c65M.", "c65N.", "c65O.", "c65P.", "c65Q.", "c65R.", "c65S.", "c65T.", "c65U.", "c65V.", "c65W.", "c65X.", "c65Y.", "c65Z.", "c66.", "c661.", "c662.", "c663.", "c664.", "c665.", "c666.", "c667.", "c668.", "c669.", "c66A.", "c66a.", "c66B.", "c66b.", "c66C.", "c66c.", "c66D.", "c66d.", "c66E.", "c66e.", "c66F.", "c66f.", "c66G.", "c66g.", "c66H.", "c66h.", "c66I.", "c66J.", "c66K.", "c66L.", "c66M.", "c66N.", "c66P.", "c66Q.", "c66R.", "c66S.", "c66T.", "c66U.", "c66V.", "c66W.", "c66X.", "c66Y.", "c66Z.", "c681.", "c682.", "c683.", "c684.", "c691.", "c692.", "c69y.", "c69z.", "x00bU", "x00bV", "x00gE", "x00gF", "x00gG", "x00Hx", "x00Hy", "x00Hz", "x00I0", "x00I1", "x00I2", "x00I3", "x00I4", "x00QU", "x00QV", "x00z6", "x029g"

ICS+LABA codes:

"c67.", "c671.", "c672.", "c673.", "c674.", "c675.", "c67x.", "c67y.", "c67z.", "c6B.", "c6B1.", "c6B2.", "c6B3.", "c6B4.", "c1D.", "c1D1.", "c1D2.", "c1D3.", "c1D4.", "c1D5.", "c1D6.", "c1Du.", "c1Dv.", "c1Dw.", "c1Dx.", "c1Dy.", "c1Dz.", "c1c.", "c1c1.", "c1c2.", "c1c3.", "c1cx.", "c1cy.", "c1cz.", "c6A.", "c6A1.", "c6A2.", "c6Ay.", "c6Az."

LTRA codes:

"cA.", "cA1.", "cA11.", "cA12.", "cA13.", "cA14.", "cA15.", "cA16.", "cA1y.", "cA1z.", "cA2.", "cA21.", "cA22."

Omalizumab codes:

"ck1.", "ck11.", "ck12.", "ck13.", "ck14.", "ck15.", "ck16."

OCS codes:

"fe6.", "fe3.", "fe31.", "fe32.", "fe33.", "fe36.", "fe37.", "fe3A.", "fe3B.", "fe3C.", "fe3r.", "fe3s.", "fe3u.", "fe4.", "fe41.", "fe42.", "fe43.", "fe44.", "fe45.", "fe4e.", "fe4f.", "fe4g.", "fe4h.", "fe5.", "fe51.", "fe52.", "fe53.", "fe5f.", "fe5m.", "fe5n.", "fe5o.", "fe5p.", "fe61.", "fe62.", "fe64.", "fe65.", "fe66.", "fe67.", "fe68.", "fe69.", "fe6a.", "fe6c.", "fe6d.", "fe6e.", "fe6f.", "fe6g.", "fe6h.", "fe6i.", "fe6j.", "fe6k.", "fe6l.", "fe6m.", "fe6n.", "fe6o.", "fe6p.", "fe6q.", "fe6r.", "fe6s.", "fe6t.", "fe6v.", "fe6w.", "fe6z.", "fe7.", "fe71.", "fe72.", "fe73.", "fe74.", "fe75.", "fe76.", "fe77.", "fe78.", "fe79.", "fe7x.", "fe7y.", "fe7z.", "x00yP", "x01Mh", "x01Na", "x01Nb", "fe11.", "fe12.", "fe1x.", "fe1y.", "fe21.", "fe22.", "fe23.", "fe24.", "fe25.", "fe26.", "x01MW"

Asthma Exacerbation

"Xa1Hd", "Xafdz", "Xafdy", "Xafdj", "XacXk", "XaINh", "38B8.", "H333.", "663y."

Asthma Hospitalization

"663d.", "8H2P."

