Childhood Adiposity and Women's Reproductive Health

by

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Statement of Originality

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University. Ethic Approval Numbers H0006020, H0010454 and H0013826.

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Statement of Co-Authorship

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The candidate (YH) was the primary author and contributed 60% to the conceptualisation of the paper, data analysis, interpretation, writing of drafts and addressing the reviewer's

comments. Author 1 (AJV) contributed to the conceptualisation of the study, acquisition of data, assisted with interpretation, critically reviewed the manuscript and helped address the reviewers' comments. Author 2 (JT) provided analytical advice, assisted with interpretation, and critically reviewed the manuscript. Author 3 (WHO) provided interpretive advice and critically reviewed the manuscript. Author 4 (TD) contributed to discussion and provided critical revision of the manuscript.

Paper 2: Located in Chapter 4

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Paper 3: Located in Chapter 5

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Chapter 4: He Y, Tian J, Blizzard L, Oddy WH, Dwyer T, Venn AJ. Associations of childhood adiposity and changes in adiposity status from childhood to adulthood with pregnancy hypertension. *Pregnancy Hypertension-An International Journal of Women's Cardiovascular Health*. 2020;19: 218-225.

Chapter 5: He Y, Tian J, Blizzard L, Oddy WH, Dwyer T, Bazzano LA, Hickey M, Harville EW, Venn AJ. 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. *Human Reproduction.* 2020 May;35(5):1185-1198.

Chapter 6: He Y, Tian J, Hickey M, Oddy WH, Dwyer T, Venn AJ. The associations of childhood adiposity with symptoms measured by the Menopause Rating Scale in women aged 45-49 years: an Australian cohort study. *Maturitas-An international journal of midlife health and beyond. Accepted September 27, 2020.*

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"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"

(Oral presentation)

March, 2019 The XXIII Annual Congress of the Perinatal Society of Australian and New Zealand, Gold Coast, Australia – 17 March to 20 March 2019

"Associations of childhood adiposity and changes in adiposity status from childhood to adulthood with pregnancy hypertension"

(Oral presentation)

October, 2017 2017 Australian and New Zealand Obesity Society Conference, Adelaide, Australia – 04 Oct to 06 Oct 2017 "Association of childhood obesity with female infertility in adulthood: a 25-year follow-up study"

(Oral presentation)

Conferences Presentations Arising from the Thesis

September, 2017 2017 Graduate Research Conference Hobart, Australia – 07 Sep to 08 Sep 2017

"Association of childhood obesity with female infertility in adulthood: a 25-year follow-up study"

(Poster presentation)

List of Abbreviations

ASHFS	Australian Schools Health and Fitness Survey
BMI	Body mass index
BHS	Bogalusa Heart Study
BBS	Babies sub-study of the Bogalusa Heart Study
CDAH	Childhood Determinants of Adult Health
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DBP	Diastolic blood pressure
DGI	Dietary guidelines index
DXA	Dual x-ray absorptiometry
FSH	Follicle stimulating hormone
FTO	Fat mass and obesity-associated gene
GEE	Generalized estimating equations
GnRH	Gonadotropin-releasing hormone
HPO	Hypothalamic-pituitary-ovarian
HT	Hormone therapy
IOTF	International Obesity Task Force
LH	Luteinizing hormone
MRS	Menopause Rating Scale
NICE	National Institute for Clinical Excellence
NIH	National Institute of Health

List of Abbreviations

NNS	National Nutrition Survey
NR	Possible diagnostic criteria but not required to be present
PCOS	Polycystic ovary syndrome
PH	Pregnancy hypertension
PS	Prospective study
R	Required for diagnosis
RR	Relative risk
SBP	Systolic blood pressure
SEIFA	Socio-Economic Indexes for Areas
SD	Standard deviation
SHBG	Sex hormone-binding globulin
STRAW	Stages of Reproductive Aging Workshop
SWAN	Study of Women's Health Across the Nation
UK	the United Kingdom
USA	the United States of America
VMS	Vasomotor symptoms
WC	Waist circumference
WHO	World Health Organization
WHtR	Waist-to-height ratio

Abstract

Background: The recent global epidemic of childhood overweight and obesity has significant clinical and public health implications, including for reproductive health. Adiposity (fatness) in childhood is associated with earlier onset of puberty, menstrual irregularity and polycystic ovary syndrome (PCOS) symptoms in adolescent girls. Adiposity in adult women is associated with greater risks of reproductive disorders, for example higher rates of infertility, menstrual disorders, pregnancy complications and menopausal symptoms. As the interest in the long-term health impacts of childhood adiposity grows, there is a need to better understand how childhood adiposity associates with female reproductive health in adulthood.

Aims: This thesis aimed to investigate the associations of different measures of childhood adiposity with reproductive outcomes in women including infertility, pregnancy hypertension, menstrual irregularity, PCOS and menopausal symptoms.

Methods: Data from two population-based cohorts were used for the analyses. The Childhood Determinants of Adult Health (CDAH) study from Australia was used to investigate associations of childhood adiposity with infertility, pregnancy hypertension, menstrual irregularity, PCOS and menopausal symptoms. CDAH is a follow-up study of 8,498 children with 4,191 girls aged 7-15 years who participated in 1985 Australian Schools Health and Fitness Survey (ASHFS), with up to 1,894 women included in the analyses. The Babies sub-study of the Bogalusa Heart Study (BBS) from the United States of America (USA) was also used to investigate associations of childhood adiposity with menstrual irregularity and PCOS. The Bogalusa Heart Study (BHS) has followed-up a biracial population sample (65% white and 35% white) initially recruited at ages 3-18 years in 1973 in Bogalusa, Louisiana. The BBS sub-study of the BHS began in 2013 with a follow-up of 1,803 female participants.

Abstract

The main childhood adiposity measures described in this thesis were body mass index (BMI) and waist-to-height ratio (WHtR). Childhood overweight and obesity were defined by international age-sex-specific standards for BMI. Childhood abdominal obesity was defined as WHtR ≥0.5. Reproductive outcomes of infertility, pregnancy hypertension, menstrual irregularity, PCOS and menopausal symptoms, including vasomotor symptoms, vaginal dryness, total symptoms and three domain-specific symptoms (somatic, psychological and urogenital), were self-reported.

Results: Childhood obesity before 12 years of age, as defined by BMI, appeared to increase the risk of female infertility. Childhood adiposity was associated with increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult abdominal obesity. Childhood adiposity was not associated with vasomotor symptoms and vaginal dryness that are consistently associated with menopause, but it was associated with more severe total, somatic, psychological and urogenital menopausal symptoms that are not clearly attributable to menopause in women aged 45-49 years. In both CDAH and the BBS cohorts, childhood adiposity was associated with an increased risk of menstrual irregularity and PCOS. However, the association with PCOS was present only in white and not black participants. The risks of adverse reproductive outcomes tended to be highest in women with persistently high adiposity from childhood to adulthood.

Conclusions: Childhood adiposity has important implications for the risks of adverse reproductive health outcomes in adulthood including infertility, pregnancy hypertension, menstrual irregularity, PCOS, total and three domain-specific menopausal symptoms, but not vasomotor symptoms and vaginal dryness in women aged 45-49 years. The prevention of childhood adiposity is important for reproductive health as well as disease prevention. Furthermore, as cumulative exposure to high adiposity status across the life course was associated with significantly higher risks of these adverse reproductive health outcomes, early

intervention and prevention of high adiposity trajectories may help improve future women's reproductive health.

Chapter 1: Introduction

In this introductory chapter, an overall background for the thesis is provided. The chapter begins with the measurement of childhood adiposity and the epidemiology of childhood overweight, obesity and abdominal obesity, followed by a discussion of the aetiology of childhood adiposity, its tracking into adulthood and its adverse health consequences. Then several aspects of women's reproductive health that are the focus of this thesis are introduced and their associations with adiposity, particularly with childhood adiposity are summarized. Finally, the specific research aims of this thesis are proposed.

1.1 Measuring childhood adiposity

Adiposity is defined as the degree of body fat accumulation and in the current literature generally denotes excess body fat [1]. For the purposes of defining terms in this thesis, "overweight" and "obesity" are defined as per established classification metrics relative to body mass index (BMI). Adiposity is defined as abnormal or excess fat accumulation that presents significant risks to health which has a broader meaning than overweight and obesity.

A range of measures are available to assess adiposity with different advantages and disadvantages. The measures used in large-scale epidemiological studies and population surveys often need to be relatively easy and practical. This section will review available epidemiological methods both to clinicians and researchers for assessing childhood adiposity.

1.1.1 Body mass index

BMI is most widely used to indirectly measure overall body adiposity in the population based on relative weight. BMI is calculated as the ratio of weight in kilograms divided by height in meters squared (kg/m^2). Because this calculation requires only height and weight, which is

inexpensive, non-invasive and easy to use, it is applied often by clinicians, researchers and the general public.

In adults, the World Health Organization (WHO) classifies overweight and obesity depending on BMI values. Obesity is defined as a BMI of 30 kg/m^2 or more and overweight is defined as BMI equal to or more than 25 kg/m^2 [2]. However, in children and adolescents, there is no fixed value of BMI to help define overweight and obesity because body composition changes with normal growth and differs between boys and girls [3, 4]. Weight status in children and adolescents needs to be assessed using age- and sex-specific reference values. The following three reference standards have been commonly used to define childhood overweight and obesity by BMI [5-8] and are described below.

The first reference is the Centers for Disease Control and Prevention (CDC) growth chart from the United States of America (USA) [5]. In this USA nationally representative survey data from 1963-1995, childhood overweight and obesity have been identified as a BMI above the 85th and below the 95th centile and above the 95th centile for children of the same age and sex. However, due to data being based on the sample from the USA only, this definition is not universally accepted. The second is the WHO reference. In 2006 and 2007, WHO provided child growth standards for 0-60 months and growth reference for 5-19 years school-age children and adolescents [6, 7]. These charts are based on samples selected to represent optimal growth and there was difficulty in choosing appropriate cut-off values because z-scores were applied, and cut-off points such as z-scores of >1 for childhood overweight and z-scores of >2 for childhood obesity were chosen mainly on the basis of statistical criteria rather than on the basis of health outcomes. The third reference is the International Obesity Task Force (IOTF) definition that resolved the issue of choosing a cut-off value by linking to adult values. The IOTF developed an international definition for childhood overweight and obesity based on pooled data on children from cross-sectional surveys in 6 countries: Brazil, the United

Kingdom (UK), Hong Kong (China), the Netherlands, Singapore and the USA [8]. This definition is less arbitrary and more universal than the others and is linked to the widely accepted adult cut-off points of a BMI of 25 and 30 kg/m^2 associated with adverse health in later life [9]. In this thesis, the IOTF reference has been used to define childhood overweight and obesity.

1.1.2 Other measures of childhood adiposity

BMI values only serve as an indicator of relative weight and are an imperfect measure of adiposity which cannot distinguish between different tissues (eg, fat, muscle, bone) or different body fat distributions (eg, upper/lower, abdominal/peripheral). Other epidemiological measures of body composition include indirect measures such as waist circumference (WC), skinfold thickness and bioelectrical impedance analysis and direct measures such as underwater weighing (densitometry) and dual x-ray absorptiometry (DXA) [10, 11]. Though direct measures have been considered as the gold standards for body fat assessment, these measures are more costly and less feasible for clinical and epidemiological settings compared with indirect measures. Among all the measures of body adiposity, WC has been proposed as a simple and robust proxy for abdominal adiposity or abdominal obesity. However, for people with the same WC but different heights, the degree of abdominal fat distribution may be different. Thus, to control for the height variability, another proxy for abdominal obesity is the waist/height ratio (WHtR) which has been highly recommended for both children and adults in recent years [12, 13]. A WHtR boundary value of 0.50 has been proposed as a simple means of indicating the amount of abdominal fat accumulation as excessive and poses a risk to health [12]. There is a simple public health message for this which applies to children and adults of both sexes and all ages that states ‘keep your waist circumference to less than half your height’ [14]. In this thesis, WHtR has been considered as an important indication of childhood abdominal obesity.

1.2 Prevalence of childhood overweight, obesity and abdominal obesity

1.2.1 The global view

The global prevalence of childhood overweight and obesity has increased dramatically since the 1990s (Figure 1.1). The alarmingly increasing rate of childhood overweight and obesity and its threat to health has made childhood obesity one of the most serious public health crises challenging the medical community in the 21st century.

