# Associations of childhood adiposity with menstrual irregularity and polycystic ovary syndrome in adulthood: The Childhood Determinants of Adult Health Study and the Bogalusa Heart Study

Y. He [a], J. Tian [a], L. Blizzard [a], W.H. Oddy [a], T. Dwyer [a,b], L.A. Bazzano [c], M. Hickey [d], E.W. Harville [c], A.J. Venn [a]

[a] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia.

[b] The George Institute for Global Health, University of Oxford, Oxford, UK.

[c] Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA.

[d] Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Australia and the Royal Women's Hospital, Victoria, Australia.

Corresponding Author: Alison J. Venn, PhD, Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia. Telephone: 61-3-6226-7706; Fax: 61-3-6226-7704; E-mail: Alison.Venn@utas.edu.au

**Running title:** Childhood adiposity, menstrual irregularity and PCOS

## Abstract

**STUDY QUESTION:** Is high adiposity in childhood associated with menstrual irregularity and polycystic ovary syndrome (PCOS) in later life?

**SUMMARY ANSWER:** Overall, greater childhood BMI was associated with menstrual irregularity, and greater childhood BMI and waist/height ratio (WHtR) in white but not black participants were associated with PCOS in adulthood.

**WHAT IS KNOWN ALREADY:** Increased childhood BMI has been associated with irregular menstrual cycles and PCOS symptoms in adulthood in two longitudinal population-based studies, but no study has reported on associations with childhood abdominal obesity. Few studies have investigated whether there are racial differences in the associations of adiposity with PCOS though there has been some suggestion that associations with high BMI may be stronger in white girls than in black girls.

**STUDY DESIGN, SIZE, DURATION:** The study included 1,516 participants (aged 26-41 years) from the Australian Childhood Determinants of Adult Health study (CDAH) and 1,247 participants (aged 26-57 years) from the biracial USA Babies sub-study of the Bogalusa Heart Study (BBS) who were aged 7-15 years at baseline. At follow-up, questions were asked about menstruation (current for CDAH or before age 40 years for BBS), ever having had a diagnosis of PCOS and symptoms of PCOS.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** In CDAH, a single childhood visit was conducted in 1985. In BBS, multiple childhood visits occurred from 1973 to 2000 and race was reported (59% white; 41% black). In childhood, overweight and obesity were defined by international age-sex-specific standards for BMI and WHtR was considered as an indicator of abdominal obesity. Multilevel mixed-effects Poisson regression estimated

relative risks (RRs) adjusting for childhood age, highest parental and own education, and age at menarche.

**MAIN RESULTS AND THE ROLE OF CHANCE:** The prevalence of childhood obesity was 1.1% in CDAH and 7.5% in BBS. At follow-up, menstrual irregularity was reported by 16.7% of CDAH and 24.5% of BBS participants. The prevalence of PCOS was 7.4% in CDAH and 8.0% in BBS participants. In CDAH, childhood obesity was associated with menstrual irregularity (RR=2.84, 95% CI:1.63-4.96) and PCOS (RR=4.05, 95% CI:1.10-14.83) in adulthood. With each 0.01 unit increase in childhood WHtR there was a 6% (95% CI: 1%-11%) greater likelihood of PCOS. Overall, in BBS, childhood obesity was associated with increased risk of menstrual irregularity (RR=1.44, 95% CI: 1.08-1.92) in adulthood. Significant interaction effects between race and childhood adiposity were detected in associations with PCOS. In BBS white participants, childhood obesity was associated with PCOS (RR=2.93, 95% CI: 1.65-5.22) and a 0.01 unit increase in childhood WHtR was associated with an 11% (95% CI: 5%-17%) greater likelihood of PCOS in adulthood. In BBS black participants, no statistically significant associations of childhood adiposity measures with PCOS were observed.

**LIMITATIONS, REASONS FOR CAUTION:** The classification of menstrual irregularity and PCOS was based on self-report by questionnaire, which may have led to misclassification of these outcomes. However, despite the limitations of the study, the prevalence of menstrual irregularity and PCOS in the two cohorts was consistent with the literature. While the study samples at baseline were population-based, loss to follow-up means the generalizability of the findings is uncertain.