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3 **READ CODES USED TO DEFINE HORMONAL CONTRACEPTIVES**  
4

Read code	Description
"6147."	Combined oral contraceptive
"6148."	Mini-pill: oral contraceptive
"6152."	Intrauterine contraceptive device removed
"615B."	IUD fallen out
"615P0"	Hormone releasing IUCD fitted by other healthcare provider
"615Q."	Intrauterine contracep device removed by other hlth provider
"61KA."	Insertion of subcutaneous contraceptive
"61KC."	Insert subcutaneous contraceptive implant other healthcare provider
"61KF."	Removal of subcutaneous contraceptive implant other healthcare provider
"61R."	Intrauterine system contraception
"7E092"	Removal of intrauterine contraceptive device NEC
"7E093"	Removal of displaced intrauterine contraceptive device
"7E094"	Introduction of Mirena coil
"7E095"	Removal of Mirena coil
"7E096"	Replacement of intrauterine system
"7G2AG"	Insertion of etonogestrel implant
"7G2AH"	Reinsertion of subcutaneous contraceptive
"7G2AJ"	Insertion of etonogestrel radiopaque contraceptive implant
"7G2H5"	Removal of Norplant
"7G2H6"	Removal of hormone implant from subcutaneous tissue
"7G2H7"	Removal of subcutaneous contraceptive
"7G2H8"	Removal of hormone implant from subcutaneous tissue
"7G2HA"	Removal of Implant
"7G2HB"	Removal of etonogestrel radiopaque contraceptive implant
"7G2HC"	Removal of subcut contraceptive implant using US guidance
"9kr."	Subdermal etonogestrel implant insertion enhanced services administration
"fg41."	Not indicated
"fg42."	Not indicated
"fg49."	Not indicated
"fg4w."	Not indicated
"fg4x."	Not indicated
"fh1q."	ETHINYLESTRADIOL+NORELGESTROMIN 600mcg
"fh1r."	Evra transdermal patch
"g8"	Ethinylestradiol
"g9"	Mestranol
"ga1"	Etonogestrel diacetate
"ga2."	Levonorgestrel
"ga21."	Microval tablet
"ga22."	Norgeston tablet
"ga23."	LEVONORGESTREL 30micrograms tablets
"ga24."	NORPLANT 38mg subdermal implant
"ga25."	LEVONORGESTREL 38mg subdermal implant
"ga26."	LEVONORGESTREL 52mg intrauterine system
"ga27."	MIRENA 52mg intrauterine system
"ga28."	Levonorgestrel 750micrograms tablet
"ga2E."	UPOSTELLE 1500micrograms tablets
"ga2F."	JAYDESS 13.5mg intrauterine system
"ga2G."	LEVONORGESTREL 13.5mg intrauterine system
"ga3"	Medroxyprogesterone acetate
"ga35."	MEDROXYPROGESTERONE 150mg/1ml prefilled syringe
"ga36."	DEPO-PROVERA 150mg/1ml prefilled syringe
"ga37."	SAYANA PRESS 104mg/0.65ml susp for injection prefill device
"ga38."	MEDROXYPROGESTERONE ACET 104mg/0.65ml susp for inj device
"ga4"	Norgestrel
"ga5"	Norethisterone
"ga5z"	Norethisterone 350mcg tablet
"ga6"	Norethisterone enanthate

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3 "ga61." Noristerat 200mg/1ml oily injection  
4 "ga6z." Norethisterone oenanthate 200mg/1ml oily injection  
5 "ga7" Etonogestrel  
6 "ga8" Desogestrel  
7 "ga92." ESMYA 5mg tablets  
8 "ga9y." ULIPRISTAL ACETATE 5mg tablets  
9 "gj" Contraceptive implant  
10 "gj1" Combined contraceptive implant  
11 "gj11." NUVARING 120mcg/15mcg/24 hours vaginal delivery system  
12 "gk" Estradiol valerate  
13 "gl..." Estradiol  
14 "gl1.." Nomegestrol acetate  
15 "gl11." ZOELY 2.5mg tablets  
16 "gl12." NOMEGESTROL ACETATE+ESTRADIOL 2.5mg/1.5mg tablets  
17 "SP03A" Expulsion of intrauterine contraceptive device  
18 "x002N" Combined oral contraceptive product  
19 "x02ME" Etyndiol diacetate  
20 "X407J" Expulsion of intrauterine contraceptive device  
21 "Xa85g" Not indicated  
22 "Xaaff" Hormone releasing IUCD fitted by other healthcare provider  
23 "XaBSw" Introduction of Mirena coil  
24 "XaC3g" Removal of intrauterine contraceptive device  
25 "XaVyE" Insert subcutaneous contraceptive implant other healthcare provider  
26 "XaW9V" Not indicated  
27 "XaX5O" Reinsertion of subcutaneous contraceptive  
28 "XaXI2" Subdermal etonogestrel implant insertion ESA  
29 "XaXLs" Intrauterine system contraception  
30 "XaZZX" Replacement of intrauterine system  
31 "XE1S1" Combined oral contraceptive - use  
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## READ CODES LISTS USED TO DEFINE CONFOUNDING VARIABLES

