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Polycystic ovary syndrome, combined oral contraceptives and the risk of dysglycemia: a population-based cohort study with a nested pharmaco-epidemiological case-control study

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Abstract

Objectives: Irregular menstrual cycles are associated with increased cardiovascular mortality. Polycystic ovary syndrome (PCOS) is characterized by androgen excess and irregular menses; androgens are drivers of increased metabolic risk in women with PCOS. Combined oral contraceptives (COCPs) are used in PCOS both for cycle regulation and to reduce the biologically active androgen fraction. We examined COCP use and risk of dysglycemia (pre-diabetes and type 2 diabetes) in women with PCOS.

Research Design and Methods: Utilizing a large UK primary care database (The Health Improvement Network, THIN; 3.7 million patients from 787 practices), we carried out a retrospective population-based cohort study to determine dysglycemia risk (64,051 women with PCOS, 123,545 matched controls), as well as a nested pharmaco-epidemiological case-control study to investigate COCP use in relation to dysglycemia risk (2407 women with PCOS with [=cases] and without [=controls] a diagnosis of dysglycemia during follow-up). Cox models were used to estimate the unadjusted and adjusted hazard ratio and conditional logistic regression was used to obtain adjusted odds ratios (aORs).

Results: The adjusted hazard ratio for dysglycemia in women with PCOS was 1.87 (95% CI 1.78-1.97, $p<0.001$; adjustment for age, social deprivation, BMI, ethnicity, and smoking), with increased rates of dysglycemia in all BMI subgroups. Women with PCOS and COCP use had a reduced dysglycemia risk (aOR 0.72, 95% CI 0.59 to 0.87).

Conclusions: In this study limited by its retrospective nature and the use of routinely collected electronic general practice record data, which does not allow to exclude the impact of prescription-by-indication bias, women with PCOS exposed to COCPs had a reduced risk of dysglycemia

across all BMI subgroups. Future prospective studies should be considered to further understand these observations and potential causality.

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age (1) and is defined by irregular menses and androgen excess. Whilst previously mostly perceived as a reproductive disorder, PCOS is now recognized as a lifelong metabolic disorder with an increased prevalence of the cardiovascular risk factors insulin resistance, dyslipidemia and hypertension (2–4). An increased risk of type 2 diabetes in women with PCOS has been described in both cross-sectional (5) and cohort studies (5,6), the latter reporting a 2- to 4-fold increased risk, with type 2 diabetes diagnosed on average four years earlier in women with PCOS than in the background population (7). In a population-based cohort study, women with PCOS were also found to have an increased risk of non-alcoholic fatty liver disease (NAFLD), a significant hepatic complication of metabolic syndrome (3). A recently published prospective cohort study (8) in nearly 80,000 women with a follow-up period of 24 years described an increased risk of premature mortality, primarily due to cardiovascular disease, in women with irregular and long menstrual cycles, suggestive of PCOS as the major underlying risk factor.

Androgen excess is a cardinal feature of PCOS (1) and its severity has been shown to correlate with insulin resistance in cross-sectional studies (9–11). In the general population, type 2 diabetes risk in women increases with circulating androgen concentrations and decreasing concentrations of sex-hormone binding globulin (SHBG) (12–15). Endogenous androgen concentrations in women have also been identified as a risk factor for the development of NAFLD in PCOS, independent of body weight (3). Combined oral contraceptive pills (COCPs) are widely prescribed in women with PCOS for menstrual cycle regulation. In addition, COCPs can exert anti-androgen

effects through two distinct mechanisms. The estrogen component in COCPs increases the production of SHBG in the liver, thereby reducing the concentration of free testosterone capable of binding and activating the androgen receptor in target tissues of androgen action (16). Furthermore, some progestins used in COCPs can convey additional anti-androgenic action through androgen receptor blockade, namely cyproterone and drospirenone, while other progestins are pro-androgenic or exert no effect on the androgen receptor.

Data on the impact of COCP prescription on glucose metabolism in women are conflicting. Clinicians have previously raised concerns that COCP intake may adversely impact on glucose metabolism (17); however available evidence is limited by a lack of prospective studies, and by the confounding issue of higher ethinylestradiol content in historical formulations. Furthermore, a wide diversity of combined oral contraceptive formulations available, including differences in progestin components, makes an accurate assessment of the impact of COCP prescription on glycemia very challenging. A recent Cochrane library review concluded that current evidence suggests no significant impact on carbohydrate metabolism in women without PCOS, highlighting a paucity of large-scale prospective studies to adequately address the question (18). Conversely, it has been hypothesized that the impact of COCP on carbohydrate metabolism may be protective against incident dysglycemia, due to the impact both of raising SHBG levels and of partial androgen receptor blockade in selected formulations containing antiandrogenic progestins.

