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Exogenous sex steroid hormones and asthma phenotypes: a study protocol for a prospective cohort analysis with UK-wide primary care data

Fatima Almaghrabi,[1] Bright I Nwaru,[2] Aziz Sheikh,[3] Athanasios Tsanas,[4] Holly Tibble ,[1,5] Hilary Critchley,[6] Tracy Jackson,[4] Azhar Ali,[7] Syed Ahmar Shah [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Syed Ahmar Shah;
ahmar.shah@ed.ac.uk

ABSTRACT

Introduction The role of female sex hormones and their influence on asthma's development and natural history remain uncertain. Our study aims to enhance understanding of exogenous sex hormones' role in asthma development and manifestation, considering phenotypic heterogeneity and focusing on metabolic syndrome-linked asthma that has shown increased severity in females.

Methods and analysis A cohort study using primary care data from the Clinical Practice Research Datalink (CPRD) databases linked with additional data sources (Hospital Episode Statistics, ethnicity and deprivation) will include individuals aged 16–70 years, spanning 1 January 2005 to 31 December 2019. We will use appropriate statistical learning methods depending on the outcome: extended Cox regression for late-onset asthma; Poisson or negative binomial regression for asthma exacerbations; binary logistic regression for asthma control; and ordered logistic regression for asthma severity. Asthma exacerbation will be defined based on the American Thoracic Society/European Respiratory Society Task Force definition as the presence of either one of an asthma-related accident and emergency department visit, an asthma-related (unscheduled) hospital admission or an acute course of oral corticosteroids (OCS) with evidence of asthma-related medical event and/or review within 2 weeks of OCS prescription. Poor asthma control in any given month will be defined by the occurrence of an exacerbation episode or use of short-acting beta agonist. Asthma severity will be defined based on the British Thoracic Society asthma severity steps. Asthma phenotypes will be identified using k-means clustering. Analyses will be undertaken using both GOLD and Aurum to ensure coverage across UK nations.

Ethics and dissemination CPRD has received ethics approval from the Health Research Authority (East Midlands—Derby, REC reference number 21/EM/065) to support research using anonymised data. Approval to conduct this study was obtained through CPRD's Research Data Governance process. The results will be disseminated through academic publications and conference presentations, contributing to the understanding and practice of asthma management, particularly in the context of the impacts of exogenous sex steroid hormones.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Uses a large, country-wide, population-based cohort with rich primary care data on exogenous sex hormone prescriptions and asthma.
⇒ Uses robust statistical methods to assess potential effect modification by exogenous sex hormones on asthma outcomes and in the relationship between therapeutic interventions for metabolic syndrome and asthma outcomes.
⇒ Risk of exposure misclassification may exist due to incomplete prescription records, particularly those administered outside general practices and lack of adherence data.
⇒ Hospital Episode Statistics Accident and Emergency data linkage and patient-level deprivation data are limited to England, potentially under-representing severe asthma exacerbations and assumptions about socioeconomic status of patients from other UK nations.

INTRODUCTION

Background

The UK experiences one of the highest burdens related to asthma, with elevated rates of incidence, prevalence, healthcare utilisation and the risk of severe outcomes, including mortality.[1–4] Although asthma is more common among boys than girls in early childhood, the occurrence of asthma becomes greater in women after reaching puberty.[2 3] It is now becoming increasingly clear that female sex hormones contribute to the difference in asthma prevalence and severity between women and men.[4–7] However, the influence of exogenous sex steroid hormones on asthma's aetiology and exacerbation remains uncertain, as noted in previous studies.[8–19] To address this uncertainty, we recently conducted the largest population-based longitudinal study aimed at gaining a better understanding of the impact