### Charlson Comorbidities

"G30y.", "G30..", "G307.", "G305.", "G300.", "G32..", "14AH.", "G302.", "G303.", "G301.", "G30yz",  
 "G3011", "G30z.", "G3070", "G3071", "G30X0", "G600.", "G65z.", "G66..", "G660.", "G67y.", "Gyu66",  
 "662M.", "F11x2", "G606.", "G61X0", "G62z.", "G669.", "G6774", "S621.", "70043", "G61..", "G618.",  
 "G61X.", "G61X1", "G61z.", "G65y.", "G661.", "G68W.", "Gyu6.", "Gyu67", "S62..", "S628.", "G613.", "G63..",  
 "G667.", "G671.", "G680.", "Gyu6D", "S627.", "G63z.", "G65..", "G65zz", "G666.", "G60z.", "G6410", "G663.",  
 "G664.", "G665.", "G668.", "G671z", "Gyu65", "G633.", "G681.", "G6z..", "Gyu60", "S620.", "14A7.", "G602.",  
 "G603.", "G604.", "G662.", "G6y..", "G6..", "G60..", "G601.", "G617.", "G63y.", "G67..", "G67z.", "Gyu61",  
 "G605.", "G60X.", "G64..", "G68..", "Gyu62", "Gyu6F", "G623.", "G232.", "SP111", "G582.", "G58z.", "14A6.",  
 "G5540", "G5800", "G580.", "G5810", "G5801", "G5802", "G581.", "G5803", "14AM.", "8B29.", "G58..",  
 "662W.", "1O1..", "8H2S.", "8CL3.", "G5yA.", "H57y4", "N040A", "N040T", "Nyu45", "N0000", "N001.",  
 "N0404", "N0406", "N040J", "N060.", "Nyu1G", "K01x4", "N040G", "N040H", "N04y0", "N04y1", "N20..",  
 "F3964", "H57y1", "N04..", "N0407", "N040F", "N040P", "N2314", "N000.", "N0001", "N0405", "N041.",  
 "N0010", "N2402", "N2z..", "Nyu10", "Nyu12", "F3712", "H572.", "N0004", "N000z", "N0012", "N040B",  
 "N040D", "N040E", "N040M", "N2y..", "N0003", "N004.", "N0402", "N040C", "N200.", "2A42.", "N0403",  
 "N040L", "N2400", "N240z", "F3961", "F3966", "N0002", "N040.", "N0408", "N0409", "N040K", "N0421",  
 "N04X.", "N240.", "N2407", "Nyu11", "Nyu43", "H570.", "N047.", "E000.", "E0041", "Eu010", "Eu02z",  
 "Eu02.", "Eu002", "Eu012", "E0010", "E041.", "Eu011", "Eu000", "Eu00z", "E004.", "E0042", "E004z", "Eu00.",  
 "Eu02y", "E00..", "E001z", "Eu01z", "E0043", "E0040", "Eu001", "Eu01.", "Eu01y", "E001.", "Eu013", "Eu025",  
 "C1000", "C103.", "C1074", "C109.", "C10y.", "C101.", "C1010", "C101z", "C10y1", "66AK.", "8A13.",  
 "8H2J.", "C1030", "C103y", "C1073", "66AJ.", "C1001", "C1070", "C108.", "C1095", "C10A1", "C101y",  
 "C1084", "C1093", "C1094", "C10yz", "C10z1", "C10zz", "G73y0", "L1806", "66A5.", "C1099", "66AJz",  
 "C1020", "C107.", "C1088", "C10A0", "Cyu20", "C10..", "C1071", "C10A.", "C10B0", "C10zy", "Cyu2.",  
 "66AI.", "C100z", "C1072", "C10z.", "L180X", "C1011", "C102.", "C107z", "66AS.", "C100.", "C1021",  
 "C102z", "C103z", "C1085", "C1086", "C1097", "C10yy", "L1805", "C108E", "C1089", "C109F", "C109D",  
 "C109J", "C109G", "66AV.", "C108G", "C10D.", "C109K", "C10E.", "C10F.", "C10FJ", "C10F9", "C10FM",  
 "C10EM", "C10EE", "C10EN", "C10FN", "C10FL", "C10E8", "C10FF", "C10E9", "C10F7", "C10E4", "C10F4",  
 "C10EL", "C10F5", "8BL2.", "C10E5", "C10EK", "C10FP", "C10FD", "C10G.", "C10FG", "C10E6", "C10M.",  
 "C10N.", "C10EA", "C10H.", "C10EG", "J61..", "J615C", "C3104", "J614z", "J615z", "J6161", "C3500",  
 "J6141", "J6151", "J6160", "J614.", "J615F", "J614y", "J6153", "J615y", "J6002", "J615.", "J615B", "J616z",  