Here we tested the hypothesis that the use of COCPs decreases the risk of type 2 diabetes in women with PCOS. To this end, undertaking a population-based cohort study, we first determined the risk of incident dysglycemia, i.e. a composite outcome combining pre-diabetes and type 2 diabetes, in women with PCOS, and then examined in a nested pharmaco-epidemiological case-control study whether COCP intake impacts on this risk.

Research Design and Methods

Data Source

Datasets were derived from a UK primary care database, The IQVIA Medical Research Data (also known as The Health Improvement Network (THIN) database) has over 17 million patient records from 787 general practices (19). THIN uses Read codes, a hierarchical coding system for recording symptoms and diagnoses, and is highly suited for assessing chronic health conditions (3,12,20).

Study Population

Our study population were women aged 18 to 50 years during the study period (1st January 2000 to 31st January 2017). Women were eligible one year after registration with their general practice or from the time their practice became eligible for THIN participation (3).

Study designs

PCOS and incident dysglycemia: This matched cohort study considered women with PCOS as exposed. Exposure was ascertained by Read codes for "Polycystic ovary syndrome (PCOS)" or "Polycystic ovaries (PCO)" (3), as this composite code list reflects community prevalence (21). Each exposed woman was matched with up to two women without PCOS within the same general practice for age (±2 years) and body mass index (BMI; ±2 kg/m^2) (22,23).

Follow-up start date or the index date for the exposed patients were set to PCOS diagnosis date for incident PCOS patients or patient eligibility date for prevalent PCOS patients (patients with a diagnosis ahead of cohort entry). The index date for a matched control was set to the corresponding index date of the exposed patient to mitigate immortality time bias (24). Follow-up occurred until the earliest occurrence of: (1) outcome, (2) study end or (3) patient censorship denoted by death, deregistration from the practice, or practice withdrawing from the THIN database.

Outcomes were type 2 diabetes and dysglycemia, the latter defined as the composite outcome of prediabetes and type 2 diabetes, which were ascertained by Read codes and laboratory results (type 2 diabetes: HbA1c ≥6.5% (48 mmol/mol), fasting blood glucose ≥7 mmol/L; dysglycemia: HbA1c ≥6.0% (42 mmol/mol), fasting blood glucose ≥6 mmol/L, random blood glucose ≥11.1 mmol/L, and 2h OGTT indicated as "abnormal" or "high"). Patients with a recording of the outcome of interest (dysglycemia) or glucose lowering drug prescription at baseline were not eligible.

Risk factors of type 2 diabetes and dysglycemia among women with PCOS: To identify potential risk factors for the development of type 2 diabetes and dysglycemia within the PCOS cohort, we examined demographic risk factors, BMI, clinical features of androgen excess and prescription of COCPs at baseline as candidate risk factors.

Combined oral contraceptives and incident dysglycemia among women with PCOS: To define the impact of COCPs on dysglycemia risk, we conducted a nested case-control study. Women who developed dysglycemia during the follow-up period were cases and the remaining women were potential controls. One control per case was randomly selected after matching for age (±2 years), BMI (±2 kg/m^2), PCOS diagnosis date (±2 years) and whether PCOS was diagnosed before or after the patient became eligible to take part in the study. Index date was assigned as the date of diagnosis of dysglycemia for the cases and the same date was assigned to the corresponding control, ensuring comparable exposure window for matched case-control pairs and, therefore, avoiding time-window bias (25).

The exposure window was pre-specified and extended from one year prior to cohort entry, to avoid disregarding valid prescriptions in the immediate period after patient registration, and six months prior to index date, to exclude prescriptions that cannot be validly attributed to the development of dysglycemia.

COCP prescription was initially considered as a binary variable. COCP prescription was then categorized according to whether or not the respective progestin component exerts anti-androgen activity. Patients with no prescription of COCP formed the reference groups for both the categorical exposure variables.

Analysis

Crude incidence rates of the primary and secondary composite outcome (type 2 diabetes and dysglycemia) were estimated per 10,000 person-years. Unadjusted and adjusted hazard ratios (HRs) were obtained using Cox- model. Covariates for adjustment were selected based on biological plausibility for confounding. Covariates include age, BMI, socio-economic status, ethnicity, smoking status, record of hypertension, hypothyroidism and prescription of lipid lowering medications.