**WIDER IMPLICATIONS OF THE FINDINGS:** Greater childhood adiposity indicates a higher risk of menstrual irregularity and PCOS in adulthood. Whether this is causal or an

early indicator of underlying hormonal or metabolic disorders needs clarification. The stronger associations of adiposity with PCOS in white than black participants suggest that there are racial differences in childhood adiposity predisposing to the development of PCOS and other environmental or genetic factors are also important.

**STUDY FUNDING/COMPETING INTEREST(S):** The CDAH study was supported by grants from the Australian National Health and Medical Research Council (grants 211316, 544923 and 1128373). The Bogalusa Heart Study is supported by US National Institutes of Health grants R01HD069587, AG16592, HL121230, HD032194, and P50HL015103. No competing interests existed.

**Key words:** BMI, waist/height ratio, childhood, menstrual irregularity, polycystic ovary syndrome

## Introduction

Menstrual irregularity and polycystic ovary syndrome (PCOS) have been associated with higher risk of lower fecundity and cardiovascular diseases (Solomon, et al., 2002; West, et al., 2014) as well as some cancers (Harris, et al., 2018; Harris, et al., 2017). PCOS is recognized as the most common heterogeneous endocrine disorder, affecting 8-13% of women of reproductive age (March, et al., 2010). Irregular menstrual cycles are part of the three diagnostic criteria (National Institutes of Health, Rotterdam and Androgen Excess Society diagnostic criteria) for PCOS in addition to hyperandrogenism and polycystic ovarian morphology (Teede, et al., 2018).

General and abdominal obesity are associated with a greater risk of menstrual irregularity in adult women (Douchi, et al., 2002; Hahn, et al., 2013; Jacobsen, et al., 2012; Wei, et al., 2009). Our previous cross-sectional study suggested that obese women, defined by either BMI or waist circumference, were twice as likely to have irregular menstruation, compared with normal weight women (Wei, et al., 2009). However, the association between adult obesity and PCOS is inconclusive. Although obesity, particularly abdominal obesity, is a common trait in women with PCOS, it is not part of the diagnostic criteria. The prevalence of obesity varies among different populations and races but the prevalence of PCOS is relatively uniform (Legro, 2012). This implies that obesity might not cause PCOS or there could be geographic/ethnic differences affecting the relationship between obesity and PCOS.

Only two previous population-based longitudinal studies (Laitinen, et al., 2003; Lake, et al., 1997) have investigated the associations between childhood obesity, adult menstrual irregularity and PCOS, in which childhood BMI was the only indicator of obesity. The 1958 British birth cohort study of 5,770 girls reported that overweight and obesity at 7 years of age increased the risk of menstrual irregularity before age 33 years (Lake, et al., 1997). The

Northern Finland 1966 birth cohort of 2,007 girls suggested that overweight and obesity at age 14 years were associated with self-reported PCOS at age 31 years(Laitinen, et al., 2003). Two further papers based on the same Northern Finland cohort reported associations of weight gain (Ollila, et al., 2016) and age at adiposity rebound with PCOS (Koivuaho, et al., 2019). Another study based on clinical study samples suggested that change in z-score from weight at birth to weight in adolescence may be greater in girls with PCOS than in healthy controls (de Zegher, et al., 2017).

In this study we used two cohorts with different racial characteristics who were followed through childhood to adulthood. We aimed first to investigate the associations of obesity (including abdominal obesity) in childhood with menstrual irregularity and PCOS in adulthood and, second to determine whether these associations differed by country (Australia and USA) and race (white and black).