 "J6012", "J6143", "J6170", "J6140", "J6157", "J616.", "J633.", "J6356", "J612.", "J6142", "J6150", "J6154",  
 "J615A", "Jyu71", "J61y3", "J11..", "J110y", "J11yy", "J1201", "J1214", "J121y", "J12y4", "J12z.", "J140z",  
 "ZV12C", "761Jy", "J1102", "J1114", "J13y.", "J13yy", "J14..", "J1412", "761J1", "J1111", "J111z", "J120.",  
 "J120y", "J1301", "J1303", "J13z.", "J1400", "J14y3", "76121", "761J0", "J1020", "J1100", "J11y3", "J122.",  
 "J12y0", "J12yy", "J130.", "J130z", "J131y", "J140.", "J1402", "J14y.", "ZV127", "J1101", "J111y", "J11z.",  
 "J12yz", "J1300", "J131.", "J1313", "J140y", "J110.", "J1112", "J1203", "J124.", "J130y", "J1314", "J13y0",  
 "J13y2", "J13y4", "J1413", "761Jz", "J11y.", "J12..", "J1202", "J1204", "J1302", "J1304", "J1303", "J1403",  
 "J14y4", "761J.", "J11y4", "J1200", "J121.", "J1211", "J123.", "J12y.", "J12y2", "J1312", "J1404", "J14y1",  
 "J14yy", "J1110", "J1113", "J11y0", "J13..", "J1310", "J13yz", "J141.", "J1411", "J14y2", "J14yz", "76125",  
 "76270", "J1104", "J110z", "J111.", "J11y1", "J120z", "J1210", "J1414", "J141z", "J1103", "J11y2", "J11yz",  
 "J1213", "J121z", "J12y3", "J1311", "J131z", "J13y1", "J1401", "J1410", "J141y", "J14y0", "J14z.", "761D6",  
 "J112.", "7A134", "G713.", "G7130", "G7324", "R0543", "7A13.", "G7150", "G715.", "G73..", "G7323",  
 "G73y.", "Gyu71", "R0542", "R054z", "14AE.", "C107.", "G712.", "G7141", "G7311", "G711.", "Gyu72",  
 "G710.", "G714.", "G73z0", "Gyu74", "7A14.", "R054.", "7A113", "G71..", "G7140", "G718.", "G71z.",  
 "G7321", "G73yz", "G7322", "7A112", "7A144", "G7160", "G73z.", "G73zz", "14NB.", "2I16.", "G716.",  
 "G732.", "G7320", "R0540", "663N1", "663f.", "9OJ1.", "H300.", "H31..", "H3120", "H341.", "H354.", "H41z.",  
 "H420.", "663N.", "663N0", "663P.", "663W.", "H32y2", "H331.", "H33z.", "H356.", "H35y6", "H35z.",  
 "H35zz", "H42..", "H441.", "H47y0", "H4z..", "H581.", "663h.", "9OJA.", "H30z.", "H3101", "H311z", "H31yz",  
 "H3200", "H3202", "H32y1", "H3310", "H33zz", "H340.", "H34z.", "H35y.", "H35y5", "H43z.", "H460z",  
 "Hyu30", "SK07.", "H32..", "H32yz", "H32z.", "H330.", "H33z0", "H41..", "14B4.", "663e.", "H30..", "H33..",  
 "H3311", "H35y7", "H435.", "H4640", "H57yz", "H582.", "H3110", "H312z", "H33z2", "H34..", "H352.",  
 "H353.", "H430.", "H432.", "H440.", "H442.", "H3100", "H3121", "H313.", "H31y1", "H31z.", "H331z",  
 "H350.", "H351.", "H352z", "H35z1", "H3z..", "H40..", "H460.", "Hyu43", "173A.", "663V0", "H3111", "H312.",  
 "H321.", "H3300", "H330z", "H332.", "H43..", "H4642", "663V1", "663V2", "H310.", "H311.", "H320.",  
 "H320z", "H32y.", "H32y0", "H3301", "H35y3", "H423.", "H4641", "H4y10", "8H2P.", "H310z", "H333.",  
 "H33z1", "H3520", "H355.", "H35yz", "H410.", "H45..", "H57y.", "663V3", "H31y.", "H322.", "H35..",  
 "H3521", "H42z.", "H431.", "H434.", "Hyu40", "Hyu41", "663v.", "663q.", "663r.", "66YC.", "663s.", "663t.",  
 "663u.", "1O2..", "66YP.", "H334.", "173c.", "663N1", "663f.", "9OJ1.", "H3120", "663N.", "663N0", "663P.",