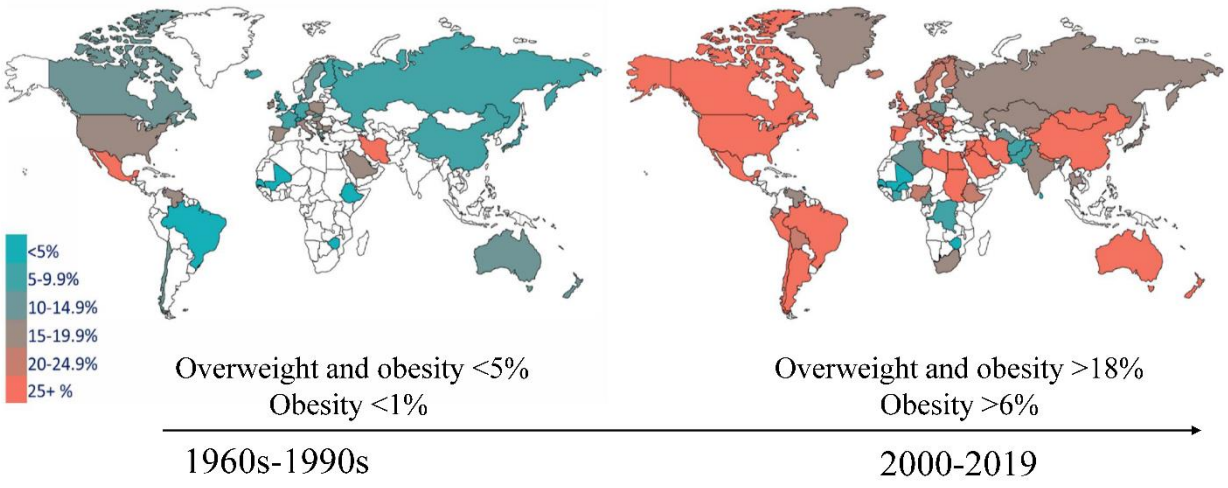


Figure 1.1 Global change in the prevalence of childhood overweight and obesity over time; Figure produced from World Obesity Federation map [15] and World Health Organization report [2]

According to a WHO report, the prevalence of overweight and obesity among children and adolescents more than quadrupled in the forty years from 1975 to 2016 (increasing from 4.0% to 18.0%) [16]. In 1975, less than 1.0% of children and adolescents aged 5-19 years were obese, however by 2016, this figure had dramatically increased to more than 6.0% (6.0% of girls and 8.0% of boys were obese) [16].

The global prevalence of childhood abdominal obesity has not been thoroughly summarized in the literature, however, several studies from different countries have suggested a consistently significant increase of the prevalence over the past few decades (Table 1.1) [14, 17-19].

Table 1.1 Overview of the prevalence of childhood abdominal obesity in USA, UK and China

Country	Survey	Childhood age	Definition of childhood abdominal obesity	Year	Prevalence of abdominal obesity (%)	
					Boys	Girls
USA	National Health and Nutrition Examination		WHtR≥0.5			
		6-19 years		1988-1994	19.3%	21.5%
		6-19 years		1999-2004	29.0%	30.5%
		6-18 years		2011-2012	29.8%	36.2%
UK			WHtR≥0.5			
	British Standards Institute Survey	11-16 years		1977	3.5%-5.5%	1.0-3.0%
	National Diet and Nutrition Survey	11-16 years		1997	17.0%	11.7%
China	China Health and Nutrition Survey	6-17 years	WC above the 90th percentile for gender and age			
				1993	3.4%-4.5%	11.1%-11.7%
				2009	3.2%-8.4%	10.8%-13.0%

Table produced from data reported in the representative cross-sectional surveys in USA [17, 18], UK [14] and China [19].

Abbreviation: UK, the United Kingdom; USA, the United States of America; WC, waist circumference; WHtR, waist-to-height ratio.

1.2.2 Childhood overweight, obesity and abdominal obesity in Australia

Australia has joined the global surge in the rise of the childhood obesity epidemic. The most recent national survey data on the prevalence of obesity in Australian children (aged 7-15 years) were available from the 1985 Australian Schools Health and Fitness Survey (ASHFS) and the 1995 National Nutrition Survey (NNS). These two time points of national data collection show that the prevalence of childhood overweight and obesity in 1985 rose considerably to 1995 [20] (Table 1.2).

Table 1.2 Prevalence of overweight and obesity among boys and girls aged 7-15 years, 1985 and 1995

	Overweight (%)		Obese (%)	
	Year 1985	Year 1995	Year 1985	Year 1995
Boys	9.3%	15.3%	1.4%	4.7%
Girls	10.6%	16.0%	1.2%	5.5%

Table produced from data reported by the Parliament of Australia [20].

The prevalence of overweight and obesity in Australian children after 1995 is available from the Australian Bureau of Statistics' National Health Survey. For children aged 5-17 years, the prevalence of overweight/obesity rose from 21.0% in 1995, 25.0% in 2007-2008 to 27.0% in 2014-2015. Since 2007- 2008, the trend of childhood obesity has remained relatively stable at

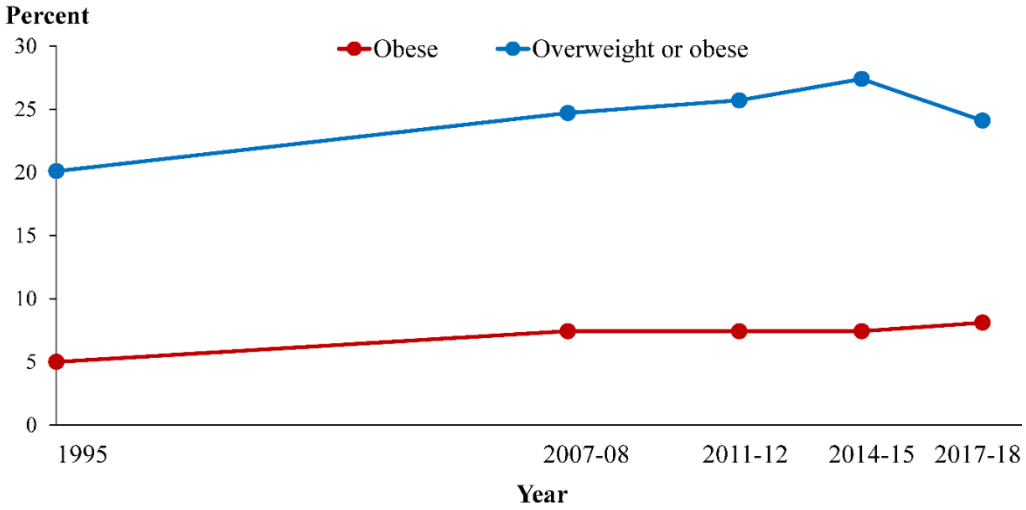


Figure 1.2 Proportion of overweight and obesity in children and adolescents aged 5-17, 1995 to 2014–15 in Australia; Figure produced from data reported by Australian Institute of Health and Welfare [21, 22]

around 7.5% [21] (Figure1.2). In 2017-2018, about 1 in 4 (24.9%) children aged 5-17 years were overweight or obese [22]. Among them about 8.1% of children were obese (Figure1.2). Similar rates of overweight and obesity were found for boys and girls in that age group (26.1% of boys, and 24.0% of girls), and for obesity alone (8.5% of boys, 7.4% of girls) [22].

The prevalence and trends of childhood abdominal obesity in Australia have been recently reported and showed to be significantly increased between 1985 and 2015 [23]. This study was based on five cross-sectional surveys (from 1985 to 2015) conducted among primary school children (aged 3-13 years) and high school adolescents (aged 10-19 years) in New South Wales, Australia (Table 1.3).

Table 1.3 Prevalence of childhood abdominal obesity among boys and girls by year in New South Wales, Australia.

	Childhood abdominal obesity [a] (%)				
	Year 1985	Year 1997	Year 2004	Year 2010	Year 2015
Primary school children					
Boys	8.4%	13.1%	6.8%	12.2%	15.5%
Girls	8.5%	9.3%	4.8%	12.1%	13.6%
High school adolescents					
Boys	10.5%	10.7%	7.2%	9.6%	15.8%
Girls	8.1%	8.4%	3.6%	7.4%	8.0%

[a] Childhood abdominal obesity was defined as waist-to-height ratio≥0.5.
Table produced from data reported by 30-year trends in overweight, obesity and waist-to-height ratio by socioeconomic status in Australian children, 1985 to 2015. International Journal of Obesity 2017 [23].

1.3 Aetiology of childhood adiposity

For most children, there is no single underlying cause of excess body fat. It is widely accepted that childhood adiposity is caused by a complex interaction between the genetic, environment and many other factors (Figure 1.3) [24]. These factors contribute to a positive imbalance between

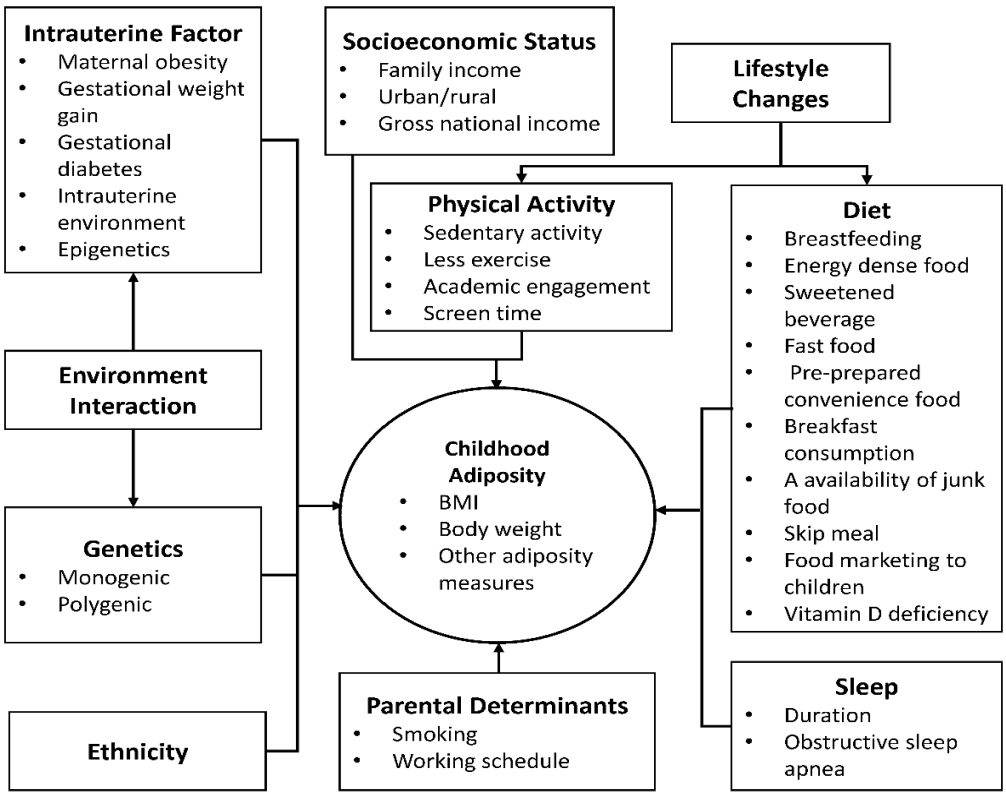


Figure 1.3 Conceptual framework describing the aetiology of childhood adiposity; Figure reproduced from Multifactorial influences of childhood obesity. Current Obesity Reports 2013 [24]

energy intake and energy expenditure and result in excess body fat accumulation in childhood at the endpoints of the developmental pathway [24].

1.4 Tracking of childhood adiposity into adulthood

Adiposity in childhood tends to track over time [25]. Childhood adiposity was strongly predictive of adiposity in adulthood, confirmed in a previous study from our team based on a 20-year follow-up of participants in the 1985 ASHFS in Australia [26]. In this study, 68% of children with overweight and obesity aged 7-15 years remained overweight or obese as young adults. On the other hand, 80% of those who were overweight or obese as young adults were a healthy weight as children.

Another study, the Bogalusa Heart Study (BHS) from the USA, demonstrated childhood BMI not only predicted adult BMI but was also associated with other adult adiposity measures as the thickness of the triceps and subscapular skinfold [27]. In 2008, a systematic review that included 25 studies provided an update of the existing evidence concerning the persistence of childhood adiposity [25]. All the included studies indicated an increased risk for those who were overweight or obese in childhood to become overweight or obese in adulthood. Among the high-quality studies, this risk has been found to be more than two times for children with overweight or obesity compared with children with normal weight. It concluded that there is a moderate likelihood of tracking of childhood overweight and obesity into adulthood. Though whether childhood adiposity is an independent risk factor for adverse adult health consequences irrespective of adult adiposity remains uncertain, its prevention is an important public health priority to help reduce the risk of adult adiposity and to prevent its short-term (for the child) and long-term (in adulthood) health consequences.

1.5 Health consequences of childhood adiposity

Adiposity in childhood and adolescence negatively affects nearly every organ system including the reproductive system with potential short- and long-term health consequences (Figure 1.4). For example, excess body fat has been associated with vitamin D and iron deficiency in children [29, 30]. Further, orthopaedic complaints, for example, fractures, musculoskeletal disorders, decreased mobility, and lower limb malalignment may be seen more frequently in children with obesity compared to children who are of normal weight [31]. In addition, respiratory disorders, including asthma, obstructive sleep apnoea and other reactive airway disease are more often observed among children with obesity [32].