## Materials and Methods

### *The Childhood Determinants of Adult Health Study: a cohort from Australia*

#### Participants

The Childhood Determinants of Adult Health Study (CDAH) study is a follow-up of participants in the 1985 Australian Schools Health and Fitness Survey (ASHFS), a nationally representative sample of 8,498 school children (4,191 girls) aged 7-15 years (Gall, et al., 2009) (Fig. 1). During 2004-06, the first follow-up (CDAH-1) was conducted when participants were 26-36 years and 1,598 female participants responded to questions on their menstrual cycle characteristics and PCOS. Among them 652 participants attended a study clinic and had plasma hormone measurements including total testosterone concentrations and sex hormone-binding globulin (SHBG) (Wei, et al., 2009). The second follow-up (CDAH-2)

was conducted during 2009-11 when participants were aged 31-41 years and 1,123 participants completed the same questions about menstrual cycles and PCOS. The current study included 1,516 women who completed questions on menstrual cycles and/or PCOS in CDAH-1 and/or CDAH-2.

The study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee. Written informed consent was obtained during childhood from parents and at each follow-up from participants.

## Childhood anthropometric measurements

BMI, calculated as weight (kg)/height $(m)^2$, was derived from measured weight and height. BMI was classified as normal, overweight or obese according to the international age-sex-specific cut-points (Cole, et al., 2000). BMI-z score was calculated based on age-sex-specific World Health Organization Child Growth standards (2006). Waist circumference was taken at the level of the umbilicus to the nearest 0.1 cm. Waist/height ratio (WHtR), calculated as waist circumference divided by height (cm), was the indicator of abdominal obesity when WHtR≥0.5 (Brambilla, et al., 2013).

## Adult anthropometric measurements

Participants who attended CDAH-1 clinics (n=2,329) had weight, height, and waist circumference measured. Participants who did not visit clinics (n=1,556) self-reported their weight and height, and a correction factor was applied to adjust for error, as described previously (Venn, et al., 2007). BMI ($kg/m^2$) was calculated from height and weight. Weight and height were self-reported at CDAH-2 and adjusted for error as described above. Adult BMI was categorized as normal (BMI<25 $kg/m^2$), overweight (25.0≤BMI≤29.9 $kg/m^2$) or obese (BMI≥30 $kg/m^2$) (2000).

## Adult menstrual irregularity and PCOS

We defined menstrual cycle length as the time from the first day of one period to the first day of the next and participants were questioned on the length of their usual menstrual cycle. Menstrual irregularity was defined as menstrual cycles ≥35 days or <25 days or reported as extremely irregular in CDAH-1 and/or CDAH-2. Women who were currently pregnant (n=31), using hormonal contraceptives (n=411) or had a hysterectomy (n=1) were excluded.

Women were defined as having PCOS if they self-reported in CDAH-1 and/or CDAH-2 that they had ever been told by a doctor or they reported two symptoms of PCOS. The symptoms were menstrual cycle ≥35 days or totally variable, and hirsutism. The validity of identifying women with PCOS by way of similar questions has been reported previously as moderately high (Taponen, et al., 2004). The presence of hirsutism was defined as ever having seen a doctor because of concern about the amount of hair on their face.

## Covariates

Age at menarche was self-reported in adulthood. Smoking history in childhood and adulthood were coded as ever or never smoked. Ever smoked in childhood was defined as having ≥10 cigarettes in their life. Former and current smokers in adulthood were defined as ever smoked. Highest parental education and own-education were classified as high school only, vocational training and any university education. Childhood alcohol consumption was classified as none (never consume alcohol), light (consume alcohol less than once/week), moderate (consume alcohol 1-2 days/week), heavy (consume alcohol 3-4 days/week) and very heavy (consume alcohol ≥ 5 days/week). Alcohol consumption in adulthood was classified according to daily alcohol intake: none (0 alcoholic drinks/day), light (0-1 alcoholic drinks/day), moderate (1-2 alcoholic drinks/day), heavy (>2-3 alcoholic drinks/day) and very

heavy intake (>3 alcoholic drinks/day) based on Australian guidelines (Australian Government, 2009).

## *The Bogalusa Heart Study: a cohort from the USA*

### Participants

The Bogalusa Heart Study (BHS) is a biracial (65% white and 35% black) prospective cohort study of cardiovascular risk factors among children and young adults from Bogalusa, LA, USA (Brook, 1981). Initial study participants aged 3-18 years were enrolled from schools in 1973 and additional participants were recruited over time. Data collection occurred approximately every 2 years for children and 5 years for adults. These cross-sectional studies of children or adults were combined to create the overall BHS population.

