# Weight Gain and Dyslipidemia in Early Adulthood Associate with Polycystic Ovary Syndrome: Prospective Cohort Study

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***Abbreviated title:*** Weight gain through life and PCOS

***Key terms:*** Polycystic ovary syndrome, body mass index (BMI), weight gain, hyperandrogenism, free androgen index (FAI).

***Word count: 3582***

***Number of figures and tables: 6***

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**Grants and funding:** The Finnish Medical Society Duodecim, the North Ostrobothnia Regional Fund, the Academy of Finland (Project grants 104781, 120315, 129269, 1114194, 24300796), the Sigrid Juselius Foundation, Biocenter Oulu, Oulu University Hospital and University of Oulu (75617), Medical Research Center Oulu, National Institute for Health Research (UK), Medical Research Council (UK).

**Disclosure statement:** The authors have nothing to disclose.

**Abstract**

**Context:** Obesity affects the majority of women with polycystic ovary syndrome (PCOS), but previous studies are inconsistent about the prevalence of obesity and the importance of weight gain in the development of the syndrome.

**Objective:** To explore the association between weight, weight gain, hyperandrogenism and PCOS from adolescence to late adulthood.

**Design:** A prospective Northern Finland Birth Cohort 1966 study including 5889 females born in 1966 and followed at the ages of 14, 31 and 46 years.

**Setting:** General community.

**Participants:** Women presenting both oligo/amenorrhea (OA) and hirsutism (H) at age 31 (N=125) or with formally diagnosed PCOS by age 46 (N=181) were compared with women without PCOS symptoms or diagnosis (n=1577).

**Interventions:** None.

**Main Outcome Measures:** Body-mass-index (BMI), weight change through life, waist circumference, Free Androgen Index (FAI), lipids, glucose, insulin, high-sensitivity C-reactive protein (hs-CRP), homeostatic model assessment for insulin resistance (HOMA-IR) and PCOS.

**Results:** Women with OA+H at age 31 or diagnosis of PCOS by age 46 had the highest BMI at all ages compared with the controls. Increase of BMI between ages 14 and 31, but not between 31 and 46, was greater in women with isolated OA (*P*=.006), OA+H (*P*=.001) and diagnosis of PCOS (*P*=.001) compared with controls. In the multivariate analysis, PCOS was significantly associated with BMI at all ages (BMI at age 31: OR=1.05 [95%CI: 1.00-1.10], FAI (OR=1.08 [95%CI: 1.03-1.14]), serum levels of insulin (OR=1.05 [95%CI: 1.00-1.09]) and triglycerides (OR=1.48 [95%CI: 1.08-2.03]).

**Conclusions:** Symptoms or diagnosis of PCOS are associated with dyslipidemia, hyperandrogenemia and significantly increased weight gain especially in early adulthood. This observation is important as it may identify a sensitive time period when weight gain plays a crucial role in the emergence of

PCOS and when preventive actions against metabolic and cardiovascular diseases should be implemented.

## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in premenopausal women, affecting 6-18% of reproductive aged women, depending on the source population and the diagnostic criteria (1,2). According to the Rotterdam criteria, PCOS is defined by the presence of at least two of the following three features: menstrual irregularities (oligo- or anovulation), hyperandrogenism (clinical and/or biochemical) or polycystic ovaries (PCO), after excluding other etiologies (3). PCOS is known to have multiple unfavorable effects on women's health probably as a consequence of both hyperandrogenism (4) and insulin resistance (3,5,6). In some reported series, more than 50 percent of PCOS women are obese, and abdominal obesity and increased visceral fat distribution are common among these women (7). However, the prevalence of obesity in reported series is widely variable, probably reflecting the nature of presenting symptoms and therefore the specialist clinic to which women with PCOS may be referred. Adipose tissue, particularly visceral adipose, is an active metabolic and endocrine organ (8) and obesity significantly exacerbates all metabolic and reproductive disturbances of the syndrome (9). Excess adiposity is associated with insulin resistance and compensatory hyperinsulinemia, and leads to decreased sex-hormone binding globulin (SHBG) synthesis in the liver and excessive androgen production in the ovaries, which all contribute to an hyperandrogenic state (7). Visceral obesity increases the risk of impaired glucose tolerance and type 2 diabetes mellitus (T2DM), metabolic syndrome and cardiovascular morbidity, and that is particularly the case in women with PCOS (10-12). Previous studies have demonstrated that women with PCOS have a worse metabolic profile, including elevated triglyceride levels that are already apparent at a young age and are independent of obesity (12,13)