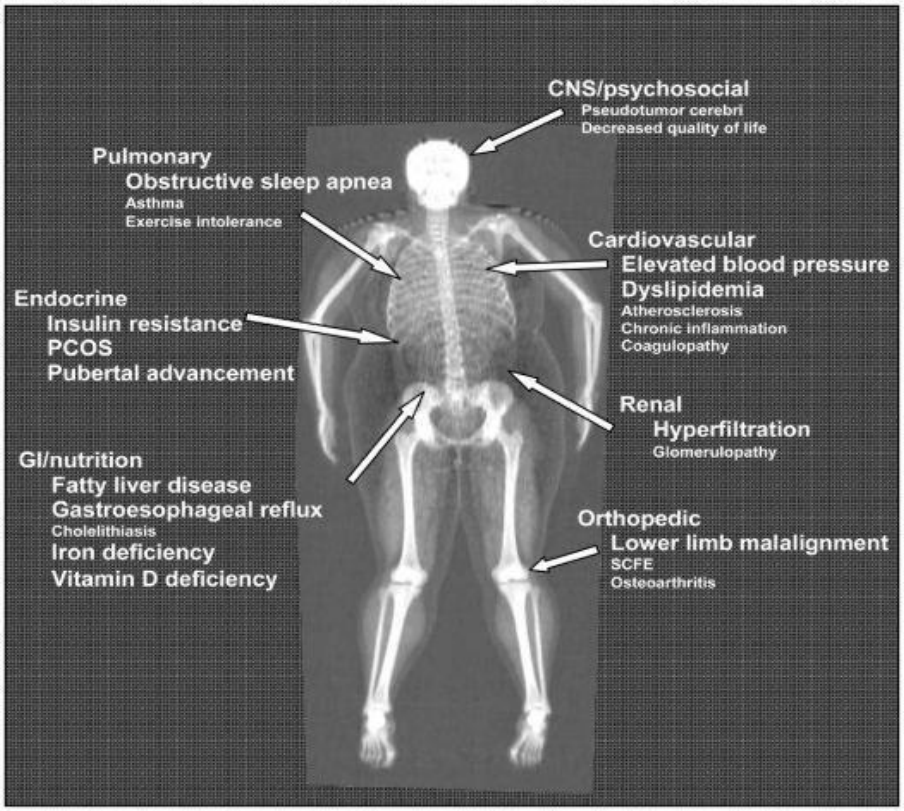


Figure 1.4 Complications associated with childhood adiposity; Figure reproduced from Childhood Obesity. Lancet 2010 [28]

Image obtained by dual energy X-ray absorptiometry from a teenage girl with BMI 38 kg/m^2.

Every possible consequence of childhood adiposity is not discussed in detail in the next section but the cardiovascular risks as the most widely studied physical consequences and psychosocial consequences as the most widespread consequences are introduced [33, 34]. In addition, here the consequences of childhood adiposity on reproductive health during adolescence and adulthood will also be touched on to bring up the topic of this thesis.

1.5.1 Cardiovascular health consequences

The cardiovascular health consequences associated with childhood adiposity are the most widely studied in the current literature. For example, a large number of high-quality studies have consistently reported that childhood adiposity increased cardiovascular risk factors in both childhood and adults. In childhood, including high blood pressure, dyslipidaemia, insulin resistance, disturbances of left ventricular structure and function and endothelial dysfunction, etc [35]. Furthermore, abdominal fatness has been suggested as a primary driver of cardiometabolic dysfunction [36]. In adulthood, many studies have shown a positive relationship between childhood adiposity and risk factors for adult cardiovascular disease (CVD), but it remains unclear whether this association is independent of adult adiposity. One previous study combined data from four cohorts and indicated that the increase in cardiovascular risk in adults was associated with childhood obesity as measured by BMI because of the tracking of obesity from childhood to adulthood [37]. Another study from our team indicated that elevated waist circumference in childhood, independent of changes in waist circumference from childhood to adulthood, was strongly associated with subsequent cardio-metabolic health in early adulthood [38]. The relative contributions of childhood and adult adiposity to cardiovascular outcomes have yet to be fully delineated.

1.5.2 Psychological consequences

In childhood, psychological morbidity is likely to be the most widespread health consequence of childhood adiposity [33]. A recent systematic review that included 53 studies (cross-sectional and longitudinal) established that childhood overweight and obesity were negatively associated with multiple psychological comorbidities during childhood, including depression, emotional and behavioural disorders, poor health-related quality of life and lower self-esteem during childhood [39]. Another systematic review included 15 prospective studies and provided support for the temporal relationship between psychological conditions including depression, behaviour disorders and low self-esteem with subsequent childhood overweight and obesity [40]. Therefore, the current literature indicates a bi-directional relationship between adiposity and psychological disorders during childhood.

In the longer term, however, fewer studies have reported the association of childhood adiposity with psychological consequences in adults. To the best of our knowledge, six population-based cohort studies have reported this long-term association [41-46]. Five of them [42-46] suggested that childhood overweight or obesity may increase risk for depression, anxiety and mood disorders in adulthood, but one study reported no association [41].

1.5.3 Reproductive health

Reproductive health in females from menarche to menopause and beyond encompasses a wide range of topics. In adolescent girls, early onset of puberty, menstrual irregularity and polycystic ovary syndrome (PCOS) symptoms are the three most prominent reproductive problems linked to childhood adiposity [47]. A recent meta-analysis indicated that girls with obesity had more than two times the risk of early puberty compared with normal weight girls [48]. The diagnosis of menstrual disorders and is difficult to make in adolescents, as menstrual irregularity, symptoms of androgen excess (e.g., acne) and multi-follicular ovary morphology could be

normal or transitory in puberty [49]. However, childhood adiposity has been considered to be associated with menstrual irregularity in adolescence, and play an important role in the development of PCOS [50, 51]. Although it is generally accepted that adult adiposity adversely affects female reproductive health including infertility, pregnancy complications, miscarriage, preterm birth, menstrual disorders, PCOS, menopausal symptoms and a number of other reproductive problems [52-54], very little is known about the long-term risk for these reproductive outcomes from childhood adiposity. In the next section 1.6, the long-term associations of childhood adiposity with several aspects of reproductive health will be captured.

In general, the associations of adiposity with male reproductive health have been much less studied. In adolescent boys, observations of the associations of overweight and obesity with pubertal timing are inconsistent with either early or delayed pubertal onset [48]. Childhood adiposity may also be associated with hypogonadism in boys but more data is needed to confirm this association [55]. In males, adult adiposity has been suggested to be associated with reduced fertility, semen quality [56] and greater risk of erectile dysfunction [57]. Similar to women's reproductive health, there is a lack of long-term follow-up studies of male reproductive health following childhood adiposity. As far as we know, only two studies have been reported indicating no association of childhood BMI with semen quality in adulthood [58, 59].

In summary, in the past few decades, while many studies have contributed knowledge on the associations of childhood adiposity with a broad range of health consequences, the long-term effects of childhood adiposity remain unclear in many aspects, including reproductive health. In the following section, reproductive health in women and its associations with adiposity, especially childhood adiposity, are reviewed.

1.6 Reproductive health in women and its association with adiposity

Within the framework of the WHO definition, reproductive health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to reproductive functions and processes [60]. Reproductive and sexual ill-health make a major contribution to the global disease burden, particularly for women, estimated to account for 21.9% of the disability-adjusted life year (DALY) lost for women compared with only 3.9% for men [61]. Here, we will cover several reproductive health outcomes in women, including infertility, pregnancy hypertension, menstrual irregularity and polycystic ovary syndrome, and menopausal symptoms, that are the focus of this thesis. For a logical order, their relationships with adult adiposity are introduced first and then their long-term associations with childhood adiposity are reviewed.

1.6.1 Infertility

Infertility is a critical component of reproductive health. The definition of infertility is different across clinical practice, epidemiological research and demographic studies. The classic clinical definition of infertility is defined as the inability to conceive after 12 months of unprotected intercourse [62]. Epidemiological and demographic definition of infertility used a two-year and five-year "exposure period" [63]. Besides, many reproductive health surveys ask women about infertility treatment and whether they had visited a doctor for help getting pregnant. These inconsistent definitions used in the studies have made the global infertility prevalence rates difficult to determine [64]. An estimate from 25 population surveys sampling 172,413 women aged 20-44 indicates a 9% prevalence of infertility (of 12 months) [65]. More recently, a study based on data from 190 countries shows that the overall burden of infertility (of more than five years) in women aged 20-44 is about 10% [66]. In Australia, infertility (of 12 months) is estimated to affect one in six couples during their reproductive life [67, 68]. Although there is no clear

evidence of a recent change to a higher prevalence of infertility, there has been an increased awareness of infertility and assisted reproduction [69].

1.6.1.1 Adult adiposity and infertility

Adiposity in women has been associated with an increased risk of infertility which has been extensively studied in the past and has been well summarised in the literature [70-73]. The United Kingdom's National Institute for Clinical Excellence (NICE) fertility guidelines has made initial advice to women concerned about delays in conception that 'Women who have a body mass index of more than 29 should be informed that they are likely to take longer to conceive' [74]. Also, abdominal obesity has been suggested to may have more impact on infertility, as it linked more with hormonal abnormalities, for example, more hyperandrogenism and insulin resistance, which can disrupt ovulation [75, 76]. Ovulatory dysfunction is the main cause of infertility in women with adiposity [70].

1.6.1.2 Childhood adiposity and infertility

The long-term relationship of childhood adiposity with infertility remains unclear. Four studies have reported the association with childhood overweight and obesity and childhood skinfold thickness as summarised in Table 1.4 Summary of four studies reporting the association between childhood adiposity and female infertility Two of them were prospective studies [77, 78] and two were retrospective studies [79, 80]. The two retrospective studies from the USA, the Nurses Health Study [79] and the Study of Women's Health Across the Nation (SWAN) [80], both reported that adolescent obesity was associated with infertility problems. However, the results from the two prospective studies are inconsistent. The 1958 British birth cohort study found childhood BMI at 7 years had little impact on later infertility [77], however, the Bogalusa Heart Study reported there was a difference in the associations by adiposity during various time periods of growth [78]. Those with childhood adiposity before age 12 (childhood obesity and high

childhood skinfold thickness) were more likely to report infertility but no association was found with childhood adiposity between ages 13-18 years. Furthermore, no study yet has reported the association with childhood abdominal obesity. Therefore, more research is required to determine the association between childhood adiposity and infertility.

Table 1.4 Summary of four studies reporting the association between childhood adiposity and female infertility

Study	Country/Year of publication	Design	Participants	Female age	Childhood age	Adiposity measure	Primary outcomes	Key findings
Rich-Edwards JW et al. [79]	USA/1994	Case control study	49,245 female nurses (cases 2,627 ovulatory infertility and controls 46,718)	25-42 years	18 years	BMI	Risk factors for ovulatory infertility	Elevated BMI at age 18 is a risk factor for subsequent ovulatory infertility
Lake JK et al. [77]	UK/1997	Prospective study	5,799 females in the 1958 British birth cohort study	33 years	7 years	BMI	Infertility	Childhood BMI had little impact on infertility
Polotsky AJ et al. [80]	USA/2010	Retrospective study	The Study of Women's Health Across the Nation (SWAN) 3,154 women	42-52 years	High school	BMI	Lifetime nulliparity and lifetime nulligravidity	Adolescent obesity is associated with lifetime nulliparity and nulligravidity in midlife
Jacobs MB et al. [78]	USA/2017	Prospective study	1,061 women Bogalusa Heart Study	45.5 years	<9-18 years	BMI; skinfold thickness	Fertility difficulties	Childhood adiposity before12 was more likely to report fertility difficulties

Abbreviation: BMI, body mass index; UK, the United Kingdom; USA, the United States of America.

1.6.2 Pregnancy hypertension

Pregnancies complicated by hypertension are associated with an increased risk of maternal morbidity [81, 82]. A WHO review identified pregnancy hypertension as a leading cause of maternal death in both developed and undeveloped countries, accounting for 9%-25% of maternal deaths [83]. Pregnancy hypertension includes four categories: gestational hypertension, pre-eclampsia, chronic hypertension and chronic hypertension with superimposed pre-eclampsia. Among them, pre-eclampsia represents the severe end of the spectrum that complicates about 3% of pregnancies, and overall hypertensive disorders affect about 5%-10% of pregnancies [84]. The definitions of pregnancy hypertension are summarized below in Table 1.5.