The Bogalusa Babies sub-study (BBS) began in May 2013 to examine the role of cardiovascular risk factors in childhood on reproductive outcomes. Women with at least one BHS visit (n=5,914) were eligible to participate. We included 1,247 female participants who were aged 7-15 years during childhood visits (to align with the CDAH study), who participated in BBS when they were aged 26-57 years, and had height and weight reported between ages 26 and 40 years to align with their report of their menstrual cycle characteristics prior to age 40 years (Fig. 2).

For child participants, parental permission and consent of the child were obtained and written informed consent was obtained from adult participants. All study procedures were approved by the Institutional Review Board of Tulane University.

## Childhood anthropometric measurements

All BHS surveys followed an identical protocol for anthropometric measurements. In the subsample of BBS used in the current study, a total of 298 participants had childhood waist and hip circumference measured. Height, weight and waist circumference were measured twice to within 0.1cm or 0.1kg and mean values obtained. BMI, BMI z-score, WHtR, obesity and abdominal obesity were calculated or classified using the same criteria as described in the CDAH study.

## Adult anthropometric measurements

Adult height and weight were recorded in the BBS (Paley, et al., 2004). Where necessary, height and weight before age 40 years were extracted from records of the BHS (Berkey, et al., 1993). BMI, overweight and obesity were calculated or classified using the same criteria as described in the CDAH study.

## Adult menstrual irregularity and PCOS

Data on menstrual cycle characteristics were collected by questioning participants on the length of the average menstrual cycle between age 16 and 40 years (excluding any time spent pregnant, receiving birth control pills or injections, after menopause, or after having both ovaries or the uterus surgically removed). Participants reporting an average menstrual cycle of ≥35 days, <25 days, or totally variable were considered to have menstrual irregularity.

The classification of PCOS was based on the presence of both menstrual cycle ≥35 days or totally variable and hirsutism, or self-reported ever having been told by a doctor that she had PCOS. Hirsutism was determined by a series questions asking about the tendency to grow dark, coarse hair on eight body sites including upper lip, chin, breast, chest between the

breasts, back, belly, upper arms and upper thighs. Those who indicated three or more sites were considered as having clinical hirsutism.

## Covariates

Race (white/black) was recorded at the initial BHS visit. As previously described (Wattigney, et al., 1999), information on age at menarche was obtained by a registered nurse. Smoking history in childhood and adulthood were coded as ever (currently or formerly at any visit) and never smoked. Highest parental and own-education were classified as high school only, vocational training, and college or more (any university). Childhood and adulthood alcohol consumption were classified as none (tried or never drink), light (drink less than once/week), moderate (drink once or twice/week), heavy (drink 3-4 times/week) and very heavy drinker (drink daily or almost every day).

## Statistical analyses

Means with SDs and numbers with proportions were used to describe participants' sociodemographic characteristics, menstrual irregularity and PCOS in each cohort from baseline to follow-up. Taking into account the multiple adult visits conducted in CDAH and multiple childhood visits in BBS, multi-level generalized linear mixed effects models with Poisson regression were employed to estimate the relative risks (RRs) and 95% CIs.

In BBS, approximately 50% of participants had missing data on age at menarche and more than 20% of participants had missing data on highest parental education. Multiple imputation by chained equations was used to impute the missing data (Azur, et al., 2011).

Covariates remaining in the final models were variables which were causally related to the outcome, imbalanced between the exposure groups and resulted in more than 10% change in

the coefficient of the principal study factor when added to the model. In analyses of the BBS, the models were additionally adjusted for race as appropriate.

Interactions between race and childhood adiposity on menstrual irregularity and PCOS in BBS were investigated in the regression model. There was no interaction between race and obesity on menstrual irregularity (*P=0.362*), however, a statistically significant race interaction was present for PCOS (*P=0.042*). Therefore, PCOS analyses in BBS were further stratified by race.