of exogenous sex hormones on asthma.[4–7] Among women of reproductive age, our study revealed that hormonal contraceptives were associated with a reduced risk of new-onset asthma[7] and a decreased likelihood of severe asthma exacerbations.[6] Additionally, among menopausal women, the use of hormone replacement therapy (HRT) was linked to a decreased risk of new-onset asthma,[4] although it was associated with an increased risk of asthma exacerbations in individuals with pre-existing asthma.[5] A key limitation of the previous studies is the lack of accounting for phenotypic heterogeneity among individuals with asthma.[20 21] A notable yet poorly understood example is obesity-linked asthma. Previous studies suggest that obese patients with asthma respond poorly to inhaled corticosteroids,[22] and a subset of obese female patients with asthma have more severe symptoms when compared with other phenotypes.[20] This is perhaps not surprising since obesity may modify the impact of exogenous sex hormones on asthma given the interaction between endogenous sex hormones and body fat mass.[23 24] However, the literature on the effect modification of obesity (as measured by body mass index (BMI)) on the association between sex hormones and asthma has reported inconsistent findings, ranging from protective effects to no effects and even elevated risks of asthma attacks.[4–7 25]

Both obesity and asthma have previously been associated with common inflammatory mechanisms.[26] Obesity is, however, one of four potential symptoms of metabolic syndrome (insulin resistance, dyslipidaemia and hypertension being the other three).[27] Association between asthma and other components of metabolic syndrome have also previously been reported, independent of obesity.[26 27] It is thus plausible to expect an association between therapeutic interventions used to treat metabolic syndrome and asthma. It is also conceivable that the studies to date were confounded by the phenotypic heterogeneity of asthma and that has made it difficult to elucidate the likely mechanisms involved that could explain the asthma-related differences between women and men. To our knowledge, no previous study has explored the role of exogenous sex steroids in the development and clinical manifestation of various asthma phenotypes among individuals with clinically diagnosed asthma. It is essential to address phenotypic heterogeneity when examining the influence of sex hormones on asthma development and clinical outcomes, with particular consideration of obesity and the role of metabolic syndrome.

Aim and objectives

The overall aim of our study is to improve our understanding of the role of exogenous sex hormones in the development and manifestation of asthma while accounting for phenotypic heterogeneity among people with asthma. Our specific objectives are to determine: (1) the association between exogenous sex hormones (hormonal contraceptives and HRT) and late asthma onset in women and whether this association varies by asthma phenotypes; (2) how exogenous sex hormones (hormonal contraceptives and HRT) affect asthma outcomes (asthma exacerbations, severity and control) in women and whether this varies by asthma phenotypes; (3) whether the association between therapeutic interventions that are used to treat metabolic syndrome on asthma outcomes (asthma exacerbations, severity and control) is different between women and men; and (4) whether the association between exogenous sex hormones and asthma is modified by the therapeutic interventions to treat metabolic syndrome.

METHODS AND ANALYSIS

Study design and population

We will undertake a retrospective open cohort study where we will use patient data using the Clinical Practice Research Datalink (CPRD).[28] CPRD is a vast and comprehensive primary care database that captures a diverse sample of the UK population in terms of age, sex and ethnicity.[29] CPRD data include two databases that contain longitudinal routinely collected electronic health records data from UK primary care practices, CPRD GOLD and CPRD Aurum. The CPRD GOLD dataset is derived from Vision general practice patient management software and includes over 2.8 million active patient records from 985 registered general practices (GPs). The vast majority of these data (98.58%) originate from Scotland, Wales and Northern Ireland. In contrast, CPRD Aurum dataset, sourced from EMIS Web general practice patient management software, contains more than 16.5 million active patient records from 1615 registered GPs. This dataset represents approximately 24.7% of the entire UK population, with all its patients registered in England. The dataset contains anonymised patient demographic details, medical diagnoses, prescribed medications and referrals to specialised healthcare services.