Table 1.5 Definitions and classifications of pregnancy hypertension

Classification	Symptoms	Onset during the pregnancy
Gestational hypertension	Blood pressure>140/90 mmHg	>20 weeks and returns to normal within 12 weeks postpartum
Pre-eclampsia	Gestational hypertension + proteinuria (defined as the urinary excretion of ≥300 mg of protein in 24 h)	>20 weeks
Chronic hypertension	Pre-existing hypertension	Before pregnancy
Chronic hypertension with superimposed pre-eclampsia	Chronic hypertension + pre-eclampsia	>20 weeks

1.6.2.1 Adult adiposity and pregnancy hypertension

Epidemiological studies show strong evidence of higher adult BMI increasing the risk of pregnancy hypertension. In a systematic review, the risk of preeclampsia doubled with each 5-7 kg/m^2 increase in pre-pregnancy BMI [85]. Abdominal obesity in women has also been suggested to be more strongly associated with pregnancy hypertension because in nonpregnant status, centrally located fat is a more potent determinant of blood pressure elevation than peripheral body fat [86], though not many studies have reported the association of pregnancy

hypertension with abdominal obesity measures [87-89]. One prospective cohort study from Australia reported that each 1 cm increase in waist circumference in women showed a 4% increased risk for pregnancy hypertension [88].

1.6.2.2 Childhood adiposity and pregnancy hypertension

For the associations with childhood adiposity, two prospective studies have reported consistent findings that higher childhood BMI increased the risk of pregnancy hypertension (Table 1.6). However, evidence for whether this association was independent of adult BMI remains unclear, as adult BMI was only considered in the study from Lake JK *et al* and they reported that the risk of pregnancy hypertension did not persist after further adjustment for adult BMI [77]. Although abdominal obesity in childhood has been suggested to have a stronger association with cardiovascular risk than childhood BMI [90], no studies have reported whether childhood abdominal obesity is associated with pregnancy hypertension. Further work is required to examine the association between various childhood adiposity measures with pregnancy hypertension, particularly if the association remains independent of corresponding adult adiposity measures.

Table 1.6 Summary of two prospective studies reporting the association between childhood obesity and pregnancy hypertension

Study	Country/ Year of publication	Design	Participants	Adult age	Childhood		Primary outcomes	Key findings
					Age	Adiposity measure		
Lake JK et al. [77]	UK/1997	PS	5,799 females in the 1958 British birth cohort	33	7	BMI	Self-reported PH	Elevated BMI in childhood is associated with increased risk of PH
Li S et al. [91]	USA/2016	PS	703 women BHS	25.5-51.3	<9-18	BMI		

Abbreviation: BMI, body mass index; BHS, Bogalusa Heart Study; PS, prospective study; PH, pregnancy hypertension; UK, the United Kingdom; USA, the United States of America.

1.6.3 Menstrual irregularity and polycystic ovary syndrome (PCOS)

The regularity of menstrual cycles is considered an important marker of healthy reproductive function in women [92]. A normal menstrual cycle is typically in the range of 25-35 days [92-95]. Irregular menstrual cycles are often defined as abnormal variation or variability in length of menstrual cycles. The clinical consensus recommendations of menstrual irregularity for women >3 years post menarche to perimenopause defines it as a menstrual cycle <21 or >35 days or <8 cycles per year [96]. It is assumed that menstrual irregularity affects 10-38% of menstruating women [97-100]. 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 [96]. PCOS is recognized as the most common heterogeneous endocrine disorder affecting 8-13% of women of reproductive age [101]. The three recommended diagnostic criteria for PCOS are summarized in Table 1.7.

Table 1.7 Recommended diagnostic criteria for polycystic ovary syndrome [102]

Signs and symptoms	National Institutes of Health Criteria 1990 (both are required for diagnosis)	Rotterdam Consensus Criteria 2003 (two out of three are required for diagnosis)	Androgen Excess Society 2006 (hyperandrogenism plus one out of remaining two are required for diagnosis)
Irregular cycles and ovulatory dysfunction	R	NR	R
Hyperandrogenism [a]	R	NR	NR
Polycystic ovaries by ultrasound diagnosis		NR	NR

Abbreviations: R, required for diagnosis; NR, possible diagnostic criteria but not required to be present.
[a] Hyperandrogenism refers to either the presence of hirsutism or biochemical hyperandrogenemia.
Table reproduced from Polycystic Ovary Syndrome: American College of Obstetricians and Gynecologists (ACOG) practice bulletin, number 194. Obstetrics and Gynecology 2018.

1.6.3.1 Adult adiposity, menstrual irregularity and PCOS

It is clear in the literature that women with obesity as well as abdominal obesity are more likely to experience menstrual cycle irregularity than women with normal adiposity status [103]. However, the cause and effect relationship between PCOS and adiposity remains unclear. A

comprehensive systematic review included 106 studies with 35 studies included in the meta-analysis concluded that women with PCOS had significantly greater risk of overweight, obesity, and central obesity [104]. However, as this is a cross-sectional investigation, the temporal relationship between adiposity and PCOS could not be determined. It has been suggested in the literature that both environmental and genetic factors are implicated in the development of PCOS [105]. The importance of the role of adiposity in the development of PCOS remains to be confirmed in longitudinal studies.

1.6.3.2 Childhood adiposity, menstrual irregularity and PCOS

To our knowledge, only two prospective population-based studies have reported the long-term associations of childhood BMI with menstrual irregularity and PCOS in adulthood and these associations with childhood abdominal obesity remain a gap in knowledge (Table 1.8).

Table 1.8 Summary of two prospective population-based cohort studies reporting the association between childhood obesity and menstrual irregularity and PCOS

Study	Country/Year of publication	Design	Participants	Adult age	Childhood		Primary outcomes	Key findings
					Age	Adiposity measure		
Lake JK et al. [77]	UK/1997	PS	5,799 females from the 1958 British birth cohort study	33	7	BMI	Menstrual irregularity	Obesity at age seven increased the risk of menstrual irregularity
Laitinen J et al. [106]	Finland/2016	PS	2,007 women from 1966 North Finland birth cohort	31	14	BMI	Self-reported PCOS	Obesity at age 14 was associated with self-reported PCOS at age 31

Abbreviation: BMI, body mass index; PCOS, polycystic ovary syndrome; PS, prospective study; UK, the United Kingdom.

Although both studies reported consistent findings of a positive association of childhood BMI with menstrual irregularity and PCOS and the literature suggests that a pathway linking childhood adiposity with menstrual irregularity and hyperandrogenemia may increase the risk of PCOS [107, 108], at the time of writing, no formal studies report an increasing prevalence of

PCOS with the rising tide of childhood obesity [50]. On the contrary, a similar prevalence of PCOS among populations and races with different prevalence of adiposity may imply that adiposity does not play a critical role in the development of PCOS [109]. Thus, further studies to investigate the associations of childhood obesity, including childhood abdominal obesity, with menstrual irregularity and PCOS in different populations and races are needed.

1.6.4 Menopausal symptoms

The term "menopause" refers to the final menstrual period and it marks the end of a woman's reproductive life. Most women become menopausal naturally between the ages of 45 and 55 years, with the median age of onset at 51 years [110]. The menopause transition starts at around 47 years [110]. It is a time from the onset of menstrual cycle changes until one year after the final menstrual period and is often accompanied by various bothersome symptoms [111]. Among these symptoms, vasomotor symptoms (VMS) and vaginal dryness are most consistently associated with the menopause transition and are attributable to ovarian aging and senescence [112]. Other symptoms such as mood changes, sleep disturbances, and urinary incontinence may be secondary to other symptoms or related to other causes that are not specific to menopause [113-115]. The measurement of menopausal symptoms has been difficult. Various tools have been developed to assess menopausal symptoms, but most of them lacked standardization, validity and reliability. The Menopause Rating Scale (MRS) is one of the common menopausal symptom scales that has been well accepted internationally. The MRS grades the self-reported severity of 11 symptoms (hot flashes and sweating i.e. VMS, heart discomfort, sleep problems, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, dryness of vagina, joint and muscular discomfort) on a standardized scale from 0 to 4 [116]. During the standardization of the instrument, three dimensions have been identified: somatic (VMS, heart discomfort, sleep problems, joint and muscular discomfort), psychological (depressive mood, irritability, anxiety, physical and mental exhaustion) and

urogenital symptoms (sexual problems, bladder problems, dryness of vagina). The high reliability and validity of the MRS from the current available methodological evidence has suggested the clinical utility of the scale in monitoring menopausal symptoms over time [116].

1.6.4.1 Adult adiposity and menopausal symptoms

For many years, more adipose in women was assumed to be protective against VMS because androgens are aromatized into estrogens in body fat [117]. However, recent studies have shown that adiposity is a key risk factor for VMS during the menopause transition and early post-menopause. Women with obesity and abdominal obesity are more likely to report VSM [118, 119]. This association may be explained by the thermoregulatory theory that hypothesizes that adipose tissue acts as an insulator resulting in elevated core body temperature, thereby increasing the occurrence and the severity of hot flashes [120]. Other physiologic mechanisms refer to the endocrine function of adipose tissue. The multiple cytokines and inflammatory factors secreted by adipose tissue may also increase the risk of VMS occurrence [121-123] and/or relate to ovarian insufficiency [124, 125]. Evidence on the association between adiposity and vaginal dryness is limited. Several cross-sectional studies have reported that there was no significant association of higher adult BMI with vaginal dryness [126, 127]. For other menopausal symptoms, adiposity was found to be associated with joint and urinary symptoms during the menopausal transition, however, it is not clearly known whether these symptoms are attributable to menopause [126].

1.6.4.2 Childhood adiposity and menopausal symptoms

Our current knowledge on how adiposity is associated with menopausal symptoms is limited to studies from adulthood. Up to now, no study has reported the long-term association of childhood adiposity with menopausal symptoms in midlife women. However, a number of epidemiological studies have investigated the influence of birthweight on age at natural

menopause but with mixed findings [128]. A systematic review included 11 studies on birth weight and age at menopause reported that nine studies indicated no association of low birth weight with age at menopause while two studies suggested that a higher birth weight was associated with early menopause [129]. Recently, another one study reported that lower birth weight was associated with natural menopause at an earlier age [130]. To our knowledge, only one study in the literature has reported the association of childhood BMI with age at menopause and indicated no association with childhood BMI at age 15 [131].

1.7 Summary

Adiposity in adulthood has a profound impact on female reproductive health with multiple adverse outcomes. However, the long-term associations of reproductive health with childhood adiposity remain understudied. Furthermore, there are gaps in the literature about how childhood abdominal obesity and the change in adiposity status from childhood to adulthood are associated with women's reproductive health. Therefore, in this thesis I will determine the long-term associations of childhood adiposity with the above-mentioned reproductive health outcomes with data available from two cohort studies. One is the Childhood Determinants of Adult Health (CDAH) study from Australia and the other is the Bogalusa Babies Sub-Study (BBS) from the USA. Both studies will be described in the next chapter, Chapter 2. The research aims of this thesis and the chapters where they are presented in detail are outlined below.

1.8 Research aims

1. To evaluate whether childhood adiposity is associated with infertility during women's reproductive years (Chapter 3).
2. To investigate the associations between adiposity in childhood, and change in adiposity status from childhood to adulthood, with pregnancy hypertension (Chapter 4).

3. To estimate the associations of childhood adiposity with menstrual irregularity and PCOS in adulthood and determine whether these differed by race (Chapter 5).
4. To examine the associations of adiposity in childhood with menopausal symptoms in women aged 45-49 years (Chapter 6).

Childhood adiposity measures in this thesis include overall adiposity measured by BMI and different abdominal adiposity measures. Childhood overweight and obesity were defined by age-sex-specific international standards for BMI and abdominal obesity defined as the waist-to-height ratio (WHtR) ≥0.5.

Chapter 2: Methods

All the studies presented in this thesis including from Chapter 3 to Chapter 6 used data from the Childhood Determinants of Adult Health (CDAH) study. Chapter 5 additionally used data from the Babies Sub-Study the Bogalusa Heart Study (BBS). The information in this chapter provides an overview of these two cohorts and the statistical methods in the studies.

2.1 The Childhood Determinants of Adult Health (CDAH) study

The CDAH study is an Australian-based cohort that followed schoolchildren who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS). So far, there have been three follow-ups. The overall aim of the CDAH study is to examine the importance of childhood factors in the development of adult cardiovascular diseases and diabetes. During the follow-ups of CDAH, reproductive health questions were included for female participants, which enables an investigation of the long-term associations of childhood adiposity with women's reproductive health over a 35-year lifespan.

2.1.1 The Australian Schools Health and Fitness Survey (ASHFS) (1985)

2.1.1.1 Participants

The 1985 ASHFS was conducted on a nationally representative sample of 8,498 Australian schoolchildren with 4,191 girls aged 7-15 years. To achieve a nationally representative sample, a two-stage probability sample was used. The first stage was the sampling of schools. Primary and secondary schools were selected to represent each state and territory of Australia with a probability proportional to the enrolment numbers of students. A total of 109 schools were finally surveyed (Figure 2.1). The second stage was the sampling of boys and girls in each age group. Samples of groups of boys and girls of each age were drawn from the total school

enrolment randomly. The measurements included in the 1985 ASHFS covered an extensive range of health, lifestyle, physical fitness and physical performance parameters. Anthropometry was conducted as part of the health measures which could help estimate childhood adiposity.