Although it is well known that obesity exacerbates PCOS symptoms and increases the risks for T2DM and cardiovascular diseases (6), the results of previous studies have been inconsistent regarding the association between weight, weight gain and prevalence of PCOS during reproductive life. Some data suggest that the adverse outcomes are mainly related to obesity (14), whereas others claim that the syndrome *per se* is the most important factor (15,16). However, many studies have been underpowered and most of them are cross-sectional, using hospital-based populations and focusing

only on obese subjects and/or women seeking for infertility treatment, and thus possibly not representing the general population. If obesity is a trigger or contributing factor for the development of PCOS in patients pre-disposed to the condition, it would be expected that the dramatic worldwide increase of obesity not only in adulthood, but also in childhood and adolescence, (17,18) would result in an increasing prevalence of PCOS with its significant health and economic burdens.

Our previous study from the Northern Finland Birth cohort 1966 (NFBC66) reported the association between body mass index (BMI) from birth to early adulthood and self-reported PCOS symptoms at age 31 (19). That study showed the importance of obesity in adolescence and in early adulthood, and crucial role of weight gain in early adulthood, in predicting PCOS symptoms at age 31. The present study had two main aims. First, by using the same study population as in the above mentioned study, to extend the follow-up time of the weight change in women with self-reported symptoms in early adulthood (31 years) or diagnosis of PCOS until late adulthood (46 years) and to compare it with the changes in weight over the same time period in healthy women. The second aim was to identify the most significant clinical, metabolic and hormonal indices in early adulthood (at age 31) that are associated with the diagnosis of PCOS by age 46.

## Materials and Methods

### Study subjects

This study is based on a unique, large, longitudinal, prospective, population-based NFBC66, comprising all expected births in 1966 in the two northernmost provinces of Finland. The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. All participants provided an informed consent.

In 1966, 5889 females were born alive. Enrollment in this database begun at the 24$^{th}$ gestational week and, so far, data collection points have been established at ages 14, 31 and 46 (Figure 1). At age 14, the adolescent females (n=5455, response rate 95%) answered a postal questionnaire, with the help of their parents, including questions about weight and height. No other clinical data were collected at that age.

At age 31, a postal questionnaire was sent to 5608 women and 4523 (81%) of them answered. The questionnaire included questions about weight and height and two questions on excessive body hair and oligoamenorrhea: 1) is your menstrual cycle longer than 35 days more than twice a year and 2) do you have excessive body hair? Pregnant women, women using hormonal contraception (n=1459) and women not permitting use of their data (n=41), were excluded from the analyses. Isolated oligoamenorrhea (isOA) was reported by 11.2% (n=330) of the women who returned the questionnaire, 10.9% (n=321) reported isolated hirsutism (isH) and 4.2% (n=125) reported both of these symptoms (OA+ H) (Figure 1). The validity of this questionnaire to distinguish PCOS cases has already been shown in our previous studies from the same cohort as the women with both OA+H present the typical metabolic and hormonal profile of PCOS (20,21).

In addition to this questionnaire, 4074 women living in Northern Finland or in the Helsinki metropolitan area were invited to a clinical examination. In total, 3127 (76%) women participated in a clinical examination including anthropometric measurements and blood samples for hormonal and metabolic parameters. Body mass index (BMI) was calculated as the ratio of weight (kg) and height squared ($m^2$). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest.