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3 "663W.", "H331.", "H33z.", "H47y0", "663h.", "9OJA.", "H3310", "H33zz", "H330.", "H33z0", "14B4.", "663e.",  
4 "H33.", "H3311", "H35y7", "H33z2", "H331z", "173A.", "663V0", "H3300", "H330z", "H332.", "663V1",  
5 "663V2", "H3301", "8H2P.", "H333.", "H33z1", "663V3", "663v.", "663q.", "663r.", "66YC.", "663s.", "663t.",  
6 "663u.", "1O2.", "66YP.", "H334.", "173c.", "B0001", "B002.", "B0022", "B0033", "B010.", "B010z", "B023.",  
7 "B060.", "B0622", "B0623", "B0710", "B0720", "B07z.", "B08.", "B082.", "B0zy.", "B105.", "B110z", "B112.",  
8 "B120.", "B140.", "B15.", "B150z", "B1612", "B161z", "B172.", "B18.", "B1801", "B18y.", "B18y0", "B18y2",  
9 "B2011", "B2012", "B203.", "B204.", "B205.", "B20z.", "B2133", "B23z.", "B26.", "B30.", "B302z", "B3055",  
10 "B3133", "B3151", "B3152", "B3153", "B323.", "B3232", "B324z", "B326z", "B3276", "B3320", "B3332",  
11 "B335.", "B3350", "B3351", "B3352", "B3356", "B336.", "B3377", "B342.", "B34yz", "B35.", "B3500",  
12 "B410.", "B43.", "B431z", "B43y.", "B45y0", "B47z.", "B480.", "B490.", "B4Az.", "B505.", "B510z", "B5150",  
13 "B5200", "B5210", "B5211", "B5230", "B5246", "B540.", "B5504", "B550z", "B5512", "B553z", "B55y0",  
14 "B55y1", "B6003", "B6006", "B600z", "B6012", "B613z", "B6140", "B6157", "B6162", "B6208", "B6216",  
15 "B6223", "B6227", "B6238", "B6243", "B6274", "B62x3", "B62x4", "B62y6", "B63.", "B630.", "B65.",  
16 "B653.", "B662.", "B675.", "B690.", "B692.", "Byu23", "Byu33", "Byu51", "ByuA2", "ByuDF", "ZV100",  
17 "ZV102", "ZV107", "B0023", "B0130", "B0131", "B01z.", "B021.", "B050.", "B0513", "B055.", "B064z",  
18 "B0731", "B103.", "B10z.", "B1100", "B111.", "B113.", "B114.", "B115.", "B16.", "B1610", "B180z", "B18y5",  
19 "B210.", "B213.", "B2130", "B2131", "B2211", "B2230", "B2241", "B22z.", "B23.", "B2414", "B24X.", "B2z.",  
20 "B3006", "B3020", "B3030", "B3032", "B305.", "B3050", "B3064", "B306z", "B3071", "B3085", "B3100",  
21 "B3120", "B3121", "B3132", "B314.", "B315z", "B3221", "B3231", "B325.", "B325z", "B3271", "B3273",  
22 "B32y0", "B330.", "B3310", "B3321", "B3333", "B3355", "B3358", "B3372", "B341.", "B345.", "B350.",  
23 "B3501", "B350z", "B3y.", "B4100", "B420.", "B44z.", "B4500", "B451.", "B451z", "B45z.", "B49.", "B49y.",  
24 "B4A10", "B4Ay.", "B500.", "B5100", "B511.", "B512.", "B512z", "B51y.", "B521z", "B524X", "B543.",  
25 "B545z", "B5500", "B554.", "B55yz", "B6.", "B600.", "B6101", "B611.", "B6111", "B6116", "B6122",  
26 "B6143", "B6154", "B61z.", "B6210", "B6211", "B6214", "B624z", "B62y1", "B62z6", "B62zz", "B631.",  
27 "B64y.", "B64y0", "B64y1", "B64yz", "B653z", "B66.", "B67.", "By...", "Byu2.", "Byu21", "Byu3.", "Byu5.",  
28 "Byu58", "Byu82", "Byu9.", "ByuD2", "ByuD6", "ByuDC", "Bz...", "ZV104", "ZV10y", "B...", "B000.",  
29 "B0040", "B00z1", "B013z", "B016.", "B02.", "B041.", "B05z0", "B0600", "B07.", "B073z", "B07y.", "B11y0",  
30 "B133.", "B136.", "B14y.", "B1500", "B1502", "B1510", "B1613", "B170.", "B180.", "B1z10", "B1zz.",  
31 "B2000", "B21.", "B2200", "B220z", "B221z", "B222.", "B224.", "B22y.", "B3000", "B302.", "B3021",  
32 "B3033", "B3054", "B3058", "B3063", "B307z", "B308.", "B3088", "B3103", "B3104", "B3110", "B3124",  
33 "B3125", "B314z", "B315.", "B322z", "B3241", "B3255", "B33.", "B3312", "B333.", "B3330", "B334.",  
34 "B337.", "B3371", "B3401", "B344.", "B347.", "B34y0", "B41y.", "B41y0", "B41y1", "B41z.", "B4302",  
35 "B431.", "B441.", "B4702", "B48z.", "B493.", "B49y0", "B4A0.", "B515.", "B515z", "B5173", "B5202",  
36 "B524.", "B5241", "B524W", "B52y.", "B541.", "B542z", "B5531", "B55y.", "B6001", "B6008", "B6015",  
37 "B6016", "B6025", "B6105", "B610z", "B6120", "B6163", "B6167", "B6168", "B61z5", "B61zz", "B620.",  
38 "B6200", "B6217", "B621z", "B6235", "B624.", "B627D", "B6303", "B64.", "B64z.", "B67z.", "B68.", "B680.",  
39 "B69.", "Byu32", "Byu70", "ByuD8", "ZV106", "B0031", "B003z", "B004.", "B0043", "B00zz", "B0110",  
40 "B013.", "B014.", "B064.", "B0641", "B06y.", "B06z.", "B071.", "B0730", "B080.", "B081.", "B0z.", "B102.",  
41 "B110.", "B12.", "B12y.", "B141.", "B1503", "B163.", "B16y.", "B175.", "B17y.", "B181.", "B18y4", "B18y6",  
42 "B1z.", "B1z11", "B200.", "B202.", "B212.", "B225.", "B2410", "B2411", "B303.", "B304.", "B3041", "B3042",  
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44 "B32y.", "B3354", "B335A", "B3370", "B3378", "B337z", "B33X.", "B34z.", "B40.", "B41yz", "B440.",  
45 "B45.", "B46.", "B49z.", "B4Ay0", "B5003", "B501.", "B5121", "B521.", "B545.", "B5451", "B5503", "B55y2",  
46 "B55z.", "B6004", "B6100", "B6102", "B6123", "B6127", "B6128", "B613.", "B6132", "B62.", "B6203",  