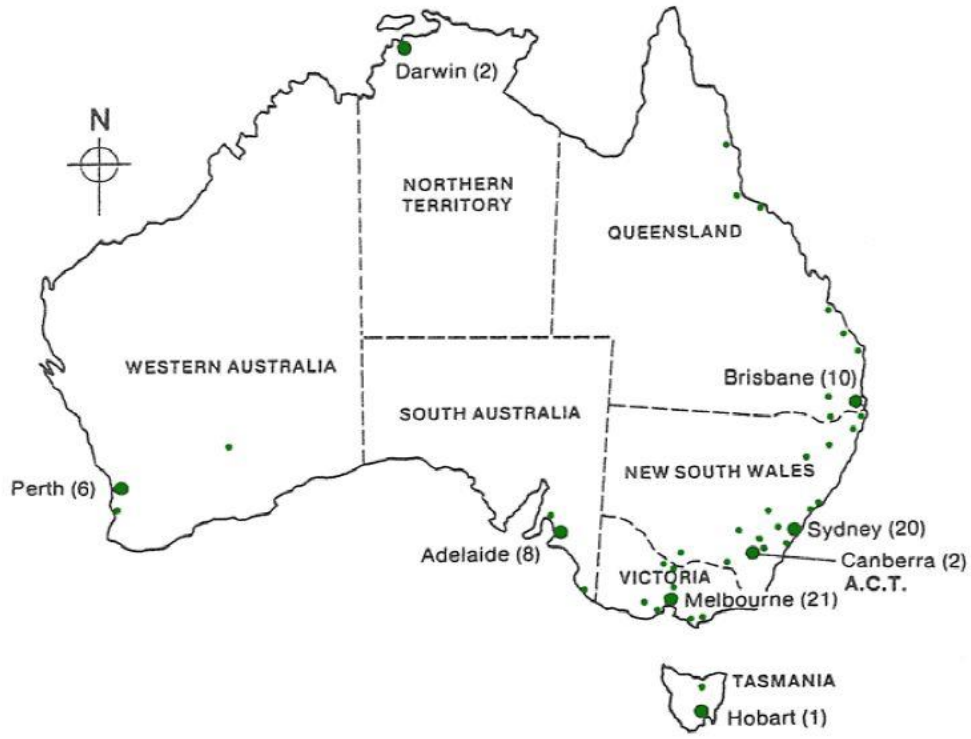


Figure 2.1 Distribution of schools surveyed in the 1985 Australian Schools Health and Fitness Survey indicated by the green dots; Figure reproduced from Australian Health and Fitness Survey 1985: the fitness, health and physical performance of Australian school students aged 7-15 years [132]

2.1.1.2 Childhood adiposity measures

Adiposity measures in this thesis included BMI and several abdominal adiposity measures (Table 2.1). BMI was calculated as weight (kg)/height $(m)^2$ and classified into normal, overweight and obese weight status by using international age- and sex-specific cut-points in childhood [8]. Waist-to-hip ratio was calculated as waist circumference (cm)/hip circumference (cm). WHtR was calculated as waist circumference (cm)/height (cm) with a WHtR≥0.5 indicating abdominal obesity [133].

The anthropometric measurements in childhood were taken at the schools by trained field staff for all the children in 1985. All these measurements were conducted in a standing position with light clothing. Weight and height were measured with shoes and socks removed. Weight was measured with beam or medical spring scales to the nearest 0.5 kg and repeated until two consecutive measures were the same. Height was measured with a Kawe Height tape or rigid measuring tape to the nearest 0.1 cm, with shoes and socks removed. Waist circumference and hip circumference were taken at the level of the umbilicus and the level of the greatest posterior protuberance of the buttocks to the nearest 0.1 cm using a constant tension tape.

Table 2.1 Summary of adiposity measures in childhood and adulthood in CDAH study

	ASHFS	CDAH-1	CDAH-2	CDAH-3
Adiposity measures				
Overall adiposity	All measured	Self-reported + clinic measured	Self-reported	Self-reported + clinic measured
BMI	✓	✓	✓	✓
BMI category	✓	✓	✓	✓
Normal	✓	✓	✓	✓
Overweight	✓	✓	✓	✓
Obese	✓	✓	✓	✓
Abdominal adiposity measures	All measured	Clinic measured for a subsample		Clinic measured for a subsample
Waist circumference	✓	✓		✓
Waist-to-hip ratio	✓	✓		✓
WHtR	✓	✓		✓
WHtR category	✓	✓		✓
<0.5	✓	✓		✓
≥0.5	✓	✓		✓

Abbreviation: ASHFS, Australian School Health and Fitness Survey; BMI, body mass index; CDAH, Childhood Determinants of Adult Health; WHtR, waist-to-height ratio.

2.1.2 CDAH-1 follow-up (2004-06)

2.1.2.1 Participants

During 2002-04, approximately twenty years after the ASHFS was conducted, a total of 6,840 participants (3,412 female) were traced and 5,170 (60.8% of original ASHFS cohort; 2,734 female) of them were enrolled in the CDAH study. As this thesis focuses on women, the following description of the study participants in the CDAH follow-ups concentrates on female participants.

During 2004-06, 1,607 women participated in the first follow-up of CDAH (CDAH-1) when aged 26-36 years and completed questionnaires including questions on infertility, pregnancy, menstrual cycle characteristics, PCOS, use of hormonal contraceptives, age at menarche, parity (Appendix A). Among them 1,225 women attended one of 34 clinics held across Australia as part of the CDAH-1. At clinics participants had a range of physical measurements made by trained staff including anthropometric measurements, blood pressure, physical fitness, vascular ultrasound examination and a blood sample was collected that was later used for hormone measurements.

2.1.2.2 Adult adiposity measures in CDAH-1

For all the anthropometrics measured at CDAH-1 clinics, participants were standing and dressed in light clothing without shoes and these measurements were not taken on pregnant women (n=82) (protocols in Appendix B). Weight was measured to the nearest 0.1kg using Heine scales and height was recorded to nearest 0.1cm with a Leicester height measure. Waist circumference was taken at the level of the narrowest point between the lower costal (10th rib) border and the iliac crest. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Waist and hip circumferences were measured with Lufkin steel (non-stretch) tape three times and were recorded to the nearest 0.5cm. If the first two measurements were the same, a third measurement was not taken. Mean waist and hip circumference were calculated.

Participants also self-reported their weight and height in the questionnaires (Table 2.1) and these values allowed estimation of, and correction for error, which has been described in detail elsewhere [26]. In brief, a sub-sample (n=1,119) of female participants who attended the clinics also self-reported their weight and height before measurements were taken by clinic staff. The difference between clinic and self-reported weight and height was used to calculate a correction

factor from a linear regression model. The agreement between self-reported and clinic BMI categories was high (κ=0.82 for females).

Adult BMI was categorized into three groups (<25, 25-29.9 and ≥30 kg/m^2). Overweight was defined as 25≤ BMI ≤29.9 kg/m^2 and obesity was defined as BMI ≥30 kg/m^2 [2]. Adult abdominal obesity was defined as WHtR ≥0.5 [13].

2.1.2.3 Reproductive outcomes in CDAH-1

Reproductive outcomes including infertility, pregnancy hypertension, menstrual irregularity and PCOS were defined by their relevant questions in CDAH-1 self-report questionnaire among female participants (Table 2.2 and Appendix A).

2.1.3 CDAH-2 follow-up (2009-10)

2.1.3.1 Participants

In 2009-10, 1,131 female participants aged 31-41 years participated the second follow-up of CDAH (CDAH-2) and completed a similar questionnaire to that used in CDAH-1. No clinics were conducted as part of CDAH-2.

2.1.3.2 Adult adiposity measures in CDAH-2

Objectively measured anthropometrics were not available in CDAH-2 (Table 2.1). Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the same correction factor applied at CDAH-1. BMI was calculated using measured height at CDAH-1 or adjusted self-reported height at CDAH-1 or at enrolment.

2.1.3.3 Reproductive outcomes in CDAH-2

In CDAH-2, reproductive outcomes including infertility, pregnancy hypertension, menstrual irregularity and PCOS was self-reported by participants using the same questions as in CDAH-1 (Table 2.2 and Appendix A).

2.1.4 CDAH-3 follow-up (2014-19)

2.1.4.1 Participants

The third CDAH follow-up (CDAH-3) was conducted between 2014-19 with 1,165 women aged 36-49 participating. During 2018-19, the Menopause Rating Scale (MRS) was included in the questionnaire and was completed by 1,007 women aged 39-49. 844 women attended one of 28 clinics held in major centres across Australia and had physical measurements made by trained staff as in CDAH-1. Blood as well as urine samples were collected in CDAH-3 clinics.

2.1.4.2 Adult adiposity measures in CDAH-3

In CDAH-3 clinics, anthropometric measurements followed the same protocols as in CDAH-1 (Appendix B). Weight, height, waist circumference and hip circumference were measured at study clinics for most participants and were not taken in pregnant women (n=11). Self-reported weight and height values (Table 2.1) were adjusted for a new correction factor derived from the CDAH-3 study sample using the method described in CDAH-1. 790 female participants self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. Similar to CDAH-1, the agreement between self-reported and clinic BMI categories was high (κ=0.88 for females).

2.1.4.3 Reproductive outcomes in CDAH-3

As indicated above, menopausal symptoms were measured by the MRS (Table 2.2 and Appendix C). This scale has been introduced briefly in the Introduction (1.6.4 Menopausal symptoms). For each of the 11 symptoms, the score (0 to 4) increases point by point with increasing severity of subjectively perceived complaints. The evaluation of each symptom, three domain-specific symptoms and the total score will be described in detail in Chapter 6.

Table 2.2 Summary of reproductive health outcomes in adulthood in CDAH study

	CDAH-1	CDAH-2	CDAH-3
Reproductive health outcomes			
Infertility	✓	✓	
	Self-reported 'yes' to either questions: • Have you ever tried to become pregnant for 12 months or more without succeeding? • Have you ever seen a doctor because you were having trouble becoming pregnant?		
Pregnancy hypertension	✓	✓	
	Self-reported 'yes' to the question: • Have you ever been told that you have high blood pressure? If yes, was this during pregnancy?		
Menstrual irregularity	✓	✓	
	First the usual menstrual cycle length was obtained by question: • How long is your usual menstrual cycle? Then menstrual irregularity was defined as reporting menstrual cycles ≥ 35 days or < 25 days or extremely irregular		
PCOS	✓	✓	
Self-reported doctor diagnosed PCOS	Self-reported 'yes' to the question: • Has a doctor ever told you that you have polycystic ovaries or polycystic ovary syndrome?		
Menstrual irregularity + hirsutism	Self-reported menstrual irregularity (defined as above) and 'yes' to the question on hirsutism: • Have you ever seen a doctor because of concern about the amount of hair on your face?		
Menopausal symptoms			✓ Measured by the MRS

Abbreviation: CDAH, Childhood Determinants of Adult Health; MRS, Menopause Rating Scale; PCOS, polycystic ovary syndrome.

2.2 The Babies sub-study of the Bogalusa Heart Study (BBS)

The BBS study is a sub-study of the Bogalusa Heart Study (BHS). The BHS is a comprehensive long-term prospective population study that started in 1973 with multiple cross-sectional and longitudinal surveys. The overall aim of the BHS is to investigate the early natural history of cardiovascular diseases. About 40 years later, BBS as a sub-study of BHS was conducted among female participants who had ever participated in the BHS. The main aim of the BBS was to examine the role of cardiovascular risk factors in childhood on reproductive outcomes.

2.2.1 The Bogalusa Heart Study (BHS) (1973)

2.2.1.1 Participants

The BHS began in 1973, started by Dr. Gerald Berenson, is a biracial (65% white and 35% black) prospective cohort study among children and young adults in the semirural town of Bogalusa, Louisiana, USA [134]. The initial cross-sectional study examined approximately 4,000 children aged 3-18 years in 1973-1974. Subsequent cross-sectional and longitudinal surveys were conducted approximately every 2 years for children aged 3-18 through 1994 and every 5

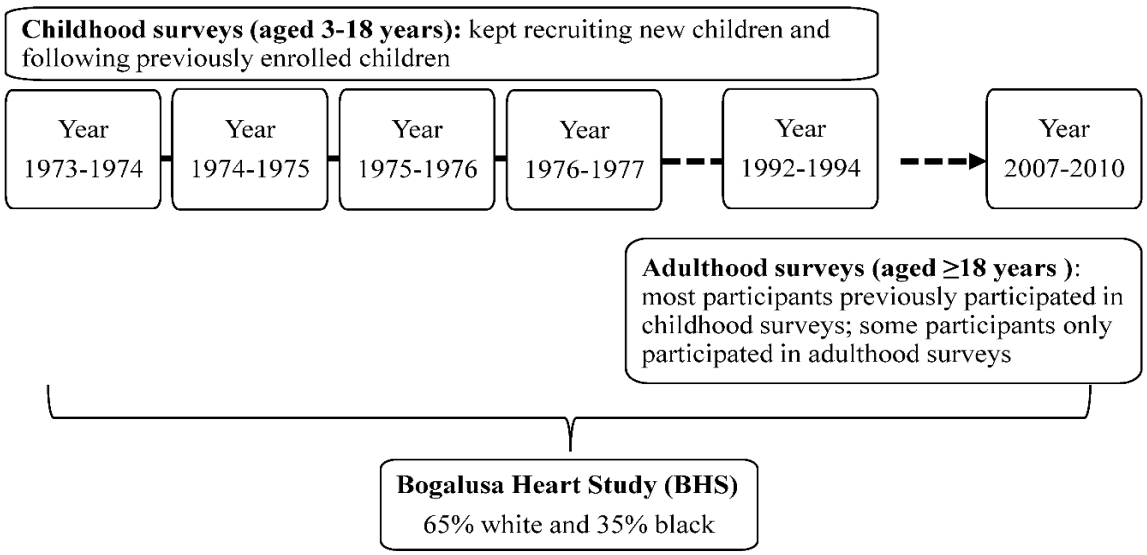


Figure 2.2 Brief schematic representation of the Bogalusa Heart Study between 1973 to 2010

years for adults from 1977 to 2010 (Figure 2.2). These cross-sectional and longitudinal studies of children or adults were combined and created the overall BHS population. To date, more than 16,000 individuals have been recruited in BHS surveys and the study is still ongoing. The serial observations from childhood to adulthood make it possible to measure the cumulative burden of risk factors since childhood. In each survey, the examination has included questionnaires, physical measurements and blood biochemistry.