At age 46, a questionnaire covering several health aspects and an invitation to clinical examination was sent. 5123 women received the questionnaire and 3706 (72%) of them answered. The questionnaire included a question “Have you ever been diagnosed as having polycystic ovaries (PCO) and/or polycystic ovary syndrome (PCOS) during your life?” and 181 “yes” (considered as women with diagnosis of PCOS). The control group included all other women without any PCOS symptoms at age 31 and without diagnosis of PCOS at age 46 (n=1577).

Furthermore, 3280 women (64.0%) participated in the clinical examinations (anthropometric measurements and blood samples).

The flowcharts of the study are presented in Figures 1 and 2.

**Laboratory methods**

At age 31, plasma glucose, and serum concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol), low-density lipoprotein cholesterol (LDL-cholesterol), triglycerides, fasting insulin, high sensitivity C-reactive protein (hsCRP) and sex hormone binding globulin (SHBG) were all assayed as previously described (20). Serum samples for testosterone (T) were assayed using Agilent triple quadrupole 6410 LC/MS equipment with an electrospray ionization source operating in positive-ion mode (Agilent Technologies, Wilmington, DE, USA). Multiple reaction monitoring was used to quantify testosterone by using d3-testosterone, with the following transitions: m/z 289.2 to 97 and 289.2 to 109 for T and 292.2 to 97 and 292.2 to 109 for d3-testosterone. The intra-assay CVs of the method were 5.3%, 1.6% and 1.2% for Tat 0.6, 6.6 and 27.7 nmol/l, respectively. The interassay CVs were 5.3%, 4.2% and 1.0% for the respective concentrations. The free androgen index (FAI) was calculated by using the equation 100×T (nmol/l)/SHBG (nmol/l). To quantify the degree of insulin sensitivity, homeostasis model assessment (HOMA-IR) values were calculated using the validated calculator available at http://www.dtu.ox.ac.uk.

BMI values at ages 31 and 46 from clinical examination and postal questionnaire were combined to create a variable where clinically measured BMI was used if available and self-reported BMI was used in other cases. The data were also analyzed using only self-reported or only clinically measured BMI values, and the results were comparable. Women were categorized into BMI groups by WHO criteria for normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$) and obese (BMI $\geq$ 30.0 kg/m$^2$) (22).

**Statistical methods**

Differences in continuous anthropometric parameters were analyzed by non-parametric Mann-Whitney U-test due to the skewed distribution of variables and the differences in categorical parameters (prevalence of overweight and obesity) by Pearson's Chi-squared test. Binary logistic regression modelling was used to determine the parameters associated with diagnosis of PCOS. We included into the multivariate binary logistic regression modelling the parameters significantly associated ($P$<.15) with the diagnosis of PCOS (23). FAI was used in the models as it is generally considered as the best indicator for biochemical hyperandrogenism in PCOS women (3). HOMA-IR

was selected for the multivariate modelling in order to estimate insulin resistance, providing information from both glucose and insulin levels, and the serum levels of LDL and triglycerides were included to the models as they are the most typical lipid disorders observed in women with PCOS and linked to cardiovascular risks (6). The maximum number of variables was limited to 5 in each model. Results were reported as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Drop out analyses were performed to study any differences between women who only participated in the 31year study (both questionnaire and clinical examination) and the follow-up women participating in both the 31 and 46 year studies (at 31 years: both postal questionnaire and clinical examination; at 46 years: a postal questionnaire or a clinical examination or both).

Statistical analyses were performed using IBM SPSS Statistics 22.0 (SPSS, Inc., 1989, 2013, IBM Corp.). *P*-value < .05 was considered statistically significant.