47 "B6234", "B623z", "B6241", "B6244", "B6245", "B6246", "B6262", "B6265", "B627X", "B62x5", "B62y2",  
48 "B62y3", "B62z0", "B62z1", "B651.", "B6512", "B6531", "B66y.", "B66y0", "B691.", "B6y1.", "Byu10",  
49 "Byu25", "Byu50", "Byu54", "Byu5A", "ByuD.", "ZV105", "B001.", "B00z0", "B012.", "B03z.", "B052.",  
50 "B060z", "B0621", "B071z", "B072z", "B101.", "B1101", "B116.", "B13z.", "B142.", "B1420", "B16z.",  
51 "B173.", "B18y1", "B18y7", "B1z1z", "B2001", "B201.", "B2010", "B21y.", "B2201", "B223.", "B232.",  
52 "B240.", "B241z", "B242.", "B3...", "B3005", "B3051", "B3056", "B305A", "B305z", "B3072", "B3083",  
53 "B31.", "B311z", "B3140", "B3141", "B31z.", "B3272", "B3341", "B3357", "B3364", "B3365", "B336z",  
54 "B3373", "B4...", "B41.", "B411.", "B412.", "B4700", "B4710", "B4711", "B48.", "B481.", "B491.", "B4A1.",  
55 "B4y.", "B5000", "B510.", "B5151", "B516.", "B5231", "B523z", "B5244", "B54.", "B5421", "B544.", "B54X.",  
56 "B54y.", "B6018", "B6026", "B6130", "B6138", "B6145", "B616.", "B61z1", "B61z6", "B622z", "B6242",  
57 "B6256", "B6260", "B6268", "B6270", "B6272", "B627C", "B62x2", "B62z2", "B6302", "B641.", "B6510",  
58 "B65z.", "B68y.", "Byu1.", "Byu11", "Byu13", "Byu24", "Byu31", "Byu53", "Byu73", "Byu8.", "ByuA0",  
59 "ByuD4", "ByuDE", "ByuE.", "ZV101", "B0000", "B0042", "B005.", "B006.", "B011z", "B015.", "B040.",  
60 "B042.", "B05y.", "B062z", "B065.", "B1110", "B11y1", "B11yz", "B123.", "B124.", "B137.", "B14.", "B143.",  
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5 "B48yz", "B4A.", "B5011", "B5104", "B5105", "B513.", "B514.", "B51y0", "B52.", "B523.", "B52z.", "B5505",  
6 "B602.", "B6021", "B6022", "B610.", "B6114", "B6133", "B615z", "B616z", "B61z4", "B6215", "B6231",  
7 "B6236", "B6251", "B6252", "B6253", "B626.", "B6271", "B6275", "B6276", "B6277", "B62y.", "B62z5",  
8 "B6530", "B67y.", "B67y0", "B681.", "B68z.", "B6z.", "Byu0.", "Byu22", "Byu40", "ByuD3", "ByuD7",  
9 "ByuD9", "B00.", "B0010", "B0011", "B004z", "B02y.", "B03y.", "B056.", "B0601", "B0620", "B0711",  
10 "B072.", "B0721", "B0732", "B0z1.", "B1...", "B10y.", "B11.", "B13y.", "B161.", "B171.", "B18z.", "B2002",  
11 "B222z", "B2z0.", "B2zz.", "B300.", "B3002", "B300C", "B3031", "B3034", "B3044", "B304z", "B3053",  
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15 "B5245", "B5511", "B553.", "B5532", "B6000", "B601.", "B6028", "B602z", "B60y.", "B6108", "B6112",  
16 "B6115", "B6125", "B6134", "B6142", "B6146", "B6204", "B6205", "B6206", "B6213", "B6220", "B6221",  
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20 "B121.", "B130.", "B14z.", "B1511", "B1512", "B1513", "B1611", "B17yz", "B1800", "B182.", "B1z0.", "B20.",  
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28 "Byu55", "Byu6.", "Byu7.", "ByuA.", "ByuD1", "ByuE0", "ZV10.", "ZV10z", "B002z", "B0032", "B0041",  
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30 "B066.", "B06yz", "B0z0.", "B10.", "B104.", "B111z", "B117.", "B134.", "B1501", "B151z", "B1z1.", "B1zy.",  
31 "B214.", "B21z.", "B220.", "B221.", "B23y.", "B2413", "B2zy.", "B300z", "B3040", "B3059", "B306.", "B3060",  
32 "B309.", "B30W.", "B30z.", "B3114", "B3122", "B3131", "B31z0", "B320.", "B3253", "B3275", "B3277",  
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38 "B6300", "B63y.", "B652.", "B660.", "B66z.", "B670.", "Byu4.", "Byu57", "Byu71", "Byu81", "Byu90", "B0...",  
39 "B000z", "B0020", "B01y.", "B022.", "B03.", "B05.", "B051.", "B0510", "B055z", "B05z.", "B062.", "B06y0",  
40 "B073.", "B084.", "B11y.", "B12z.", "B13.", "B131.", "B138.", "B151.", "B152.", "B162.", "B2013", "B201z",  
41 "B2220", "B2231", "B223z", "B226.", "B230.", "B241.", "B24y.", "B24z.", "B3004", "B3009", "B300A",  
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43 "B3340", "B3359", "B335z", "B33z.", "B42.", "B430z", "B43z.", "B450z", "B45y.", "B47.", "B4703", "B492.",  
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47 "B62x1", "B62y0", "B62z4", "B63z.", "B64y2", "B65y1", "B674.", "B67yz", "Byu12", "Byu30", "Byu52",  
48 "Byu59", "ByuA1", "ByuA3", "ByuDD", "ZV103", "B0030", "B007.", "B0100", "B011.", "B020.", "B031.",  
49 "B04.", "B04y.", "B04z.", "B0512", "B053.", "B06.", "B070.", "B074.", "B083.", "B08y.", "B08z.", "B0zz.",  
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58 "B623.", "B6240", "B62x0", "B640.", "B650.", "B651z", "B65y.", "B65y0", "B65yz", "B66yz", "B6y.",  
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 "A789X", "AyuC3", "AyuC4", "AyuC6", "A7886", "A788z", "A789A", "A7882", "A7883", "A7884", "A788V",  
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### Age