To address study objectives (1) and (2), two separate open cohorts will be derived from data of all women born between 1 January 1936 and 1 January 2000, with at least one record present during the follow-up period, that is, from 1 January 2005 to 31 December 2019. Cohort A will include women without asthma at study onset, aged 16 years or older by 1 January 2005, and lacking any asthma-specific read code in the preceding 5 years. Participants will exit the cohort on asthma diagnosis, death, practice deregistration, turning 70 years or 31 December 2019. Cohort B will comprise women with prevalent asthma, confirmed by asthma-specific read codes in the previous 5 years, under similar entry and exit criteria. For study objective (3), cohort B will be used alongside a parallel male cohort (cohort C), requiring data from men born between 1 January 1936 and 1 January 2000, with at least one record from 1 January 2005 to 31 December 2019, and any asthma-related code between 1 January 2000 and 31 December 2004. Study objective (4) will employ cohort B exclusively, focusing on women with confirmed asthma at study onset. The index date for all cohorts will be the study entry date, necessitating a 5-year look-back

period post registration to ensure accurate asthma status determination.

Sample size estimation

For the study's objectives, minimum sample sizes were calculated for 90% power at a 0.05 alpha level. For objective (1), detecting a 30% reduction in incident asthma with hormonal contraceptive or HRT requires 10 767 women, assuming a 6.6% incidence among unexposed (equal to the asthma incidence previously reported[30]) and a 4:1 ratio of unexposed to exposed (our previous studies found 16–26% of women using hormonal contraceptives or HRT[4 7] and a 20% use will give a ratio of 4).

For objective (2), detecting a 20% risk reduction in asthma exacerbations among women with asthma using sex hormones requires 13 350 women, assuming a 13% incidence among unexposed (in our previous studies looking at women with asthma who did not use hormonal contraceptives or HRT, 10–16% women experienced an asthma exacerbation episode during follow-up[5 6]).

For objective (3), detecting up to a 10% risk difference between men and women with asthma requires 24 446 individuals, with adjustments for potential confounding factors and sensitivity analyses likely necessitating larger sample sizes. By including all eligible individuals in CPRD, the study aims to address primary objectives, adjust for confounders and perform rigorous analyses with precise estimates.

Exposure

The primary exposure for study objectives (1) and (2) will be the use of hormonal contraceptives and HRT, which will be further categorised into subtypes based on their composition and use, in line with our previous work.[4–7] The relevant prescription codes are provided in online supplemental appendix 1 for GOLD and online supplemental appendix 2 for Aurum.

For hormonal contraceptives, the subtypes will include:

- Combined oestrogen and progestogen contraceptives, such as oral contraceptive pills, patches and vaginal rings.
- Progestogen-only contraceptives, including the progestogen-only pill, injectables, implants and hormonal intrauterine devices.

For HRT, the subtypes will include:

- Oestrogen-only HRT, typically prescribed for women without a uterus, delivered as oral tablets, patches or gels.
- Combined oestrogen and progestogen HRT, commonly used for women with a uterus, available as oral tablets, patches or gels.

The primary exposure for study objectives (3) and (4) will be the various therapeutic interventions that are used to treat metabolic syndrome. Our approach will involve assessing the impact of grouping all drugs within each of the four conditions linked to metabolic syndrome: diabetes (BNF (British National Formulary) Codes 0601*); hypertension (BNF Codes 0205*); obesity (BNF Codes 0405*); and dyslipidaemia (BNF Codes 0212*). Specifically, we will analyse the collective effect of all drugs under each individual condition to understand their combined impact on asthma outcomes. Subsequently, we will explore the overall effect by combining all drugs across any of the four conditions. This approach will provide insights into the overall impact of therapeutic interventions, considering both condition-specific and combined effects. The relevant product codes, BNF codes and the associated description for these drugs are provided in online supplemental appendix 3 for GOLD and online supplemental appendix 4 for Aurum.