**Results**

***BMI and BMI change from adolescence (14 years) to late adulthood (46 years) in women with symptoms or diagnosis of PCOS***

Women with self-reported OA+H at age 31 as well as women with diagnosis of PCOS by age 46 had significantly greater BMI values and greater prevalence of obesity compared with the control women at all three time-points (14, 31 and 46 years) (Table 1 and Figures 3 and 4). These women exhibited also significantly greater abdominal obesity, measured by waist circumference, both at age 31 and 46 compared with the control women ($P < .001$ for both comparisons) (Table 1).

Women presenting with isOA or isH at age 31 had significantly greater BMI at ages 14, 31 and 46 as well as greater abdominal obesity. These women also presented more often with overweight and obesity than the control women (Table 1, Figures 3 and 4).

The weight change between ages 14 and 31 was significantly greater in women with self-reported OA+H, isOA and in women with diagnosis of PCOS by age 46 compared with the change in the control women between ages 14 and 31, but this was not the case between ages 31 and 46 (Table 1, Figure 4). Of note, women presenting with both OA+H at age 31 and the women with both symptoms at age 31 and diagnosis of PCOS at age 46 exhibited the greatest prevalence of obesity

and the most important weight gain from adolescence to late adulthood (Figures 3 and 4 and Supplemental Fig. 1).

Women with both isOA at age 31 and diagnosis of PCOS by age 46 had significantly greater BMI at age 14 ($P$ = .009), 31 ($P$ < .001) and 46 ($P$ = .002) when compared with the women with isOA at age 31 but without diagnosis of PCOS by age 46. Women with both isH at age 31 and diagnosis of PCOS by age 46 did not significantly differ as regards of BMIs or change of BMI when compared with women with isH at age 31 and without diagnosis of PCOS by age 46 (Supplemental Fig. 1).

The subgroup of women without any symptoms at age 31 but with diagnosis of PCOS by age 46 (n=33) had similar BMI as the control group at ages 14 (19.15±1.9 vs. 19.08±2.4 kg/m$^2$) and 31 (24.22±4.0 vs. 23.61±4.2 kg/m$^2$), but their BMI was significantly greater at age 46 (28.24±5.4 vs. 26.34±5.3 kg/m$^2$, $P$ = .028).

***Risk factors for reporting diagnosis of PCOS by age 46***

Univariate and multivariate binary logistic regression analyses were used to reveal the association of different parameters at age 31 with diagnosis of PCOS by age 46 (Table 2).

*Univariate analysis*

As expected, both isOA (OR=9.32 [95%CI: 5.75-15.12]) and isH (OR= 7.80 [95%CI: 4.69-12.97]) were the most significant indices that were associated with diagnosis of PCOS by age 46. Furthermore, BMI at all three time points, as well as waist circumference at ages 31 and 46, were also significantly associated with the diagnosis of PCOS. Of these, BMI at age 31 was the strongest predictor (highest $R^2$-value .028). Importantly, the change in BMI between 14 and 31 years ($R^2$-value = .013), but not between 31 and 46 years, was a significant risk factor for PCOS. Additionally, at age 31 serum concentrations of T, SHBG, FAI, fasting insulin, LDL, CRP, total cholesterol, triglycerides and HOMA-IR were significantly associated with diagnosis of PCOS by age 46 (Table 2).

*Multivariate analysis*

Multivariate models were used to identify the most significant variables associated with the diagnosis of PCOS by age 46. In the models I-III, the most significant index at age 31 associated with the

diagnosis of PCOS by age 46 was FAI (Table 2, Model I- III). Serum levels of FAI, T, SHBG, insulin and triglycerides at age 31 were significantly associated with diagnosis of PCOS independently of obesity (Table 2, Models IV-VIII). After the addition of isOA or isH to the models, all other indices lost their significance (Table 2, Models I-III). BMI at age 31 remained a significant factor for PCOS together with isOA (Supplemental Table 1, models V and VII) and SHBG remained significant together with isH (Supplemental Table 2, model VII).