The following sensitivity analyses were conducted. First, we repeated the analysis by using the United States Centres for Disease Control and Prevention (CDC) growth reference to calculate BMI z-score and to classify childhood weight status (Harris, et al., 2018). Second, the analysis was repeated after excluding persons who may have been of black (n=8) or other non-white race (n=35) in CDAH (race was inferred from the childhood questionnaire including the information on father's and mother's country of birth and language spoken at home) to compare with the results in BBS white participants. Third, associations were examined with the change between birthweight z-score and BMI z-score in childhood in a subsample of BBS (n=788) with the relevant information on birthweight and gestational age available from birth certificates (Chen, et al., 2012). Fourth, as hyperandrogenism is also a key diagnostic feature for PCOS, the association of childhood adiposity with biochemical hyperandrogenism was analysed in a subsample of CDAH (n=652) who attended CDAH-1 clinics and were not using hormonal contraceptives. Biochemical hyperandrogenism was assessed by calculated free testosterone levels (cFT) (Vermeulen, et al., 1999). The association of childhood adiposity with hirsutism was also analysed in CDAH and BBS. Fifth, we restricted our sample in BBS to women who were aged under 40 years at follow-up to ensure reporting of current menstrual characteristics and excluding retrospective reports from women aged 41-57 years. Last, a subgroup of underweight children was classified to

investigate the associations of underweight in childhood with menstrual irregularity and PCOS in adulthood.

All analyses were performed using STATA software, version 15.0 (Stata Corp., College Station, TX, USA); a p-value of <0.05 was considered statistically significant.

## Results

### *Participant characteristics*

Our sample included 1,516 participants from the CDAH study and 1,247 (white: 730; black: 517) participants from the BBS. Anthropometric and sociodemographic characteristics of participants in the two cohorts are shown in Table I. On average, BBS participants had a higher childhood BMI z-score and WHtR than CDAH participants. The prevalence of childhood obesity and abdominal obesity was 1.1% and 5.3% in CDAH and 7.5% (white: 5.2%; black: 10.8%) and 22.5% (white: 20.2%; black: 23.8%) in BBS. At follow-up, the mean age in CDAH-1 was 31.5 years, and 36.4 years at CDAH-2. In BBS, the mean age was 44.1 years. The prevalence of menstrual irregularity was 16.7% in CDAH and 24.5% in BBS (white: 25.4%; black: 23.2%). The prevalence of PCOS was 7.4% in CDAH (the average of CDAH-1 and CDAH-2) and 8.0% (white: 10.7%; black: 4.3%) in BBS. Identification of PCOS by menstrual characteristics and hirsutism alone classified seven more participants with PCOS in CDAH and 16 more participants in BBS.

### *Childhood adiposity and menstrual irregularity*

Table II shows the associations of childhood adiposity with menstrual irregularity in CDAH and in the overall BBS. In CDAH (after adjusting for childhood age, age at menarche, highest parental and their own education), compared with normal weight girls, the risk of reporting menstrual irregularity was almost three-fold in those who were obese in childhood. Similarly,

296 in the BBS, when further adjusted for race, childhood obesity was associated with nearly
297 twice the risk of having menstrual irregularity.

298 *Childhood adiposity and self-reported PCOS*

299 In CDAH, childhood obesity defined by BMI and childhood abdominal obesity defined by
300 WHtR were significantly associated with an increased risk of self-reported PCOS (Table III).
301 A 0.01 unit increase in childhood WHtR was associated with a 5% increased likelihood of
302 self-reported PCOS. In the BBS sample overall, results were consistent with CDAH:
303 childhood obesity was associated with a higher risk of self-reported PCOS and every 0.01
304 unit increase in WHtR was associated with 8% greater likelihood of PCOS (Table III).

305 *Racial differences in the associations of self-reported PCOS in BBS*

306 Significant racial differences were observed in the associations of childhood adiposity with
307 self-reported PCOS, but not with menstrual irregularity, in BBS white and black participants
308 (Table IV). Childhood obesity and a 0.01 unit increase in WHtR were both associated with an
309 increased risk of PCOS in BBS white participants, but no significant associations of
310 childhood obesity or WHtR with PCOS were found in BBS black participants.