Socio-economic status was presented using Townsend score (26–28). Ethnicity was categorized based on UK 2011 census classification. Smoking status was categorized as currently smoking, discontinued and never smoked. Selection of Read Code lists exposure, outcome and covariates were based on methods and codes set out in previous publications (3,12,20,29) (**Suppl Table 1**). BMI was categorized as per WHO guidelines, with non-standard BMI categorization of South Asian women as per the recommended guidelines (30).

Sensitivity Analyses

Sensitivity analyses were performed to assess the extent of misclassification and survival bias. The exposure was, firstly, restricted to women with PCOS-specific diagnostic codes and, secondly, to those with a PCOS diagnosis during the study period (incident patients) (31).

In addition, in the nested-case control study, we investigated if control selection based on risk set sampling altered our findings, allowing a patient to serve as a control for multiple patients

diagnosed with dysglycemia while patients not diagnosed with dysglycemia at the similar time of follow-up could serve as controls before they developed dysglycemia.

Subgroup analyses

To check if risk of type 2 diabetes and dysglycemia are independent of BMI status, we conducted subgroup analyses within each BMI category.

Analyses for predictors of dysglycemia

In the cohort restricted to women with PCOS, Cox regression analysis was used to identify statistically significant predictors of type 2 diabetes and dysglycemia. In addition to covariates mentioned in the primary analysis, prescription of COCPs and variables characteristic of androgen excess and prescription of anti-androgen therapy with single agent drugs were also considered as candidate predictors.

Analysis of nested case-control study

Conditional logistic regression was performed to obtain unadjusted and adjusted ORs for dysglycemia based on exposure to COCP. The adjusted model included all covariates in the primary analysis, plus prescription of metformin and anti-androgen therapy.

Results

Study population characteristics

64,051 women with PCOS and 123,545 women without PCOS and matched for age, sex and general practice were included in the study (**Suppl. Figure 1, Table 1**). The median follow-up period was 3.5 years [interquartile range (IQR) 1.4-7.2 years]. Mean age of the whole cohort was 30.5 (SD 7.1) years, median BMI 25.6 (IQR 22.1-31.4) kg/m^2, respectively. Age, BMI, deprivation quintiles (Townsend index) and smoking status had no apparent imbalance in distribution between the two groups. Women with PCOS were more likely to be documented as South Asians (4.8 vs 2.9%), hypothyroid (3.4% vs 2.1%), and hypertensive (2.2% vs 1.6%) at baseline (**Table 1**). COCPs were prescribed for 43.4% of the PCOS exposed women before the index date; 22.5% of the women with PCOS were prescribed COCPs with an anti-androgenic progestin component (drospirenone or cyproterone acetate) (**Table 1**).

Risk of type 2 diabetes and dysglycemia

In the primary analysis, the incidence rate of type 2 diabetes among the exposed and the unexposed were 48.7 and 22.8 per 10,000 person years during a median follow-up of 3.39 (IQR 1.34-7.16) and 3.47 (IQR 1.39 - 7.18), respectively, equating to a doubling in risk of type 2 diabetes among women with PCOS (HR 2.13, 95% CI 1.98 to 2.29, p<0.001).

Adjustment for age, deprivation quintiles, BMI category, ethnicity, smoking status and hypothyroidism did not alter the estimated hazard ratio (aHR 2.04, 95% CI 1.89 to 2.20, p<0.001) (**Suppl. Table 2**).

When analysing the effect of PCOS on the composite outcome (dysglycemia), a similar effect was observed (aHR 1.87, 95% CI 1.78 to 1.97, p<0.001). The incidence rates of dysglycemia were 96.3

and 49.4 per 10,000 person years among women with and without PCOS during a median follow-up of 3.32 (IQR 1.32-7.03) and 3.44 (IQR 1.38 - 7.11), respectively (**Suppl. Table 2**).

Sensitivity analysis

The strength of association between PCOS and type 2 diabetes did not decrease when the analysis was restricted to women with incident diagnosis of PCOS (aHR 1.98, 95% CI 1.70 to 2.31, p<0.001) and to women with PCOS-specific codes (aHR 2.17, 95% CI 1.88 to 2.51, p<0.001). This was similarly observed for dysglycemia (Incident cohort: aHR 1.95, 95% CI 1.76-2.16, p<0.001; PCOS-specific cohort: aHR 1.93, 95% CI 1.75 to 2.13, p<0.001) (**Suppl. Table 2**).