*Drop Out analysis*

Of the women who had participated in the 31year data collection, 536 did not participate in the 46 year data collection and 2568 participated in both data collections. There were no significant differences between dropout (n=18) and follow-up (n=63) groups of women with self-reported OA+ H at age 31.

**Discussion**

The NFBC66 data set provides a unique opportunity to investigate the relationships between weight and change in weight from adolescence until late adulthood, PCOS symptoms, and diagnosis of PCOS. In the present analysis, weight, weight gain, serum levels of triglycerides as well as hyperandrogenemia in early adulthood emerged as significant risk factors associated with PCOS later in life. The women with isOA, both OA+H, and those with the diagnosis of PCOS, experienced significantly greater weight gain in early adulthood and through life, indicating the importance of an active screening for these symptoms as well as of the role of weight management already at adolescence.

In the present study, women with OA+H as well as those with both OA+H at age 31 and diagnosis of PCOS by age 46 exhibited the greatest weight gain and also the highest prevalence of obesity throughout life, suggesting that the presence of both symptoms already in early adulthood is associated with the most severe form of the syndrome. Previous studies addressing the relationship between BMI and PCOS have been inconclusive. A study from Greece reported that BMI was similar in PCOS and referent groups (15), which may be due to the fact that the prevalence of obesity in women with PCOS shows great variation between different cultures (9), probably as a result of

different lifestyle and dietary habits. In this study, obesity was present in 34% of the women with the diagnosis of PCOS, which is greater than in Italy (14%) (24), but lower than in USA (74%) (16). Selection bias, such as the use of hospital based populations (24) or smaller sample size (15) may also explain these discrepancies.

The present data analysis was able to strengthen our previous findings (19) and to extend the observations by follow-up until late adulthood, showing that weight gain in early adulthood, but not later, is significantly associated with symptoms or diagnosis of PCOS. Our results are consistent with a recent longitudinal study (25), showing that obesity and greater weight gain between ages of 20 and 30 were associated with PCOS status at age 27-30. This observation is important as it may identify a sensitive time period for the development of PCOS. All these findings also emphasize the importance of weight management in early life to avoid the onset of PCOS or attenuate its severity. The slower weight gain in late adulthood in our population may be due to improvements of diet and exercise because of a better recognition and uptake of healthy lifestyle recommendations (26), but it also might reflect a predisposition of women with PCOS for an early development of overweight/obesity. The presence not only of both symptoms, but also of isOA or isH, were the most significant factors associated with PCOS diagnosis in the multivariate analyses and with weight as well as weight gain in early adulthood. This lends emphasis to the importance of screening for these symptoms early in life.

In line with previous studies (7,19,27), we found that abdominal obesity was also strongly associated with the syndrome and increased in a similar manner to BMI from early to late adulthood. One of the few studies prospectively investigating the changes of abdominal obesity in PCOS women showed that women with PCOS experienced a progressive increase in waist-hip ratio even in the absence of weight gain between ages of 20-25 and 40-45 years (28). The development of abdominal obesity may be more strongly linked to PCOS as it has been shown to contribute to hyperinsulinemia and reduce insulin sensitivity (29). In keeping with this observation, in the present study, serum insulin levels at age 31 were significantly associated with diagnosis of PCOS by age 46, independently of BMI. Of note, a recent study has suggested that the differences in insulin resistance

289 between PCOS and healthy women may also arise from functional differences in visceral adipose
290 tissue between the two groups (30).

