

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Exogenous sex steroid hormones and asthma in females: protocol for a population-based retrospective cohort study using a UK primary care database
AUTHORS	Nwaru, Bright; Simpson, Colin; Soyiri, Ireneous; Pillinger, Rebecca; Appiagyeyi, Francis; Ryan, Dermot; Critchley, Hilary; Price, David; Hawrylowicz, Catherine; Sheikh, Aziz

VERSION 1 – REVIEW

REVIEWER	Francisco Gómez Real 1-University of Bergen, Institute of Clinical Sciences, 2- Haukeland University Hospital, Department of Obstetrics and Gynecology, Bergen, Norway
REVIEW RETURNED	20-Nov-2017

GENERAL COMMENTS	<p>COMMENTS:</p> <p>This study is very much needed, as the literature on the role of hormonal contraceptives (HC) and hormonal replacement therapy (HRT) is unclear, as the authors point out. A project taking advantage of a large dataset as the one described has the potential to contribute substantially to the research of exogenous sex hormones and asthma, however, there are important challenges that makes this field very difficult. There is potential for improving the protocol.</p> <p>My concerns are:</p> <p>1) The associations between HC and HRT with asthma, although very interesting, will not necessarily “provide robust evidence that will inform potential causation and provide the direction for further mechanistic work” (lines 49-50, page 2), unless careful considerations of indications for use of HC and HRT are made. Confounding by indication bias need to be described in more detail. Which indications do they have information on and how is the quality of this information?</p> <p>In the case of HC, is there information in the OPCR data about indications for use of HC besides contraception, i.e. endometriosis or PCOS? This should be clarified.</p> <p>There is literature pointing in the direction of endometriosis or PCOS or its proxies (menstrual irregularity) being related to increased asthma risk. This literature is not mentioned. These may be indications for HC use, and should therefore be mentioned.</p> <p>In the case of HRT, the main reason for using HRT are symptoms related to the menopausal transition. Will the authors be able to disentangle whether the potential observed associations between HRT and asthma are due to HRT itself or to the condition behind use of HRT, namely menopause – or indications for removing the ovaries? There is literature about this, which is not comprehensively reviewed.</p>
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	<p>As authors point out, a weakness of the study will be that reproductive and menopausal status of females are based only on the age of the women. How will the authors account for this?</p> <p>2) The reference categories in the different analyses are not exhaustively described. I.e. in the case of HC, what will be the reference category for using one type of HC? Those using another type of HC? Those not using HC at all? Will women using HC due to PCOS be excluded?</p> <p>In the case of HRT, the consideration of groups to be compared is particularly important. Age at natural menopause is an important factor to consider. There is literature pointing in the direction of menopause itself and early menopause being related to poorer lung health. Will the authors i.e. be able to compare those using HRT due to earlier natural menopause with those with HRT at later natural menopause?</p> <p>In the case of women using HRT after surgical menopause, will they be compared to women not using HRT after removal of ovaries? Or to women of same age using HRT and which are naturally menopausal? A discussion on groups to be compared would be very much appreciated.</p> <p>3) The literature background is not comprehensive. There is an important body of literature on hormonal status among women and respiratory health, which should be included in the background and commented on. In particular, it is important to include literature that tries to disentangle the role of menopause itself.</p>
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REVIEWER	Hayley Scott The University of Newcastle, Australia
REVIEW RETURNED	24-Jan-2018

GENERAL COMMENTS	<p>This manuscript describes the protocol for a large, retrospective cohort study that will examine whether use of hormonal contraception and HRT are associated with asthma onset and clinical outcomes in reproductive aged and peri/post-menopausal aged females. I believe this manuscript is suitable for publication after a few minor amendments:</p> <ul style="list-style-type: none"> • Reference 5 does not appear to be the correct citation, as the study was conducted in non-asthmatic women. • Please specify if BMI is measured or self-reported. • How will level of adherence to asthma medications be determined? • How will asthma severity be defined specifically? Is this a validated way to report asthma severity? • You will require a substantial sample size. How many people do you anticipate will be available on the database? And how many will have the data available that you require? • Another important reference that examined OCP use in relation to ACQ and sputum neutrophils is: Scott HA, Gibson PG, Garg ML, Upham JW, Wood LG. Sex hormones and systemic inflammation are modulators of the obese-asthma phenotype. Allergy. 2016; 71: 1037-1047. This could be cited along with references 10-14.
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VERSION 1 – AUTHOR RESPONSE

REVIEWER: 1

Reviewer Name: Francisco Gómez Real

Institution and Country: 1-University of Bergen, Institute of Clinical Sciences
2- Haukeland University Hospital, Department of Obstetrics and Gynecology Bergen, Norway

Comment:

This study is very much needed, as the literature on the role of hormonal contraceptives (HC) and hormonal replacement therapy (HRT) is unclear, as the authors point out.

A project taking advantage of a large dataset as the one described has the potential to contribute substantially to the research of exogenous sex hormones and asthma, however, there are important challenges that makes this field very difficult.

Response:

We thank the reviewer for the positive comments.

Comment:

There is potential for improving the protocol.