Subgroup analysis stratified by BMI

In subgroup analyses, women with PCOS had an increased risk of type 2 diabetes in all BMI categories compared to women without PCOS in the same BMI category (Normal/Underweight category - BMI <23 kg/m^2 among women of South Asian ethnicity / <25 kg/m^2 among women of all other ethnic groups aHR 1.88, 95% CI 1.42 to 2.51, p<0.001; Overweight category - BMI 23-27.5 kg/m^2 among women of South Asian ethnicity / 25-29.9 kg/m^2 among women of all other ethnic groups: aHR1.92, 95% CI 1.56 to 2.35, p<0.001; Obesity category - BMI ≥27.5 kg/m^2 among women of South Asian ethnicity/ ≥30 kg/m^2 among women of all other ethnic groups: aHR 1.88, 95% CI 1.72 to 2.06, p<0.001) (**Figure 1A**). Similar findings were observed for the composite outcome (dysglycemia) (**Figure 1A**).

Risk factors for type 2 diabetes and dysglycemia among women with PCOS

When analyzing the cohort of women with PCOS to identify risk factors for type 2 diabetes, PCOS-specific variables emerged as significant risk factors, namely anovulation (aHR 1.21, 95% CI 1.08 to 1.35. p=0.001) and hirsutism (aHR 1.20, 95% CI 1.05 to 1.36, p=0.007). Conversely, prescription of COCPs emerged as a protective factor, with similar effects observed for COCPs

with (aHR 0.84, 95% CI 0.73 to 0.97, p=0.020) and without an anti-androgenic progestin component (aHR 0.83, 95% CI 0.72 to 0.94, p=0.005). The same risk factors and protective factors were observed for the composite dysglycemia outcome (**Suppl. Table 3**).

Nested case-control analysis - the effect of oral contraceptives on risk of dysglycemia

Of the 64,051 women with PCOS in the base cohort, 0.45% (n=2,885) developed dysglycemia during follow-up who were assigned as the cases in the nested case-control study (**Table 2**). The remaining 61,166 (95.5%) women were considered as potential controls. 478 cases could not be matched to a control based on age, BMI, PCOS diagnosis date and incident/prevalent status of PCOS diagnosis. Therefore, our final analysis included 2,407 cases and corresponding 2,407 matched controls.

Mean age at index date was 38.9 (8.3) years and mean age at PCOS diagnosis was 28.8 (14.4) years and was similar between cases and controls. BMI at cohort entry was similarly distributed between cases and controls (mean (SD) 32.7 (7.0) vs 32.6 (7.0) kg/m^2). Compared to controls, cases were more likely to be from a deprived background (Townsend 5: 17.0% vs 12.3%), more likely to be smokers (26.6% vs 20.8%) and of South Asian ethnicity (10.0% vs 3.2%). At cohort entry, there was also a higher proportion of cases with concurrent hypothyroidism (10.6% vs 7.8% in controls). Altogether, 679 (28.2%) cases and 815 (33.9%) controls were prescribed COCPs during the exposure window. Among those prescribed COCPs, the median COCP prescription count per person during the exposure window was 3 (IQR 1 to 7).

When adjusted for age, smoking status, BMI category, ethnicity, Townsend score, baseline hypothyroidism, hypertension and prescription of isolated anti-androgen drugs, metformin and lipid lowering medication at baseline, women with PCOS exposed to COCP were seen to have a reduced risk of dysglycemia (aOR 0.74, 95% CI 0.65 to 0.85, p<0.001). For every issued COCP

prescription recorded within the exposure window, there was a 2% reduction in the odds of dysglycemia (aOR 0.98, 95% CI 0.96 to 0.99, p=0.004) (**Figure 1B**).

When COCP prescription issue count was categorized as (1) no prescription, (2) prescription count ≤3, and (3) prescription count >3 within the exposure window, a dose-responsive reduction in the risk of dysglycemia was observed (in reference to no prescription of COCP, aOR of dysglycemia when prescription count ≤3 = 0.80, 95% CI 0.67 to 0.96, p=0.017 and aOR when prescription count >3 = 0.67, 95% CI 0.55 to 0.81, p<0.001) (**Figure 1B**).