311 *Influence of weight status from childhood into adulthood*

312 The relative risk of menstrual irregularity by change of weight status from childhood to
313 adulthood is displayed in Table V. Compared with participants who had persistently normal
314 BMI in childhood and adulthood, those who became overweight or obese in adulthood
315 reported a higher risk of menstrual irregularity in BBS. Participants who were persistently
316 overweight/obese since childhood had significantly higher risks of menstrual irregularity in
317 both CDAH and BBS.

No significant association of any weight status category from childhood to adulthood with PCOS was found in BBS black participants (Table VI). In white participants, those who were overweight or obese in childhood only, or persistently overweight or obese from childhood to adulthood, had a significantly increased risk of PCOS (Table VI).

## *Sensitivity analyses*

Similar estimates were found in sensitivity analyses in which the United States CDC standards were used to calculate childhood BMI z-score and classify childhood obesity according to BMI (Supplementary Table SI, Table SII and Table SIII). When women of non-white races (n=43) were excluded in CDAH, the associations between increased childhood BMI and menstrual irregularity remained statistically significant. The associations between increased childhood BMI, WHtR and PCOS also remained statistically significant with only small changes in the mean coefficients (-2.5%-11.20%). In a subsample of participants who had birthweight and gestational age in BBS (n=788), we found the z-score increment between weight at birth and BMI in childhood was associated with increased risk of menstrual irregularity and PCOS in white participants but no statistically significant association was found in black participants (Supplementary Table SIV).

In a subsample of participants who attended CDAH-1 clinics (n=652), childhood BMI z-score (β= 2.82 pmol/l, 95% CI: 1.67-3.98) and childhood WHtR (β= 0.59 pmol/l, 95% CI: 0.33-0.86) were positively associated with cFT in adulthood. In CDAH, childhood BMI z-score (RR=1.50, 95% CI: 1.30-2.00) and WHtR (RR=1.07, 95% CI: 1.01-1.12) were positively associated with hirsutism at follow-up; similar associations of childhood BMI z-score (RR=1.61 95% CI: 1.25-2.09) and WHtR (RR=1.13, 95% CI: 1.05-1.21) with hirsutism were found in BBS white but not black participants.

When restricting the sample to women who were aged under 40 years in the analysis of menstrual irregularity in BBS (n=431) (Supplementary Table SV), the risks of menstrual irregularity remained elevated for participants with high childhood adiposity, although less so, and achieved borderline significance for childhood obesity (RR=1.50, 95% CI 0.94-2.41, *P=0.090*) and childhood abdominal obesity (RR=1.55, 95% CI 0.99-2.41, *P=0.055*). No significant associations of childhood underweight in CDAH (n=14) and BBS (n=22) with menstrual irregularity and PCOS in adulthood were found.

## Discussion

This study is the first to report the association of childhood abdominal obesity with menstrual irregularity and PCOS in adulthood, using data from two independent large prospective cohorts in two countries. Overall, in both cohorts, childhood obesity but not abdominal obesity was associated with greater risks of menstrual irregularity. A significant racial difference was observed in the associations of childhood obesity and abdominal obesity with PCOS, with significant associations found in white participants, but not in black participants. The risks of menstrual irregularity and PCOS were consistently significantly higher in participants with persistent overweight/obesity since childhood.

The positive association between childhood obesity and adulthood menstrual irregularity is consistent with prior findings from the 1958 British birth cohort (Lake, et al., 1997). Though some studies have suggested that the distribution of body fat in adult women may be a risk factor of menstrual irregularity cross-sectionally (Douchi, et al., 2002; Wei, et al., 2009), no statistically significant association of childhood abdominal obesity with menstrual irregularity was found in CDAH and BBS. The mechanisms underlying the associations of greater childhood BMI with menstrual irregularity in adulthood may include a series of hormonal factors. Childhood obesity is a risk factor for increased concentrations of

testosterone, LH, insulin, and reduced concentrations of SHBG in adulthood (Elizondo-Montemayor, et al., 2017; Marcovecchio and Chiarelli, 2013). These changes may cause a disruption of normal ovulation and menstrual irregularity.