Age was calculated using date of birth rather than read codes

### Height

"229.."

### Weight

"22A.."

### Gravidity/Pregnancy

"615C.", "6166.", "6174.", "621.", "6211.", "6212.", "6213.", "6214.", "6215.", "6216.", "6217.", "6218.", "6219.", "621  
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 5 "L1692", "L16A1", "L16A2", "L16y1", "L16y2", "L1701", "L1702", "L1711", "L1712", "L1721", "L1722",  
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 34 "L4662", "L46y1", "L46y2", "L46z1", "L46z2", "Ly0..", "Ly1..", "Lyu3.", "Lyu50", "Lyu51", "Lyu52", "Lyu53",  
 35 "Lyu54", "Lyu55", "Lyu56", "Lyu57", "Lyu58", "7CC1.", "7CC2.", "7CC4.", "7CCZ.", "7D5..", "7D51.",  
 36 "7D52.", "7D53.", "7D54.", "7D55.", "7D56.", "7D5Z.", "7D61.", "7D6Z.", "7E131", "7E133", "7E190",  
 37 "7E060", "7E066", "7E07.", "7E070", "7E071", "7E072", "7E07y", "7E07z", "7E08.", "7E080", "7E081",  
 38 "7E082", "7E084", "7E085", "7E086", "7E087", "7E088", "7E08A", "7E08B", "7E08C", "7E08y", "7E08z",  
 39 "7E0E2", "L0..", "L02..", "L0300", "L09..", "L090.", "L0900", "L0901", "L0902", "L0903", "L0904", "L090y",  
 40 "L090z", "L091.", "L0910", "L0911", "L0912", "L091z", "L092.", "L0920", "L0921", "L0922", "L0923",  
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 42 "L094.", "L095.", "L096.", "L0960", "L0961", "L0962", "L0963", "L0964", "L0965", "L0966", "L0967",  
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 44 "L09y4", "L09yz", "L09z.", "L10zz", "L264.", "L2640", "L2641", "L2642", "L264z", "Lyu0.", "Lyu02",  
 45 "Lyu05", "g18..", "g181.", "g182.", "g14..", "g141.", "g14z.", "a6a..", "a6a1.", "a6a4.", "a6a5.", "g183.", "g184.",  
 46 "7E080", "7E084", "7E08A", "7E08B", "7E08C", "7CC2.", "7E070", "7E071", "7E088", "7CC4.", "7CCZ.",  
 47 "7E0E2", "7E07.", "7E072", "7E07y", "7E07z", "7E081", "7E085", "Lyu05", "7D61.", "7E060", "7E066",  
 48 "L02..", "L10zz", "L264.", "L2640", "L2641", "L2642", "L264z", "7E131", "7E190", "7D52.", "7E133", "7D53.",  
 49 "7D51.", "L0300", "7CC1.", "7E087", "7E086", "7D5..", "7D54.", "7D55.", "7D56.", "7D5Z.", "7D6Z.", "L097.",  
 50 "L0970", "L0971", "L0972", "L0973", "7E082", "L0..", "L09..", "L090.", "L0900", "L0901", "L0902", "L0903",  
 51 "L0904", "L090y", "L090z", "L091.", "L0910", "L0911", "L0912", "L091z", "L092.", "L0920", "L0921",  
 52 "L0922", "L0923", "L0924", "L0925", "L0926", "L092z", "L093.", "L0930", "L0931", "L0932", "L0933",  
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 54 "L0966", "L0967", "L096z", "L09y.", "L09y0", "L09y1", "L09y2", "L09y3", "L09y4", "L09yz", "L09z.",  
 55 "Lyu0.", "Lyu02", "7E08.", "7E08y", "7E08z"