Women with PCOS exposed to COCPs had a reduced risk of dysglycemia irrespective of the type of progestin component (COCPs with anti-androgenic progestin: aOR 0.76, 95% CI 0.63-0.91, p=0.003; COCPs with progestin without anti-androgen activity: aOR 0.72, 95% CI 0.59-0.87; p<0.001) (**Figure 1B**, **Suppl. Table 4**).

Metformin prescription within the exposure window period was associated with increased risk of dysglycemia (metformin: aOR 1.50, 95% CI 1.24 to 1.81, p<0.001), suggestive of possible prescription-by-indication bias for those at increased risk. Findings in the sensitivity analysis incorporating a risk set sampling approach showed a similar result (aOR 0.76, 95% CI 0.63 to 0.91, p=0.003).

Conclusions

Employing a rigorous nested case-control pharmaco-epidemiological analysis we found that women with PCOS exposed COCPs had a reduced risk of developing dysglycemia across all BMI subgroups. Our study is also the largest to report glycemic outcomes in a primary care cohort of women with PCOS, demonstrating a two-fold increased risk of incident type 2 diabetes and dysglycemia in women with PCOS of any BMI.

Our finding of an increased type 2 diabetes risk in women with PCOS is consistent with recent population studies from Denmark and Finland (7,32) and hospitalization data from Australia (33), all reporting a 2- to 4-fold increased type 2 diabetes risk in PCOS. Using the Australian Longitudinal Study on Women's Health, Kakoly et al. demonstrated that a diagnosis of PCOS was one of the most influential predictors of incident type 2 diabetes in women, even after adjusting for BMI and family history (34). Few population studies have looked specifically at the composite outcome of dysglycemia, which takes into account a spectrum of impaired glucose regulation ranging from impaired glucose tolerance and impaired fasting glucose through to overt hyperglycemia (35,36). Crucially, our data highlight that normal weight women with PCOS were also at increased risk of type 2 diabetes and dysglycemia. This parallels our previous finding of increased NAFLD risk in normal weight women with PCOS (3), further challenging the notion that PCOS-related metabolic complications are only relevant in the context of obesity.

These data suggest that, rather than obesity in isolation, PCOS-specific factors, including androgen excess, underpin the increased metabolic risk. Our study found that those women with PCOS and hirsutism, a clinical feature of androgen excess, had a further increased risk of dysglycemia. In a population-based cohort study using the same primary care population database, we previously documented an independent link between serum testosterone and incident diabetes risk in women

(12). We demonstrated that the risk of incident T2DM increased significantly in women with a serum testosterone levels above 1.5nmol/l compared to the reference cohort with levels <1nmol/l; the risk was two-fold higher in women with serum testosterone values >3.5nmol/l. We also demonstrated in a small cross-sectional cohort study that women with increased circulating androgen concentrations had a higher risk of an abnormal oral glucose tolerance test (OGTT) result, with the OGTT-derived insulin sensitivity index (ISI) correlating inversely with circulating androgen burden (9). A recent meta-analysis (37) demonstrated that women with increased serum testosterone had a 60% higher risk of type 2 diabetes than women with normal testosterone levels. Furthermore, a recent large-scale genome association study in 425,097 participants of the UK biobank demonstrated that the risk of type 2 diabetes in women increased in line with increasing circulating testosterone concentrations (15).

The association between female androgen excess, insulin resistance and type 2 diabetes is undoubtedly complex. Insulin resistance promotes androgen excess by upregulating ovarian androgen generation and peripheral androgen activation in adipose tissue (38,39); the latter increases lipid accumulation in the adipocyte and, once adipocyte lipid storage capacity is exhausted, fatty acid overspill (39), which is intricately linked to metabolic dysfunction. Abnormalities in skeletal muscle metabolic function have also been described in PCOS, with altered muscle mitochondrial energy biogenesis in the context of androgen excess likely to drive disturbances in glucose metabolism (40,41). Rodent-based studies also support a direct role for androgens in pancreatic beta-cell dysfunction, driving insulin hypersecretion, oxidative injury and consequent beta cell failure (42). These data have recently been underpinned by a study utilizing human pancreatic islets, demonstrating that intracrine activation of testosterone to the most potent androgen, 5α-dihydrotestosterone (DHT) increases glucose-stimulated insulin secretion (43).