My concerns are:

1) The associations between HC and HRT with asthma, although very interesting, will not necessarily “provide robust evidence that will inform potential causation and provide the direction for further mechanistic work” (lines 49-50, page 2), unless careful considerations of indications for use of HC and HRT are made. Confounding by indication bias need to be described in more detail. Which indications do they have information on and how is the quality of this information? In the case of HC, is there information in the OPCRCD data about indications for use of HC besides contraception, i.e. endometriosis or PCOS? This should be clarified. There is literature pointing in the direction of endometriosis or PCOS or its proxies (menstrual irregularity) being related to increased asthma risk. This literature is not mentioned. These may be indications for HC use, and should therefore be mentioned. In the case of HRT, the main reason for using HRT are symptoms related to the menopausal transition. Will the authors be able to disentangle whether the potential observed associations between HRT and asthma are due to HRT itself or to the condition behind use of HRT, namely menopause – or indications for removing the ovaries? There is literature about this, which is not comprehensibly reviewed.

Response:

We thank the reviewer for these important points. On the basis of the suggestions, we have now expanded our description of confounding by indication and added further literature in this respect. In particular, in the case of hormonal contraceptives, we have added information that we will take into account other indications for use of hormonal contraceptives besides contraception, including endometriosis, PCOS, menorrhagia, acne, and metrorrhagia. In the case of use of HRT, other indications besides symptoms of menopausal transitions will be taken into account, including endometriosis, indications for removal ovaries such as uterine fibroids, and heavy menstrual bleeding. For both hormonal contraceptives and HRT, indications for use are available in the OPCRCD database and the quality of this information is very good (please see the corrections in the section on Confounders on page 4 as well as in the analysis section on page 5)

Comment:

2) As authors point out, a weakness of the study will be that reproductive and menopausal status of females are based only on the age of the women. How will the authors account for this?

Response:

We have now added information on the determination of menopausal status based on the age of women (please see the section on Exposure on page 4).

Comment:

3) The reference categories in the different analyses are not exhaustively described. I.e. in the case of HC, what will be the reference category for using one type of HC? Those using another type of HC? Those not using HC at all? Will women using HC due to PCOS be excluded? In the case of HRT, the consideration of groups to be compared is particularly important. Age at natural menopause is an important factor to consider. There is literature pointing in the direction of menopause itself and early menopause being related to poorer lung health. Will the authors i.e. be able to compare those using HRT due to earlier natural menopause with those with HRT at later natural menopause? In the case of women using HRT after surgical menopause, will they be compared to women not using HRT after removal of ovaries? Or to women of same age using HRT and which are naturally menopausal? A discussion on groups to be compared would be very much appreciated.

Response:

We have included additional information on the comparison of the different exposures (please see the section on Exposure on page 4)

Comment:

4) The literature background is not comprehensive. There is an important body of literature on hormonal status among women and respiratory health, which should be included in the background and commented on. In particular, it is important to include literature that tries to disentangle the role of menopause itself.

Response:

We have included additional discussion and literature to the aspects on menopause and use of hormonal contraception (please the Introduction section on page 3).

REVIEWER: 2

Reviewer Name: Hayley Scott

Institution and Country: The University of Newcastle, Australia

Comment:

This manuscript describes the protocol for a large, retrospective cohort study that will examine whether use of hormonal contraception and HRT are associated with asthma onset and clinical outcomes in reproductive aged and peri/post-menopausal aged females. I believe this manuscript is suitable for publication after a few minor amendments:

Comment:

1) Reference 5 does not appear to be the correct citation, as the study was conducted in non-asthmatic women.

Response:

We have now corrected reference 5.

Comment:

Please specify if BMI is measured or self-reported.

Response:

BMI is measured in the OPCR database and not reported.

Comment:

How will level of adherence to asthma medications be determined?

Response:

Within the OPCRCD database, we have previously developed an algorithm to longitudinally measure adherence in the context of inhaled corticosteroid use in asthma. We will adapt that algorithm when assessing adherence to asthma medications in this study. We have now expanded this aspect of the paper with reference to our previous paper on the topic (please see page 4).

Comment:

How will asthma severity be defined specifically? Is this a validated way to report asthma severity?

Response:

We have now expanded on the definition of severity for our study – indicating that we will employ the BTS/SIGN guidelines, and algorithms for implementing this have already been developed within OPCRCD (please see section on Outcomes, page 5).

Comment:

You will require a substantial sample size. How many people do you anticipate will be available on the database? And how many will have the data available that you require?

Response:

We have included additional information on the section on sample size estimation, indicating that the OPCRCD current has over 5 million patients and we estimate that at least five hundred thousand of these will meet our inclusion criteria for this study (please see page 6).

Comment:

Another important reference that examined OCP use in relation to ACQ and sputum neutrophils is: Scott HA, Gibson PG, Garg ML, Upham JW, Wood LG. Sex hormones and systemic inflammation are modulators of the obese-asthma phenotype. Allergy. 2016; 71: 1037-1047. This could be cited along with references 10-14.

Response:

We thank the reviewer for the suggested literature, which we have now included in our paper.

VERSION 2 – REVIEW

REVIEWER	Hayley Scott Centre for Healthy Lungs, The University of Newcastle, Australia
REVIEW RETURNED	21-Mar-2018
GENERAL COMMENTS	I have no further comments.