2.2.1.2 Childhood adiposity measures

All BHS surveys adhered to an identical protocol for anthropometric measurements taken by trained examiners [135]. The children wore underpants, a short-sleeved examination gown, and socks. Height and weight were measured using a stadiometer and balance team metric scale. The values were recorded twice to within 0.1cm or 0.1kg and mean values were obtained. Waist circumference was measured midway between the lowest rib and the superior border of the iliac crest, with a flexible tape and was measured three times. The average of the three waist circumference measurements was used in all analyses. In this thesis, BMI and WHtR as the indicators of childhood overall adiposity and abdominal obesity were used (Table 2.3). They were calculated and classified as described in CDAH.

Table 2.3 Summary of adiposity measures in childhood and adulthood in BHS and adiposity measures in adulthood in BBS

Adiposity measures	Childhood in BHS	Adulthood in BHS	BBS
Overall adiposity	All measured	All measured	Self-reported
BMI	✓	✓	✓
BMI category	✓	✓	✓
Normal	✓	✓	✓
Overweight	✓	✓	✓
Obese	✓	✓	✓
Abdominal adiposity measures	Measured in a subsample		
WHtR	✓		
WHtR category	✓		
<0.5	✓		
≥0.5	✓		

Abbreviation: BHS, Bogalusa Heart Study; BBS, the Babies sub-study of Bogalusa Heart Study; BMI, body mass index; WHtR, waist-to-height ratio.

2.2.1.3 Adult adiposity measures

Anthropometric measurements in adulthood followed the same method as described in childhood. BMI was calculated from objectively measured weight and height (Table 2.3).

2.2.2 The Babies sub-study of BHS (BBS) (2013)

2.2.2.1 Participants

Beginning in May 2013, a sub-study of BHS was conducted to re-contact and enrol 5,914 women with at least one previous BHS visit. Until November 2017, 1,803 women participated in and formed the BBS study. 93% of these women were aged 25-58 years with at least one visit in BHS prior to age 18 years. Each participant was interviewed for 15-30 minutes regarding her and her family's reproductive history, either by telephone survey by a trained interviewer or by self-completed questionnaire at the BHS field clinic.

2.2.2.2 Adult adiposity measures

Current weight was self-reported by participants during the interview in BBS (Table 2.3). Height was extracted from participants' records from BHS visits and the most recent height measured during a visit at age 16 or older was used. If the adult height value was not available, the multiplier method was used to estimate height [136]. This is a method to predict the adult height based on the information of childhood height, age and sex. BMI, overweight and obesity were calculated and classified using the same criteria as described in the CDAH study.

2.2.2.3 Reproductive outcomes

The reproductive outcomes of menstrual irregularity and PCOS in BBS were used and their definitions were similar to those in CDAH (Table 2.4 and Appendix D).

Table 2.4 Summary of reproductive health outcomes in BBS

Reproductive outcomes	BBS
Menstrual irregularity	
	First the usual menstrual cycle length was obtained by question: • Between the ages of 16 and 40, about how long was your average menstrual cycle (time from first day of one period to the first day of the next period)? (select one only) a) <25 d; b) 25-34 d; c) 35-60 d; d) More than 60 d; e) Totally variable Then menstrual irregularity was defined as selecting average menstrual of options a) or c) or d) or e)
PCOS	
Self-reported doctor diagnosed PCOS	Self-reported 'yes' to the question: • Have you ever been told by a doctor that you had PCOS?
Menstrual irregularity + hirsutism	Self-reported menstrual irregularity (defined as above) and hirsutism (determined by indicating three or more sites as below): • During your menstruating years (not including during pregnancy), did you have a tendency to grow dark, coarse hair on your (circle all that apply) a) upper lip? b) chin? c) breast? d) chest between the breast? e) back? f) belly? g) upper arms? h) upper thighs?

Abbreviation: BBS, the Babies sub-study of Bogalusa Heart Study; PCOS, polycystic ovary syndrome.

2.3 Statistical analysis

Statistical analyses for each study are presented in Chapter 3 to Chapter 6 in detail.

Covariates adjusted for in final models in Chapter 3 to Chapter 6 were those that were significant predictors of the outcome and/or that satisfied the conditions for the factor to be a confounder. The three conditions are that:

(1) There are plausible grounds to believe that the putative confounding factor is a cause of the outcome;

(2) The only relationship that the putative confounding factor has with the principal study factor (exposure) and outcome is not as an antecedent or an intermediate on the pathway from the principal study factor (exposure) to the outcome;

(3) Adding a covariate for the putative confounding factor to the regression model resulted in a change of more than 10% in the estimated coefficient of the covariate for the principal study factor (exposure).

Overall, all the statistical analyses were performed using Stata software (Stat Corp., College Station, TX). A p-value of <0.05 was considered statistically significant.

Chapter 3: Association of childhood adiposity with female infertility in adulthood: a 25-year follow-up study

The following text in Chapter 3 has been published in the *Fertility and Sterility (Appendix E 1)*

3.1 Abstract

Objectives: To evaluate whether childhood obesity is associated with infertility in women's reproductive-aged life.

Design: Prospective longitudinal study.

Setting: A childhood cohort from 1985 Australian Schools Health and Fitness Survey.

Intervention(s): None.

Patient(s): 1,544 girls aged 7 to 15 years in 1985 and completed questionnaires at follow-up in 2004-2006 and/or 2009-2011.

Main outcome Measure(s): Infertility was defined as having difficulty conceiving (had ever tried for 12 months or more to become pregnant without succeeding) or having ever seen a doctor because of trouble becoming pregnant.

Result(s): At ages from 7 to 11 years, girls at both the lower and upper end of the BMI z-score had increased risk of infertility. Compared with normal weight girls, those with obesity aged 7-11 years were more likely in adulthood to report infertility (adjusted relative risk (aRR): 2.94, 95% confidence interval (CI): 1.48-5.84), difficulty conceiving (aRR: 3.89, 95% CI: 1.95-7.77), or having ever seen a doctor because of trouble becoming pregnant (aRR: 3.65, 95% CI: 1.90-7.02) after adjusting for childhood age, follow-up length, highest parental education and marital status.

Conclusion(s): Childhood obesity before 12 years of age appears to increase the risk of female infertility in later life.

3.2 Introduction

The increase in obesity among children and adolescents is of great concern around the world [137]. In Australia, one in four children aged 5-17 years were overweight or obese in 2014-2015 which is twice the recorded prevalence in 1986 [138]. Substantial evidence suggests that obesity in women is associated with a wide range of gynaecological disorders including infertility [139, 140]. Obesity during childhood and adolescence has been linked with early puberty, menstrual disorders and PCOS [141]. From the life course perspective of female reproductive health, it is important to determine whether childhood obesity has long-term effects on infertility in adulthood, typically defined clinically as a failure to conceive after regular unprotected intercourse or attempting pregnancy for 12 months or more [142].

Few studies have investigated the association of childhood obesity with female infertility and the findings were not consistent. In a study of 3,327 British girls, Lake and colleagues [77] reported little impact of childhood BMI at the age of 7 years on infertility 26 years later defined by achieving a pregnancy after more than 12 months. However, participants were restricted to women with a live birth from their first pregnancy. BMI cut-points were defined using an index of relative weight (weight expressed as a percentage of the standard weight for age, height, and sex). More recently, a report based on 1,061 participants in the Bogalusa Heart Study in USA showed that girls with obesity prior to 12 years of age were more likely in later life to have tried to become pregnant without success. Weight status was defined according to age and gender specific BMI percentiles and based on USA CDC and Prevention statistics (e.g. ≥ 95th percentile for obesity) [78]. A limitation of this study is that it determined whether participants had 'ever tried to become pregnant and were unable to' but did not specify a time interval and may have resulted in misclassification of infertility. In addition, male factors (e.g. poor semen quality) are commonly reported causes of infertility [69] and not the outcome of interest: neither of these studies were able to exclude them.

The aim of the present study was to examine the association between different measures of body composition at age 7-15 and infertility at age 26-41 in a large population-based sample of Australian women with consideration of a wide range of potential confounders.

3.3 Methods

3.3.1 Participants

The CDAH study is a follow-up of 8,498 children which included 4,191 girls who participated in the 1985 ASHFS, a nationally representative sample of Australian school children aged 7-15 years (herein referred to as "baseline") [143]. At baseline, all children had physical assessments and those aged 9-15 years completed questionnaires. During 2002-2004, a total of 3,412 women participants were traced and 2,734 women agreed to participate in the CDAH study (Figure 3.1). During 2004-2006, when the participants were aged 26-36 years, 1,596 women completed questions on reproductive health (CDAH-1). The second follow-up (CDAH-2) was conducted during 2009-2011, when participants were aged 31-41 years and 1,129 women completed questions on reproductive health. After combining two follow-ups, a total of 1,754 women who answered reproductive health questions at CDAH-1 or CDAH-2 or both were eligible for the study.

The study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee. Written informed consent was obtained at both time points.

3.3.2 Childhood body composition measurement

BMI, calculated as weight (kg)/height $(m)^2$, was derived from measured height and weight with weight status defined using international age- and sex-specific cut-points [8] and was transformed into BMI z scores based on age- and sex-specific standardisation of the full childhood cohort (n=4189 girls). Waist circumference was taken at the level of the umbilicus to the nearest 0.1

cm. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Waist-to-hip ratio was calculated by dividing waist by hip circumference. WHtR was calculated by dividing waist circumference by height and dichotomized into < or ≥ 0.5. Abdominal obesity was defined as WHtR ≥ 0.5 [133].

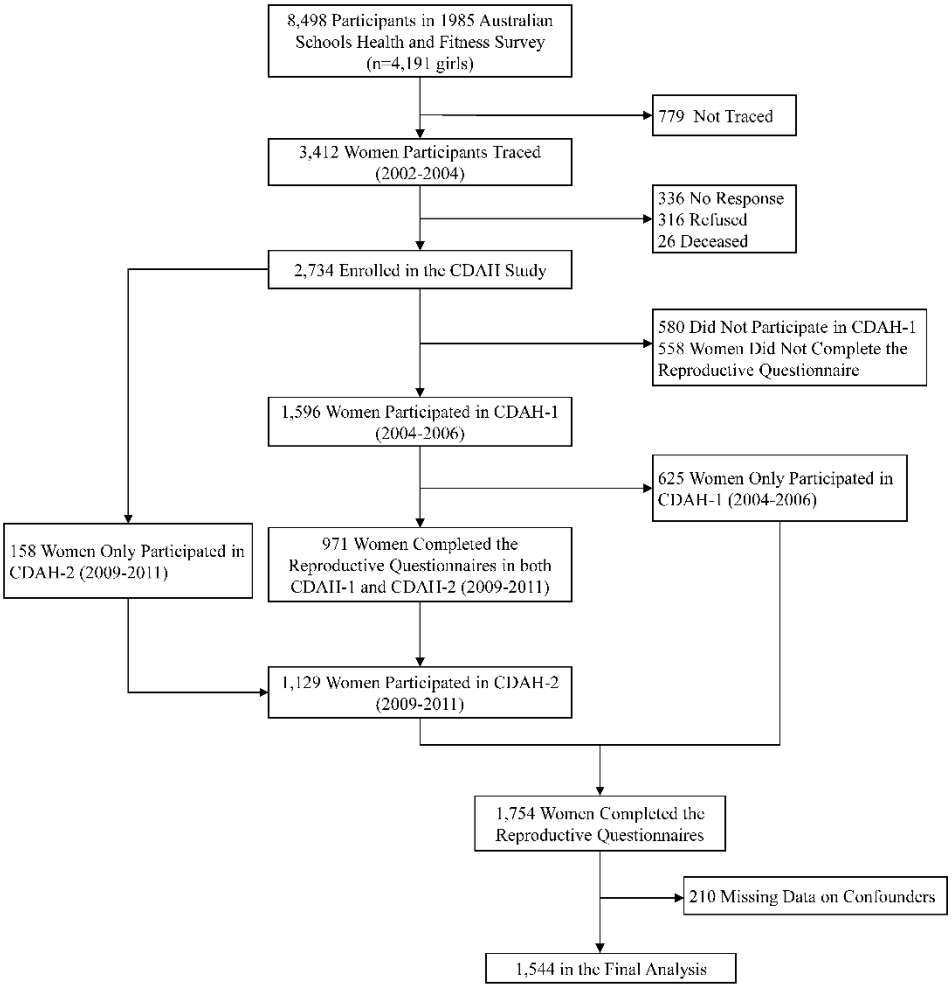


Figure 3.1 Selection of participants for the Childhood Determinants of Adult Health (CDAH) study, Australia, 1985-2011

3.3.3 Adult body composition measurement

At CDAH-1, weight and height were measured at study clinics for most. A sub-sample of these participants also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. The difference between clinic and self-reported weight and height was used to calculate a correction factor from a linear regression model. Participants who did not visit a study clinic self-reported their weight and height, and a correction factor was applied to adjust for error [26]. BMI (kg/m^2) was calculated from height and weight.

Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the correction factor applied at CDAH-1. BMI was calculated using measured height at CDAH-1 or adjusted self-reported height at CDAH-1 or at enrolment.

Adult BMI was categorized into three groups (<25, 25-30 and ≥30 kg/m^2). Overweight was defined as $25 \leq BMI \leq 29.9$ kg/m^2 and obesity was defined as $BMI \geq 30$ kg/m^2 [2].

3.3.4 Adult infertility measurement

In the reproductive questionnaire of CDAH-1 and CDAH-2, women were asked to answer 'yes' or 'no' to questions 'Have you ever tried to become pregnant for 12 months or more without succeeding?' and 'Have you ever seen a doctor because you were having trouble becoming pregnant?' Infertility was recorded if they responded 'yes' to either of the two questions. Women were further asked whether any of the following investigations had been undertaken if they reported having seen a doctor because of difficulty conceiving: hormone test, laparoscopy and partner's semen test. Participants were also asked about any diagnosis they had been given including ovulatory problem, tubal problem, male factor, unexplained fertility problem or any other female problem with a written specified reason. We categorized the answers into tubal, male, ovulatory (including ovulatory problem, polycystic ovary syndrome,

hyperprolactinaemia, hypogonadotrophic, hypergonadotrophic and premature ovarian failure), endometriosis, unexplained, other and uterine factors.

3.3.5 Covariate measures

Childhood factors considered as covariates included age, age at menarche (self-reported in adulthood), socioeconomic position based on area of residence (high, medium high, medium low, or low), highest parental education (reported in adulthood as high school only, vocational training, any university education), smoking experimentation (none, a few puffs, < 10 cigarettes in their life, and ≥ 10 cigarettes in their life), alcohol consumption (never, less than once per week, more than once per week) and total physical activity (mins/week). Sociodemographic characteristics were self-reported at follow-ups. Adult covariates included highest level of education attained (classified as for childhood), socioeconomic position based on area of residence (classified as for childhood), marital status (single, married/living as married, separated/divorced/widowed), smoking status (never, ex-smoker, current smoker), alcohol consumption (non-drinker, light drinker, moderate drinker, heavy/very heavy drinker), and total physical activity (mins/week). Follow-up length was also considered as a potential confounder.

3.3.6 Statistical analyses

Subgroup analyses by child age (7-11 years and 12-15 years) were undertaken because of reported differences in the association of onset of obesity in childhood with later infertility [78]. Univariable and multivariable log-binomial regression was used to derive risk ratio (RR) estimates for the association between body composition and infertility before and after adjustment for potential confounders. If the log binomial model failed to converge, RRs were estimated using Poisson regression with robust standard errors to correct for the misspecification of the binomial errors [144-147]. Covariates kept in the final model were variables

associated with the exposure and the outcome, and resulted in more than 10% change in the coefficient of the principal study factor when added into the model.

Restricted cubic regression splines based on 4 knot points were used to present associations between childhood BMI z score and infertility [148]. The x-axis on the graph goes from the 5th to the 95th percentile of childhood BMI z score.

The following sensitivity analyses were conducted. First, we excluded those who reported male infertility to examine if it had biased the observed association between childhood obesity and having ever seen a doctor because of trouble becoming pregnant. Second, we restricted our sample to women who were married or living as married. Third, we considered the effect of loss to follow-up using inverse probability weighting. The completed factors available at baseline used to determine the weights were childhood age, school type and state of residence. Fourth, childhood BMI was classified alternatively as normal (<85th percentile), overweight (85th-94th percentile) or obese (≥95th percentile) based on age- and sex-specific USA CDC norms [149] and age- and sex-specific childhood BMI in our 1985 ASHFS cohort. Fifth, 210 participants with missing data on confounders were excluded for this study and most were missing the confounder-parental education (n=182). To increase the statistical power of the study, multiple imputation by chained equations was used to impute the highest parental education.

All analyses were performed using STATA software, version 14.2 (Stata Corp., College Station, TX); a *p*-values of <0.05 was considered statistically significant.

3.4 Results

3.4.1 Participant characteristics

This study included 1,754 women who reported fertility outcomes. Of these participants, 971 completed both follow-up surveys, 625 participated in only the first follow-up and 158 women participated in only the second follow-up. Participants who had missing data on confounders (210 women) were excluded, leaving 1,544 women for the final analysis.

The anthropometric and sociodemographic characteristics of participants at childhood and adulthood are shown in Table 3.1. At baseline, 17 (1.1%) children were obese, 116 (7.5%) were overweight and 80 (5.2%) children had abdominal obesity as defined by BMI cut-points and WHtR category, respectively. The mean age at follow-up was 34 years (range 26-41). There were 346 (22.4%) women who reported experiencing infertility in adulthood, including 264 (17.1%) who reported ever having tried for more than 12 months to become pregnant without succeeding and 281 (18.2%) who had ever seen a doctor because of trouble becoming pregnant. Participants with lower parental education in childhood and those who were married or living as married in adulthood were more likely to report infertility.

Compared with those who did not participate in the follow-up, those who did participate were slightly older (11.0 vs 10.8 years; P=0.003), had marginally lower BMI (18.2 vs18.4 kg/m^2; P=0.009) and were less likely to have abdominal obesity (5.2% vs 8.3%; P<0.001) at baseline.

Table 3.1 Characteristics of women in childhood (1985) and adulthood (2004–2011), Childhood Determinants of Adult Health study[a]

Characteristics	Ever tried for≥12 months to become pregnant without succeeding		Ever seen a doctor because of trouble becoming pregnant		Any fertility problem [c]	
	Yes (n=264)	No (n=1279)	Yes (n=281)	No (n=1263)	Yes (n=346)	No (n=1198)
Childhood						
Age, years, Mean(SD)	11.5(2.4)[b]	10.9(2.5)	11.4(2.5)[b]	10.9(2.5)	11.4(2.4)[b]	10.9(2.5)
SEIFA disadvantage (%)						
High	24.3	27.5	28.9	26.4	25.8	27.2
Medium-high	30.3	28.7	27.6	29.4	29.7	28.8
Medium-low	37.2	38.1	36.9	38.2	37.8	38.0
Low	8.3	5.7	6.7	6.1	6.7	6.0
Waist circumference, cm, Mean(SD)	63.2(8.1)[b]	61.9(7.7)	62.9(8.1)	62.0(7.7)	63.0(8.0)[b]	61.9(7.7)
Waist-to-hip ratio, Mean(SD)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.82(0.06)
Body-mass index, kg/m^2, Mean(SD)	18.4(3.0)	18.1(2.7)	18.4(3.0)	18.1(2.7)	18.4(3.0)	18.1(2.7)
BMI category (%)						
Normal	90.1	91.6	89.6	91.8	89.9	91.8
Overweight	8.0	7.4	8.6	7.3	8.7	7.2
Obese	1.9	0.9	1.8	1.0	1.5	1.0
Smoking experimentation (%)						
None	55.7	59.2	57.9	58.7	57.1	59.0
A few puffs	20.8	21.9	19.7	22.2	20.2	22.2
<10 cigarettes	8.6	7.2	8.8	7.1	8.7	7.0
>10 cigarettes	14.9	11.7	13.6	12.0	13.9	11.8
Parental education (%)						
University education	20.1[b]	29.1	23.8	28.4	22.5	29.0
Vocational training	37.1	33.0	34.9	33.5	35.3	33.3
High school	42.8	37.9	41.3	38.2	42.2	37.7
Alcohol assumption (%)						
Never	72.9	69.5	70.2	70.0	72.5	69.3
Less than once per week	22.6	24.6	25.0	24.1	22.3	24.9
More than once per week	4.5	5.9	4.8	5.9	5.2	5.8
Physical activity, mins/week, Mean(SD)	384(342)	398(376)	396(378)	395(368)	388(353)	398(375)
Age at menarche, years, Mean(SD)	13.1(1.3)	13.2(1.3)	13.1(1.3)	13.2(1.3)	13.1(1.3)	13.1(1.3)
Adulthood						
Age, years, Mean(SD)	33.5(2.9) [b]	34.2(3.5)	33.4(2.9) [b]	34.3(3.5)	33.4(2.8) [b]	34.2(3.5)
SEIFA disadvantage (%)						
High	26.9	24.1	25.6	24.9	26.0	24.4

Medium-high	25.4	22.9	19.9	23.5	23.4	23.2
Medium-low	23.9	25.2	24.9	25.2	24.0	25.3
Low	23.9	27.8	29.5	26.3	26.0	27.1
Body-mass index, kg/m^2, Mean(SD)	25.7(5.8)	25.2(5.4)	25.4(5.6)	25.3(5.5)	25.5(5.6)	25.3(5.4)
BMI category (%)						
Normal	56.2	60.2	58.1	59.7	57.5	60.1
Overweight	23.7	24.1	22.3	24.2	23.1	24.1
Obese	20.1	15.7	19.6	16.1	19.4	15.8
Smoking status (%)						
Never smoker	54.2	55.3	55.7	55.2	55.4	55.2
Ex-smoker	25.0	26.9	26.4	26.5	25.8	26.7
Current smoker	20.8	17.8	17.9	18.3	18.8	18.1
Self-education (%)						
University education	45.1 [b]	47.1	46.4	46.8	45.2 [b]	47.2
Vocational training	22.4	28.2	24.3	28.0	23.8	28.4
High school	32.6	24.7	29.3	25.2	31.0	24.5
Marital status (%)						
Single	2.7 [b]	22.4	2.5 [b]	22.5	2.9 [b]	23.5
Married/living as married	93.2	72.7	94.0	72.7	93.4	71.5
Separated/divorced/widowed	4.2	4.9	3.6	4.8	3.8	4.9
Alcohol consumption (%)						
Non-drinkers	29.5 [b]	21.4	24.5	22.3	27.2 [b]	21.5
Light drinkers	57.9	56.9	59.7	56.5	57.4	56.8
Moderate drinkers	10.3	16.2	13.2	15.8	12.4	16.2
Heavy /very heavy drinkers	2.3	5.6	2.6	5.4	3.0	5.5
Physical activity, mins/week, Mean(SD)	755(512)	766(495)	732(500)	770(497)	743(488)	769(501)
Follow-up length, years, Mean(SD)	22.6(2.5)		22.6(2.5)		22.5(2.5)	

Childhood overweight and obesity were defined according to the international cut-points

Abbreviations: BMI, Body-mass Index; SEIFA, Socio-Economic Indexes for Areas; SD, standard deviation

[a] Sample size ranges from 873-1543 due to missing data on some covariates

[b] P<0.05

[c] Women who answered yes to any one of the two related infertility questions

3.4.2 Infertility

After adjustment for age, follow-up length, parental education and marital status, compared with women with normal childhood weight between 7 and 11 years (Table 3.2), those who were obese as children were more likely to report infertility (RR=2.94, 95% CI 1.48-5.84), having ever tried for more than 12 months to become pregnant without succeeding (RR=3.89, 95% CI 1.95-7.77) and having ever seen a doctor because of trouble becoming pregnant (RR=3.65, 95% CI 1.90-7.02). This association was not evident for the group aged 12 to 15 years at baseline. No significant association was found between other adiposity indicators (waist circumference, waist-to-hip ratio and WHtR≥0.5) in childhood and infertility in adulthood, including when abdominal adiposity measures were adjusted for childhood BMI.

The association between childhood BMI z score and relative risk of infertility in adulthood is shown in Figure 3.2. There was a U-shaped association of BMI z score with infertility in the 7 to 11 years group (Figure 3.2 A), with the risk significantly higher in children with z score over 1.05 or less than -0.80. No significant association was observed for those in the 12 to 15 years group (Figure 3.2 B).