It is known that PCOS and menstrual irregularity are strongly correlated. We found that the positive associations of childhood BMI and WHtR with self-reported PCOS in adulthood were strong in CDAH and BBS white participants. Menstrual irregularity is part of the diagnostic criteria for PCOS (Teede, et al., 2018), and childhood obesity was correlated with menstrual irregularity in the current study, therefore, this may explain the observed associations. Phenotypic features (including menstrual irregularity and hyperandrogenism) of PCOS are known to be regulated by obesity cross-sectionally, typically involving a distribution of central fat (de Zegher, et al., 2018; Legro, 2012). Our finding of the positive associations between childhood BMI, childhood WHtR and cFT in adulthood in a subsample of participants in CDAH suggested that higher childhood adiposity increased the risk of hyperandrogenism. Childhood obesity as well as abdominal obesity may act to promote menstrual irregularity and hyperandrogenism in those at higher risk of PCOS.

No significant association of adiposity with PCOS was found in BBS black girls. A previous cross-sectional study by Christensen, et al. (2013) also reported that the association between BMI and PCOS was weaker in black girls than white girls. The literature has indicated that although there are substantial racial differences in the prevalence of obesity, the prevalence of PCOS is similar in different races (Azziz, et al., 2004; Knochenhauer, et al., 1998; Wolf, et al., 2018). In our study, BBS black participants had a higher prevalence of childhood obesity than white participants (10.8% versus 5.2%, respectively), but their prevalence of PCOS was lower than white participants (4.3% versus 10.7%, respectively). The explanations for this racial difference are unclear. It is possible that lower socioeconomic status and poorer health service access and utilisation among black women may result in a lower rate of diagnosis

(Merkin, et al., 2016). These factors may thereby dilute the associations observed in black participants. However, in BBS, a stronger association of childhood adiposity with hirsutism was still observed among white compared to black participants. While previous studies have suggested that black women with PCOS have increased risk of metabolic syndrome and cardiovascular disease compared with white women with PCOS (Chan, et al., 2017; Hillman, et al., 2014), the associations of adiposity with PCOS between races have not been clearly defined. We are the first to report in longitudinal studies that there are racial differences in how childhood adiposity associates with the development of PCOS.

The lack of association of childhood adiposity with PCOS in black participants also suggests that high childhood adiposity is not the only driver of adult PCOS and many other factors may play a role in PCOS development and progression. Prenatal androgen exposure has been proposed as a cause of PCOS although the evidence from human studies is inconsistent (Hickey, et al., 2009). Familial trends in PCOS are reported, but no specific genetic association has been reported and more research is necessary to define the genetic basis (Crespo, et al., 2018). Environmental factors, including health-related behaviours or lifestyles and economic disadvantage, are potentially involved in the aetiology, prevalence, and modulation of PCOS (Merkin, et al., 2016). It is likely that there are genetic, molecular and environmental factors that contribute to the racial differences in childhood adiposity-related PCOS.

The risks of menstrual irregularity and PCOS were significantly higher in women with persistent overweight/obesity since childhood in both CDAH and BBS, consistent with findings from the Northern Finland 1966 birth cohort study (Laitinen, et al., 2003). Furthermore, in our study, for white participants in BBS, we found for the first time that women who were overweight/obese in childhood but not in adulthood also reported a

414 significantly higher risk of PCOS, suggesting independent effects of childhood adiposity that
415 need to be confirmed in larger studies.

416 There are several limitations in our study. First, menstrual cycle characteristics and PCOS
417 were self-reported by questionnaire. Previous studies have suggested that women's
418 retrospective self-report of menstrual length can be prone to error (Small, et al., 2007) and the
419 agreement between diary records and retrospectively recalled menstrual cycle length was
420 moderate (Jukic, et al., 2008). Self-reported PCOS likely tends to underestimate prevalence
421 (Varanasi, et al., 2018; Wang, et al., 2018). Also, if the accuracy of self-reported menstrual
422 cycle length and PCOS differed by obesity status, then our effect estimates might have been
423 biased. However, previous studies have shown no evidence of this (Jukic, et al., 2008;
424 Laitinen, et al., 2003; Small, et al., 2007).