A recent cohort study (8) in nearly 80,000 women with a follow-up period of 24 years described an increased risk of premature mortality, primarily due to cardiovascular disease, in women with irregular cycles. COCPs are routinely used for menstrual cycle regulation in women with PCOS. Our study is the first population-based study investigating the hypothesis that COCPs might mitigate the risk of dysglycemia in women with PCOS, with anti-androgen activity conferred by an estrogen-mediated increase in SHBG as the proposed mechanism. Studies examining the impact of COCPs on glucose metabolism have reported conflicting results and most are limited by small participant numbers and significant heterogeneity in COCP use. A 2016 Korean population study of 6,554 postmenopausal women found those who took the COCP during their reproductive years for more than 6 months had a 37% increased risk of T2DM (44). However, a more recent study examining the NHANES database between 2007 and 2018 found that COCP use in over 6,000 women aged 35-50 years who met matching criteria had a 29% reduced risk of T2DM compared to never-users (45). A further limitation is the tendency in previous studies to extrapolate data from otherwise healthy female patient groups to women with PCOS, who are likely to manifest a biologically distinct set of risk factors for dysglycemia. The first cohort of the Nurses' Health Study followed 2276 healthy women for a median of 12 years from 1976 and found that risk of type 2 diabetes was increased by 10% in women with previous COCP use compared to those who never took the medication (46); however, these data reflect the use of older COCP preparations with higher ethinylestradiol concentrations between the 1970s and 1990s. A recent Cochrane library review found no convincing evidence of glycemic risk associated with COCP prescription in women without PCOS (18), while a 2011 meta-analysis of the limited evidence in women with PCOS suggested neither adverse nor beneficial impact of COCPs on glucose homeostasis (47). A 2017 systematic review and meta-analysis highlighted the urgent need for further studies to

understand the relationship between glucose metabolism and COCP use in both lean and obese women with PCOS (48). Our study improves our understanding in this regard and indicates the need for prospective, randomized controlled trials on the impact of COCPs on the risk of type 2 diabetes and dysglycemia. We found that following adjustment for confounding factors women with PCOS and COCP use had a 27% reduction in the relative risk of incident dysglycemia, with the highest reduction in patients receiving higher numbers of COCP prescriptions. When analyzed separately, women with PCOS and COCP use had a similarly reduced risk of dysglycemia when exposed to COCPs with and without anti-androgenic progestin components, suggesting that the estrogen-induced increase in SHBG may be the primary driver of the risk-mitigating effect. However, this finding is potentially limited by the lower number of patients receiving anti-androgenic COCPs. Cyproterone acetate and drospirenone are progestins with anti-androgenic properties, as opposed to progestins such as desogestrel or levonorgestrel which have neutral or pro-androgenic effects (49). While cyproterone acetate and drospirenone exert anti-androgen activity via androgen receptor blockade, their anti-androgen activity is considerably smaller than recently approved novel anti-androgens mainly employed in the treatment of prostate cancer (50). Our finding that women using metformin and women using single agent anti-androgen therapy had an increased risk of incident dysglycemia is very likely reflective of a confounding-by-indication bias (51). Accordingly, the women with PCOS at highest risk of dysglycemia based on metabolic or androgen phenotype may have been systematically prescribed metformin and single agent anti-androgen therapy. It is possible that our observation of reduced dysglycemia risk in women with PCOS on COCPs may also reflect a prescription-by-indication bias, whereby those women with cardiovascular risk factors such as obesity, dyslipidemia and hypertension were less likely to have been prescribed the COCP. However, we believe that this is less likely from closer

review of the data; in our nested pharmaco-epidemiological study, 26% of women had a BMI in the obese range, and one quarter of women with a BMI above 35kg/m^2 took COCPs during the follow up period. We have also carefully adjusted our analysis for metabolic phenotype by including BMI, hypertension and dyslipidemia as variables.

Our study has a number of notable limitations, including the above-mentioned prescription-by-indication bias issues, and others that are common to retrospective data using electronic general practice databases. The definition of women with no PCOS was based on the absence of any Read code in relation to PCOS and not on systematic diagnostic assessment to exclude PCOS. Therefore, the proportion of women with PCOS was also much lower than the published community prevalence data for PCOS (52). Another limitation is that we used the Read code for polycystic ovaries (PCO) as indicative of PCOS. However, in a sensitivity analysis limited to women with PCOS Read codes we documented similar findings, excluding the use of the PCO Read code as a significant limitation. Higher testing rates for type 2 diabetes among women with PCOS may also have resulted in over-estimating the effect size, however, the effect size observed for type 2 diabetes in our study is similar to existing literature (53). It was also not possible to adjust for more specific lifestyle factors such as physical activity, energy intake or fibre consumption within a large population database as utilized in the present study. To explore the possibility of right censoring bias, the median follow-up and the loss to follow-up pattern was compared between patients with and without PCOS. There was no systematic difference observed between the two groups and therefore the assumption of non-informative censoring was reasonable for the time-to-event analysis in this study, limiting the possibility of right censoring bias.