For all exposures, we will use the 'as-treated' approach, which in the context of cohort studies means that the exposure status will be time-varying and an individual patient's exposure status can switch during follow-up. The exposure status in all the study objectives will be determined on a yearly basis: the presence of any prescription for a given drug class in a given year will be taken to mean that the patient is exposed. Based on this, we will construct further duration-based exposure variables which are: previous (anytime in the past); current use (prescribed during the current study year); and duration of use (none, 1–2 years, 3–4 years, 5 years or more). The exposure in a given year will only be counted if it occurs before the outcome of interest.

Outcome

For study objective (1), the primary outcome will be new-onset asthma defined as the first general practitioner (GP)-recorded asthma-specific event (any of the 121 asthma-specific codes that have previously been validated in CPRD and found to have high sensitivity and specificity[31]). The relevant codes are provided in online supplemental appendix 5 for GOLD and online supplemental appendix 6 for Aurum.

For study objectives (2) and (3), the primary outcomes will be three asthma-related outcomes: asthma exacerbation, asthma control and asthma severity. Asthma exacerbations will be defined based on the American Thoracic Society/European Respiratory Society Task Force definition[32] as the presence of either one of an asthma-related accident and emergency (A&E) department visit, an asthma-related (unscheduled) hospital admission or an acute course of oral corticosteroids (OCS) with evidence of asthma-related medical event and/or review within two weeks of OCS prescription. This definition has previously been validated in various UK-wide primary care databases.[33] The relevant codes are provided in online supplemental appendices 7 and 8 for GOLD and online supplemental appendices 9 and 10 for Aurum . Since the route to hospital admission is likely either via A&E visits or referrals from primary care, we anticipate that access to primary care and Hospital Episode Statistics A&E will help us capture all asthma-related admissions. The relevant codes for asthma control and severity are provided in online supplemental appendix 11 for GOLD and online supplemental appendix 12 for Aurum.

Statistical analysis

In study objective (1), baseline characteristics will be compared between groups with and without asthma onset during the study period using Pearson's χ^2 test. Extended Kaplan-Meier curves will describe survival functions based on categories of use of hormonal contraceptives and HRT. Survival analysis, employing multilevel mixed effects extended Cox regression, will determine associations, treating exposures and covariates as time-varying and considering clustering effects. HRs with 95% CIs will be computed and compared via forest plots.

For study objective (2), baseline characteristics will be compared using Pearson's χ^2 test and differences in mean. Separate analyses for each outcome class will be conducted, using Poisson or negative binomial regression for exacerbations, binary logistic regression for control and ordered logistic regression for severity. Risk ratios with CIs will be computed, employing multilevel mixed effects models to address clustering effects. Subgroup analyses will be conducted for different age groups within menopausal women.

Study objectives (3) and (4) focus on therapeutic interventions for metabolic syndrome-linked conditions and their relationship with asthma outcomes, considering exogenous sex hormones as a potential effect modifier. Similar statistical approaches will be used as in study objective (2), with multilevel mixed effects models to address clustering. Interaction terms between therapeutic interventions and exogenous sex hormones will assess effect modification, with stratified analyses if significant. Analyses will initially consider overall asthma and then separately for each asthma phenotype.

To prevent unintentional patient disclosure in small subgroups, careful suppression of results with low counts will be implemented. Researchers accessing the data will undergo training in statistical disclosure control principles.

Overall, the study will employ rigorous statistical methods to investigate associations between exogenous sex hormones, therapeutic interventions and asthma outcomes, considering potential effect modification and addressing clustering effects while ensuring patient confidentiality.

Prior to the main analyses, the data will undergo relevant quality checks, including relevant variable categorisation (rescaling where appropriate) and checks for missingness. We will only include all variables with a maximum of 35% missing values rate. Variables with missing data, other than age and/or sex (exclusion criteria), will be handled using multiple imputations.[34] We will specifically create a new category called 'missing' to impute the missing data in variables with missing not-at-random criteria such as smoking.[35] For any variables that fulfil the missing-at-random criteria such as BMI, we will adopt a regression-based method to impute the missing values.[36]

CPRD trusted research environment (TRE)

All analysis will be conducted in the CPRD TRE. TREs, alternatively referred to as secure data environments or Data Safe Havens, represent highly secure computing environments. These environments grant approved researchers remote access to data specifically for public health research purposes. Within these environments, both the data and analytical tools are centralised, resembling a secure reference library in functionality. These analytical tools include R and RStudio, which will be used for data analysis in this study.