291 Hyperandrogenemia in early adulthood was an important risk factor for diagnosis of
292 PCOS in later life. Although the evidence is still weak, the development of PCOS has been proposed
293 to be a consequence of an exposure to androgen excess in the intrauterine environment possibly
294 leading to an altered programming of the fetus's ovarian androgen production and hypothalamic-
295 pituitary function. The phenotype is further modified by mainly dietary and secondary genetic factors
296 explaining the heterogeneous nature of the syndrome (31). Moreover, it has been proposed that lean
297 women with PCOS have the most severe defect in the ovarian steroidogenesis and thus they do not
298 need any exogenous factors to provoke development of PCOS, whereas women with mild defect need
299 the contribution of obesity, abdominal obesity or insulin resistance to develop the full-blown
300 syndrome (4,32). The present results support this hypothesis as the most significant factors associated
301 with diagnosis of PCOS were obesity and hyperandrogenemia in early life. In line with this, previous
302 studies have suggested that PCOS manifested itself after a significant weight gain (7) and that obesity
303 was strongly associated with hyperandrogenemia already in adolescence (33,34), with a higher risk of
304 PCOS and infertility problems in later life (35).

305 Dyslipidemia at age 31 (elevated serum levels of LDL and triglycerides) was
306 significantly associated with the diagnosis of PCOS and the association with serum levels of
307 triglycerides remained significant independently of BMI. Elevated triglycerides, a well-established
308 risk factor for the development of atherosclerosis and cardiovascular morbidity in later age, especially
309 in women (36), has been shown to be manifest in young women with PCOS independently of obesity
310 (13). The present observation fits also well with recent epidemiologic data indicating that PCOS has
311 profound medical implications for the health of women by increasing the prevalence of ischemic heart
312 and cerebrovascular diseases (37,38).

313 The main strength of the present study is that it is a prospective population based
314 cohort study, with the longest follow-up compared with previously published longitudinal cohort
315 studies which have investigated the association of weight and weight gain with PCOS diagnosis

(16,25,28). Moreover, the present study consists of a research population with high participation and response rates. Dropout rates were similarly low, and there was no difference between the symptomatic dropout and follow-up subjects in metabolic and hormonal indices. Furthermore, anthropometric parameters were not merely self-reported. Limitations include self-reported symptoms and diagnosis of PCOS. Hirsutism is subjective and may be over-reported. However, we have previously shown that self-reported isolated hirsutism does correlate with increased androgen secretion in this population (20,21). The questionnaire at age 46 did not distinguish between polycystic ovaries (PCO) on ultrasound and PCOS. However, it is expected that women with only PCO morphology would exhibit milder hormonal and metabolic disorders and thus the differences between the groups would be even greater after excluding women with PCO only.

**Conclusions**

The results of this prospective population-based cohort study indicate that BMI, and especially weight gain in early adulthood, plays a crucial role for the emergence of PCOS and that women with PCOS present with an unfavorable lipid profile already in early adulthood. We were also able to show that isOA or isH, screened by a simple questionnaire at the time of early adulthood, are good predictors for the diagnosis of PCOS in later adulthood and can be used to identify the women at risk. Given the worldwide progression of the obesity epidemic, (17,18) our results suggest that an increasing prevalence of symptomatic PCOS can be expected in the future and emphasize the role of weight management during adolescence and early adulthood. Possible prevention or postponement of symptoms of PCOS would have major beneficial effects on individual's health and quality of life and decrease significantly the health and economic burden of the syndrome.

**Acknowledgements**

We thank T. Nordström for her help with the statistical analyses and the late Professor Paula Rantakallio (The founder of NFBCs).

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**Figure legends**

**Figure 1.** Flow chart of the study

**Figure 2.** Description of women with diagnosis of PCOS by age 46 according to the 31-year status.

**Figure 3.** Prevalence of overweight and obesity in the women with PCOS and PCOS related symptoms. The difference in the prevalence of overweight and obesity between different groups were analyzed by Chii squared test.* $P < .05$, ** $P < .01$ and *** $P < .001$ compared with the prevalence in controls in the same age group.

**Figure 4.** BMI at the different time points according to the presence of PCOS and PCOS related symptoms. BMI values are reported as mean ± SE at each time point and the differences between groups were analyzed using Mann-Whitney U-test. * $P < .05$, ** $P < .01$ and *** $P < .001$ for the comparison with controls in the same age group.