In conclusion, we demonstrated that women with PCOS have a significantly increased risk of dysglycemia that persisted after adjusting for BMI, corroborating the recommendation that women

with PCOS should be systematically screened for type 2 diabetes irrespective of body weight category. In our nested pharmaco-epidemiology study, we found that women with PCOS and exposure to COCPs had a lower risk of incident dysglycemia. Though the limitations of our study design preclude ascertainment of causality, we hypothesize that a beneficial effect of COPs might be conveyed by an estrogen-induced increase in hepatic SHBG production. This increase would result in a decrease in the biologically active, unbound circulating androgen fraction and this reduction in androgen excess could have metabolically beneficial effects including a decrease in risk of dysglycemia. However, to definitively establish causality a large-scale randomized trial evaluating the efficacy of COCPs in reducing the risk of dysglycemia in women with PCOS would be required, with careful comparison of the potential additional benefit of COCPs containing anti-androgenic progestin components.

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Author Contributions

KN, WA, BK and MOR developed the research question and designed the study; LA and DS contributed to the design of the study. KN, WA, BK, MOR and AS designed the analysis, interpreted the results, and drafted the manuscript. LA and DS contributed to the design of the study. All authors reviewed and revised the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict-of-interest Statement

The authors declare that there are no relevant conflicts of interest to disclose.

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Figure Legends

Figure 1: Risk of type 2 diabetes and dysglycemia among 64,051 women with PCOS compared to 123,545 matched controls and according to BMI subgroup (population-based cohort study; Panel A). Adjusted odds ratio (aOR) for risk of dysglycemia according to the prescription of combined oral contraceptive pills (COCPs) (Panel B) overall and according to prescription counts and type of progestin component, respectively, in the nested pharmaco-epidemiological case-control study **(**2407 women with PCOS with a diagnosis of dysglycemia during follow-up [=cases] and 2407 women with PCOS without a diagnosis of dysglycemia [=controls]).

Table 1: Baseline characteristics of participants of the population-based cohort study stratified by their PCOS exposure status.

	Women with PCOS (n=64,051)	Women without PCOS (n=123,545)
Age in years [Mean (SD)]	30.4 (7.0)	30.5 (7.1)
BMI in kg/m^2 [Median (IQR)]	25.9 (22.2-31.9)	25.4 (22.0-30.8)
BMI Categories in kg/m^2 [n (%)]*		
Normal/Underweight	23,490 (36.6)	48,360 (39.1)
Overweight	12,734 (19.8)	25,229 (20.4)
Obese	17,591 (27.5)	29,907 (24.2)
Missing	10,236 (16.0)	20,049 (16.2)
Smoking status [n (%)]		
Non-smoker	37,311 (58.3)	71114 (57.6)
Discontinued	9,044 (14.1)	16,285 (13.2)
Smoker	14,674 (22.9)	28,284 (22.9)
Missing	3,022 (4.7)	7,862 (6.4)
Ethnicity [n (%)]		
Caucasian	30,597 (47.8)	50.206 (40.6)
Black	1,464 (2.3)	2,636 (2.1)
Chinese	582 (0.91)	883 (0.7)
South Asian	3,085 (4.8)	3,517 (2.9)
Mixed Race	897 (1.4)	1645 (1.3)
Missing	27,426 (42.8)	64,658 (52.3)
Townsend deprivation score [n (%)]		
1 (least deprived)	11,270 (17.6)	21,839 (17.7)
2	10,280 (16.1)	19,866 (16.1)
3	12,064 (18.8)	23,471 (19.0)
4	11,530 (18.0)	22,623 (18.3)
5 (most deprived)	8,182 (12.8)	16,186 (13.1)
Missing	10,725 (16.7)	19,560 (15.8)
Baseline comorbidity [n (%)]		
Hypothyroidism	2172 (3.4)	2585 (2.1)
Hypertension	1420 (2.22)	2030 (1.64)
Baseline medication [n (%)]		
Any COCP	27,768 (43.4)	66,332 (53.7)
COCP without anti-androgenic progestin	25,481 (39.8)	64,157 (51.9)
COCP with anti-androgenic progestin	14,437 (22.5)	12,336 (10.0)
Drospirenone	4,944 (7.7)	6,550 (5.3)
Cyproterone	11,069 (17.3)	7,305 (5.9)
Single agent anti-androgen therapy¬		
Cyproterone	444 (0.69)	
Other anti-androgen drugs^	42 (0.07)	
Lipid lowering medication	410 (0.64)	534 (0.43)