### **Smoking**

**Current smoking:**

"137.", "1372.", "1373.", "1374.", "1375.", "1376.", "137a.", "137b.", "137c.", "137C.", "137d.", "137D.", "137e.", "137f.", "137G.", "137h.", "137H.", "137J.", "137m.", "137M.", "137o.", "137P.", "137Q.", "137R.", "137V.", "137X.", "137Y.", "137Z.", "Ub1tI", "Ub1tJ", "Ub1tK", "Ub1tR", "Ub1tS", "Ub1tT", "Ub1tU", "Ub1tV", "Ub1tW", "XaBSp", "Xallu", "XalkW", "XalkY", "Xaltg", "XaJX2", "XaLQh", "XaWNE", "XaZIE", "XE0og", "XE0oi", "XE0oq", "XE0or"

**Ex-smoking:**

"1377.", "1378.", "1379.", "137A.", "137B.", "137F.", "137j.", "137K.", "137L.", "137N.", "137O.", "137S.", "137T.", "Ub0p1", "Ub1na", "Xa1bv", "XaQ8V", "XE0oj", "XE0ok", "XE0ol", "XE0om", "XE0on", "XE0op", "137K0", "XaQzw"

**Passive smoking:**

"13WF.", "XM1Jh", "13WF4", "137I.", "137I0", "Ub0pe", "Ub0pf", "Ub0pg"

**Non-smoking:**

"137I.", "XE0oh", "137U.", "XaFvq"

**Gynaecology Conditions****Endometriosis**

"7E0D8", "BBL1.", "K50.", "K500.", "K5000", "K5001", "K5002", "K500z", "K501.", "K502.", "K503.", "K5030", "K5031", "K5032", "K5033", "K503z", "K504.", "K5040", "K5041", "K504z", "K505.", "K5050", "K5051", "K5052", "K505z", "K506.", "K50y.", "K50y0", "K50y1", "K50y2", "K50y3", "K50yz", "K50z.", "Kyu90"

**Polycystic ovary syndrome (PCOS):**

"C164.", "C165.", "C164."

**Menstrual bleeding complaints identified under coding terms menorrhagia, metrorrhagia, menometrorrhagia:**

"151C.", "1572.", "1573.", "K5A0.", "K5920", "151G.", "K5921", "K594.", "K594z", "K595.", "K596.", "K599.", "K59y3", "158.", "K592.", "K592z", "K598.", "K59yx."

**Acne:**

"Myu6F", "2FG5.", "679g0", "M25y6", "M2610", "M2611", "M261E", "M261F", "M261H", "M261J", "M261K", "M261X", "Myu68", "M261.", "M261z", "M261A"

**Bilateral salpingo-oophorectomy (BSO):**

"159B.", "7E100", "7E101", "7E102", "7E111", "7E113", "7E115"

**Hysterectomy BSO:**

"7E045", "7E047", "7E048", "7E049", "7E04B", "7E056"

**Hysterectomy:**

"7E043", "7E04A", "7E04F", "7E04G", "7E055", "7E04.", "7E044", "7E04C", "7E04E", "7E04y", "7E04z", "7E05.", "7E053", "7E054", "7E05y", "7E05z"

**Fibroids:**

"B78.", "B780.", "B781.", "B782.", "B78z.", "B791.", "B7910", "B7911", "B7912", "B791z", "B79y.", "B79z.", "BBK.", "BBK0.", "BBK00", "BBK01", "BBK03", "BBK05", "BBK06", "BBK0z", "BBK1.", "BBK10", "BBK1z", "BBK2.", "BBK20", "BBK2z", "BBK38", "BBL2.", "L115.", "L1150", "L1151", "L1152", "L115z", "L241.", "L2410", "L2411", "L2412", "L2413", "L2414", "L241z", "15A9.", "7A54A", "7E061", "7E062", "7E06y", "7E0D0", "7E0DC"

**Others:**

"K59.", "K590.", "K5900", "K5901", "K590z", "K591.", "K5910", "K5911", "K5912", "K5913", "K591z", "K593.", "K59y.", "K59y2", "K59yz"