425 A second potential limitation of this study was the exclusion of women using hormonal
426 contraception (28.4%) in the analysis of menstrual irregularity in CDAH. Since hormonal
427 contraception is commonly prescribed for menstrual irregularity (Bulletins—Gynecology,
428 2013), we may have under-estimated the prevalence of menstrual irregularity. Third, we have
429 limited information on the age at which PCOS was diagnosed in the two cohorts. Only in the
430 second follow-up in CDAH were participants asked to report the age when their PCOS was
431 diagnosed (ages ranged from 14-36 years with only four participants reporting the diagnosis
432 of PCOS before age 18 years). It has been suggested that adolescents with characteristics of
433 PCOS should be reassessed at or before full reproductive maturity, at 8 years post menarche
434 (Teede, et al., 2018) to confirm a diagnosis. In this study, participants reporting a diagnosis of
435 PCOS during adolescence may have been misclassified. Fourth, the diagnostic criteria for
436 PCOS have recently changed (Teede, et al., 2018) and there may have been differences in
437 how PCOS was diagnosed in Australia compared to the USA. Despite all of these limitations,

438 we showed that the prevalence of menstrual irregularity and PCOS in the two cohorts was
439 consistent with the literature (March, et al., 2010; Weller and Weller, 1998).

440 Finally, some characteristics of those continuing in the study differed from those lost to
441 follow-up, and this might limit the generalizability of the findings. In CDAH, non-
442 participants had higher BMI and WHtR values, on average, in childhood than the
443 participants, indicating the current sample may have comprised healthier participants.
444 However, if non-participants were also more likely to have menstrual irregularity and PCOS
445 in adulthood than participants, the effect of this bias would be to underestimate the magnitude
446 of the associations observed. Participants in the BBS were more likely to be black (41%
447 versus 34%) compared with the rest of the study cohort, but childhood BMI was similar
448 among participants and non-participants (Wang, et al., 2018).

449 Strengths of our study include that this is the first prospective study to investigate the long-
450 term associations between childhood abdominal obesity measures and menstrual irregularity
451 and PCOS. Second, we used two independent cohorts from two countries and reported
452 consistent findings. Third, we were able to consider associations by race in BBS.

453 In conclusion, greater childhood BMI was associated with an increased risk of menstrual
454 irregularity in adulthood in both CDAH and BBS. Greater childhood BMI and WHtR were
455 associated with an increased risk of PCOS in adulthood in CDAH, and in BBS white
456 participants. These risks were significantly higher in women with persistent
457 overweight/obesity since childhood. No significant association of adiposity with PCOS was
458 found in BBS black participants, suggesting there are racial differences in childhood
459 adiposity associating with the development of PCOS, and other environmental or genetic
460 factors are important. Whether high childhood adiposity is causal or an early independent

indicator of underlying hormonal or metabolic disorders related to PCOS needs further clarification.

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## Authors' roles

Y.H. performed the statistical analysis and drafted the manuscript. J.T. provided analytical and interpretive advice and helped draft the manuscript. L.B. assisted with the data analysis and provided interpretive advice. W.H.O. provided interpretive advice and helped draft the manuscript. T.D. was involved in conceptualization of the study and provided interpretive advice. L.A.B. helped with acquisition of data and provided interpretive advice. M.H. provided interpretive advice and provided critical revision of the manuscript. E.W.H helped with acquisition of data, provided interpretive advice and critical revision of the manuscript. A.J.V. was involved in the conceptualization of the study, acquisition of data, and helped draft the manuscript. All authors have reviewed and approved the final manuscript.

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## Conflict of interest

There is no conflict of interest.

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## Figure legends

**Figure 1** Flow chart of the study population for the Childhood Determinants of Adult Health Study in Australia, 1985–2011.

CDAH: Childhood Determinants of Adult Health

**Figure 2** Flow chart of the study population for the Bogalusa Heart Study in the USA, 1973–2017.

PCOS: polycystic ovary syndrome