BMI - Body mass index; COCP - Combined Oral Contraceptive Pill; *Normal/Underweight: <23.5 kg/m² for patients of South Asian ethnicity & <25 kg/m² for patients of all other ethnic groups, Overweight: 23.5-27.5 kg/m² for patients of South Asian ethnicity & 25-30 kg/m² for patients of all other ethnic groups, Obese = ≥27.5 kg/m² for patients of South Asian ethnicity & ≥30 kg/m² for patients of all other ethnic groups; ^includes dutasteride, enzalutamide, finasteride, flutamide, and spironolactone ; ¬ PCOS relevant variables summarized only for the PCOS exposed cohort; NOTE: Patients with impaired glucose regulation or glucose lowering drug prescription at baseline not included in the cohort

Table 2: Baseline characteristics of women with PCOS included in the nested case-control study. Cases and controls are matched women with and without a diagnosis of dysglycemia during follow-up, respectively.

Variable	Women with PCOS and a diagnosis of dysglycemia (Cases) (n=2407)	Women with PCOS and without a diagnosis of dysglycemia (Controls) (n=2407)
Age at index date (dysglycemia diagnosis for cases) [Mean (SD)]	38.89 (8.32)	38.84 (8.27)
Age at PCOS diagnosis [Mean (SD)]	28.84 (14.43)	28.76 (14.00)
BMI (kg/m^2) [Mean (SD)]	32.72 (6.98)	32.59 (7.03)
BMI Categories [n (%)]		
Normal/Underweight	270 (11.2)	305 (12.7)
Overweight	439 (18.2)	437 (18.2)
Obese	1322 (54.9)	1289 (53.5)
Missing	376 (15.6)	376 (15.6)
Townsend deprivation score [n (%)]		
1 (least deprived)	351 (14.6)	481 (20.0)
2	359 (14.9)	436 (18.1)
3	473 (19.7)	457 (19.0)
4	471 (19.6)	420 (17.5)
5 (most deprived)	408 (17.0)	295 (12.3)
Missing	345 (14.3)	318 (13.2)
Smoking status [n (%)]		
Non-Smoker	1306 (54.3)	1354 (56.3)
Discontinued	295 (12.3)	362 (15.0)
Smoker	639 (26.6)	501 (20.8)
Missing	167 (6.9)	190 (7.9)
Ethnicity [n (%)]		
Caucasian	999 (41.5)	1099 (45.7)
Mixed Race	38 (1.6)	21 (0.87)
Chinese/middle eastern/others	21 (0.87)	13 (0.54)
Black	80 (3.3)	40 (1.7)
South Asian	241 (10.0)	77 (3.2)
Missing	1028 (42.7)	1157 (48.1)
Concurrent Conditions at baseline [n (%)]		
Hypothyroidism	256 (10.6)	188 (7.8)
Hypertension	623 (25.88)	179 (11.59)
Prescription of drugs within the exposure time window [n (%)]		
Contraceptives		
No Pill	1728 (71.8)	1592 (66.1)

COCP without anti-androgenic progstin	301 (12.5)	389 (16.2)
COCP with anti-androgenic progestin*	378 (15.7)	426 (17.7)
Single agent anti-androgen therapy ^	41 (1.7)	23 (0.96)
Metformin	417 (17.3)	330 (13.7)
Lipid lowering medication	150 (6.23)	119 (4.94)

BMI - Body mass index; COCP - Combined Oral Contraceptive Pill; *Normal/Underweight: <23.5 kg/m² for patients of South Asian ethnicity & <25 kg/m² for patients of all other ethnic groups, Overweight: 23.5-27.5 kg/m² for patients of South Asian ethnicity & 25-30 kg/m² for patients of all other ethnic groups, Obese = ≥27.5 kg/m² for patients of South Asian ethnicity & ≥30 kg/m² for patients of all other ethnic groups; *cyproterone acetate/drospirenone; ^cyproterone acetate/flutamide/finasteride