Limitations of study design

The study presents some limitations. First, patient exposure status may be misclassified if certain data, such as exogenous sex hormone prescriptions, are not recorded in GP data. Additionally, the study lacks data on medication adherence, potentially leading to assumptions that may not reflect reality. Asthma diagnoses and outcomes might be inaccurately classified based on historical GP records, possibly resulting in a large group of unspecified asthma cases. Data linkage for hospital emergency visits is limited to patients in England, potentially missing severe asthma episodes in other UK nations. Moreover, deprivation data for patients outside England are only available at the practice level, which may lead to inaccuracies. The use of k-means clustering relies on predefining the expected number of clusters, impacting results. Despite efforts to mitigate these limitations, residual confounding may persist due to the observational nature of the study.

Patient or user group involvement

We work closely with the Asthma Centre UK Centre for Applied Research led by the University of Edinburgh which has a dedicated Patient and Public Involvement (PPI) group. Women living with asthma have been actively involved in helping identify and prioritise the research objectives in this protocol and the associated research grant application (where one of the coinvestigators (TJ) is a PPI expert). For this protocol, we conducted two interactive meetings attended by five women with asthma from across the UK. The preliminary idea was presented, and through substantial discussions, we collaboratively created the research objectives.

We will continue to work closely with the PPI group at all stages of the research study including commenting and refining the plain English summary and ensuring that the PPI group's perspectives are thoroughly embedded throughout the research plans. We will undertake regular meetings (already budgeted for in our grant awarded) with the PPI group to discuss the project as it progresses and supporting members to contribute to our understanding of the findings of the study. The PPI group will play an active part in developing the key messages from the study that are of interest to the people it impacts, and we will work together in disseminating our findings to the public via website, social media, conferences, and public engagement events around the study.

ETHICS AND DISSEMINATION

Ethics

CPRD holds ethics approval from the Health Research Authority (East Midlands—Derby, REC reference number 21/EM/065) to facilitate research using anonymised data.[28] Approval for this specific study was granted through CPRD's Research Data Governance process.[28]

Dissemination

We will report the findings of the study following the recommendations of Strengthening the Reporting of Observational Studies in Epidemiology and REporting of studies Conducted using Observational Routinely collected health Data statements. All the analysis source codes will be made available publicly at the GitHub website (https://github.com/syedahmar). Furthermore, we will capitalise on the dissemination infrastructures of the Asthma UK Centre for Applied Research (eg, the X feed and dynamic website) and the University of Gothenburg to publicise our findings to clinicians, academics, patients and reproductive health channels. We will ensure that during the reporting stage, we preserve confidentiality at the reporting stage and any cells that have a count of <5 count are protected through secondary suppression.

Author affiliations
[1]Usher Institute, The University of Edinburgh, Edinburgh, UK
[2]Krefting Research Centre, University of Gothenburg, Gothenburg, Sweden
[3]Division of Community Health Sciences, The University of Edinburgh, Edinburgh, UK
[4]The University of Edinburgh, Edinburgh, UK
[5]Asthma UK Centre for Applied Research, Edinburgh, UK
[6]Obstetrics and Gynaecology, The University of Edinburgh, Edinburgh, UK
[7]Center for National Health Insurance, Jeddah, Saudi Arabia

X Holly Tibble @hollytibble

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ORCID iDs
Holly Tibble http://orcid.org/0000-0001-7169-4087
Syed Ahmar Shah http://orcid.org/0000-0001-5672-0443

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