Table 3.2 Associations between body composition measures in childhood with fertility problem in adulthood stratified by childhood age, Childhood Determinants of Adult Health study, 1985–2011

Body Composition	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility [a]				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—
Overweight	69	0.80	0.41-1.57	0.85	0.45-1.61	69	1.18	0.71-1.98	1.30	0.82-2.07	69	1.12	0.70-1.80	1.21	0.80-1.84
Obese	8	**2.59**	**1.04-6.43**	**3.89**	**1.95-7.77**	8	2.36	0.95-5.85	**3.65**	**1.90-7.02**	8	1.94	0.78-4.80	**2.94**	**1.48-5.84**
Waist circumference	864	1.01	0.98-1.03	0.99	0.97-1.02	864	1.01	0.98-1.03	1.00	0.97-1.03	864	1.01	0.99-1.03	1.00	0.97-1.02
Waist-to-hip ratio	864	0.90	0.67-1.20	0.97	0.72-1.29	864	0.82	0.63-1.09	0.88	0.67-1.16	864	0.88	0.69-1.13	0.98	0.77-1.24
Waist-to-height ratio															
<0.5	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—
≥0.5	49	0.99	0.49-2.00	1.17	0.60-2.27	49	0.87	0.43-1.75	1.02	0.52-1.99	49	1.04	0.59-1.84	1.29	0.76-2.18
Age 12 to 15 years															
BMI category															
Normal	622	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—
Overweight	47	1.40	0.86-2.28	1.18	0.75-1.87	47	1.16	0.67-1.99	1.06	0.64-1.76	47	1.26	0.81-1.95	1.11	0.72-1.70
Obese	9	1.12	0.33-3.85	1.05	0.33-3.37	9	1.10	0.32-3.77	1.03	0.32-3.27	9	0.88	0.26-3.00	0.90	0.26-3.12
Waist circumference	679	1.01	0.99-1.03	1.01	0.99-1.03	680	1.01	0.99-1.03	1.00	0.98-1.02	680	1.01	0.99-1.02	1.00	0.99-1.02
Waist-to-hip ratio	679	1.18	0.91-1.53	1.18	0.90-1.53	680	1.23	0.95-1.58	1.23	0.95-1.59	680	1.15	0.92-1.43	1.14	0.91-1.43
Waist-to-height ratio															
<0.5	647	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—
≥0.5	31	1.28	0.69-2.38	1.24	0.70-2.18	31	1.11	0.57-2.16	1.07	0.57-2.01	31	1.13	0.64-2.00	1.09	0.65-1.82

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.
Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.
[a] Women answered yes to any one of the two related infertility questions.

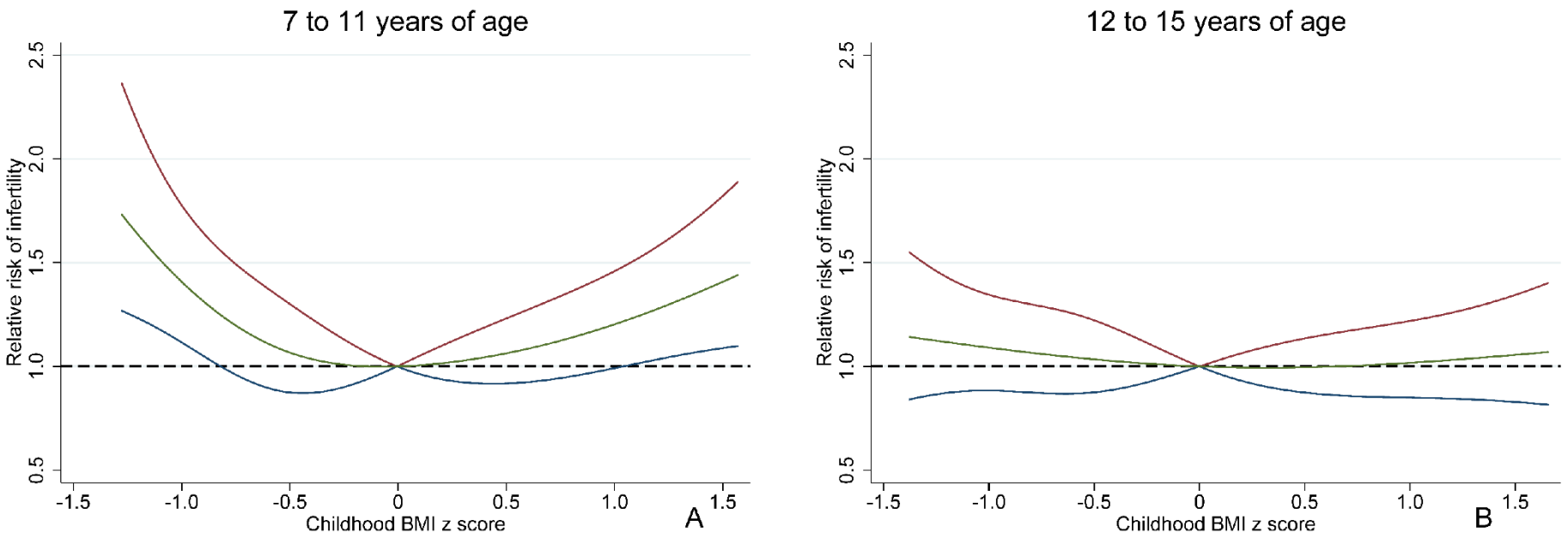


Figure 3.2 Relative risk (RR) of infertility and childhood BMI z score, adjusting for age, and parental status at baseline, follow-up length and marital status at adulthood

7 to 11 years group (A) and 12 to 15 years group (B). The dashed line indicates an RR of 1. The green lines indicate the RR for the association between childhood BMI z score and adult infertility. The blue and red lines indicate the upper and lower bounds of the 95% confidence interval for the association. The axes on the graph go from 5th to 95th percentile of the childhood BMI z score distribution, which range from -1.28 to 1.57 in 7 to 11 years age group (A) and from -1.38 to 1.69 in 12 to 15 years age group (B).

3.4.3 Cause of infertility

Most women who had ever seen a doctor because of trouble becoming pregnant reported one or more infertility causes and infertility investigations (Appendix3-1). Endometriosis was a less common cause of infertility in those who were overweight or obese in childhood (15.1% in normal vs. 3.3% in overweight/obese, *P*=0.10). Similar proportions of women had infertility investigations irrespective of their childhood BMI category (Appendix3-1).

3.4.4 Influence of adiposity from childhood into adulthood

The proportions and the number of women who reported infertility by adiposity status from childhood to adulthood are displayed in Appendix3-2 and Appendix3-3. For consistently normal weight participants (normal weight in childhood and adulthood), the prevalence of infertility was 21.6%, and for consistently overweight/obese participants (overweight/obese from childhood to adulthood), the corresponding figure was 27.9%. Though a higher prevalence of reported infertility was observed in the persistently overweight and obese group, it did not reach statistical significance (*P*=0.37). After adjustment for childhood age and parental education at baseline, length of follow up, adult education, marital status and alcohol consumption in adulthood, the risk of infertility was significantly higher in women who were persistently overweight or obese from childhood (ages 7-11) into adulthood than those who had consistently healthy weight (Appendix3-4).

3.4.5 Sensitivity analysis

Similar results were observed after excluding women who reported infertility due to male factor (n=20) and endometriosis (n=39). Compared with those of normal weight in childhood, the risk of having ever seen a doctor because of trouble becoming pregnant in the obese group was 3.69 (95% CI 1.94-6.99) and 4.16 (95% CI 2.14-8.06) respectively for those aged 7 to 11 years at

baseline. When restricting the sample to women who were married or living as married (and who it might be assumed would have a greater likelihood of becoming pregnant), the risks of infertility (RR=3.15, 95% CI 1.37-7.25), having ever tried for more than 12 months to become pregnant without succeeding (RR=4.12, 95% CI 1.78-9.50) and having ever seen a doctor because of trouble becoming pregnant (RR=3.84, 95% CI 1.78-8.25) remained significantly higher in those who were obese at ages 7 to 11 years. Sensitivity analyses conducted by reanalysing the data with inverse probability weighting produced similar patterns of results as the unweighted analyses and the changes in the magnitude of significant associations were small, ranging from 1.5 to 3.3 % (Appendix3-5). Further analysis using USA CDC and our cohort internal cut-points of 85th and 95th childhood BMI percentiles showed similar significant associations of childhood obesity and infertility in the 7 to 11 years group (Appendix3-6 and Appendix3-7). Similar results were observed when re-run the analyses in a larger sample of 1,726 by using multiple imputation for highest parental education.

3.5 Discussion

Our findings indicate that being obese before the age of 12 years is associated with impaired fertility in later life and a U-shaped relationship between childhood BMI z score and infertility. A previous study also suggested an inverted U-shaped between BMI in adolescence and number of children [150]. Some evidence suggests that body fat distribution in women may have more impact on fertility than obesity [151], but our results did not support this association in relation to children's WHtR. No appreciable differences in the associations of waist circumference, waist-to-hip ratio and abdominal obesity in childhood were found with later infertility in adulthood.

Current evidence on the association of childhood obesity and adult infertility is not consistent. Similar to our finding, a study from the USA reported that obesity before age 12 years was

associated with an increased likelihood of having ever tried to become pregnant without success [78]. In contrast, the analysis from a British cohort study showed that weight during childhood did not predict subsequent fecundity, but it did find that obesity at the age of 7 years was associated with increased menstrual irregularities by age 33 years [77]. The reasons for the inconsistent results may be the use of different methods to sample study populations, for example, the British cohort study was limited to women with a live birth from their first pregnancy.

The explanation for the difference in associations by age group is unclear but there may be cumulative impacts of childhood obesity on adult infertility whereby girls who are obese at a younger age (i.e. 7-11 years in this study) have more impaired fertility, and/or that the pre-pubertal phase is a more sensitive window for the effects of high BMI on the development of reproductive capacity than later pubertal or post-pubertal stages of development. A recent study in rodents suggests that early-onset obesity induces reproductive deficits in adult female rats by reducing the number of oocyte and preantral follicles and inhibiting the luteinizing hormone surge [152]. In humans, early-onset obesity is associated with the earlier puberty and earlier maturation of the hypothalamic-pituitary-ovarian (HPO) axis which may impact on the development of the reproductive system in girls [153]. Increased estrogen produced by greater body fat and accelerated aromatization of adrenal and ovarian androgens in adipose tissue promotes earlier adrenarche, pubarche and thelarche, which may have unfavourable influences on the HPO axis, ovarian function, oocyte quality, endometrial receptivity, or any combination of these factors in the long-term [154]. In addition, obesity in childhood is an important factor contributing to the presence and severity of PCOS in adolescents, which may increase the risk of subsequent anovulatory infertility [79, 155, 156]. In our study, we failed to detect an association between high childhood adiposity and infertility due to ovulatory dysfunction. It is plausible

that obesity disrupts endocrine homeostasis with long-term effects on infertility, however, the mechanisms involved in reducing reproductive potential are still poorly understood.

Our finding that endometriosis as a cause of infertility was less common in those in the childhood overweight/obese group (3.5%) than the normal weight group (15.1%) was similar to findings from a recent meta-analysis which pooled 11 studies of participants with ages ranging from 16 to 65 years and reported that higher BMI was associated with lower risk of endometriosis in adulthood [157]. Further, results from our sensitivity analysis suggest that male infertility did not bias the observed association between childhood obesity and infertility in adulthood.

The strengths of our study are a relatively contemporary cohort with childhood body composition measurements taken in 1985 and follow-ups conducted during women's reproductive years. Although the Bogalusa Heart Study measured skinfolds in childhood, to our knowledge our study is the first to have reported the associations of various abdominal obesity indicators in childhood with adult infertility including waist circumference, waist-to-hip ratio and waist-to-height ratio. In addition, our definition of having difficulty conceiving specified a time interval of having ever tried ≥12 months and is more consistent with definitions used in clinical practice [158]. Moreover, we demonstrated associations with infertility of BMI z score as a continuous variable as well as obesity defined by age- and sex- specific BMI ≥ 95th percentile.

Some limitations should be acknowledged. First, the sample size in the childhood obese group is small. The prevalence of obesity in girls using international BMI cut-points was only 1.1%. However, similar findings were shown with continuous BMI z scores and sensitivity analyses in our study. Second, we could not distinguish primary infertility (no prior pregnancies) and secondary infertility (infertility following at least one prior conception), which is important for

evaluating women's ability to have children and exploring the aetiology of infertility. Third, our measure of infertility relied on self-reported problems. However, the prevalence of infertility in our study is consistent with Australian estimates of approximately one in six couples experiencing a delay of greater than 12 months to achieve a planned pregnancy during their reproductive life [64, 67]. Although infertility diagnoses and investigations are self-reported, these are likely to be important events for women, and women should be able to recall specific diagnoses and investigations that have been undertaken.

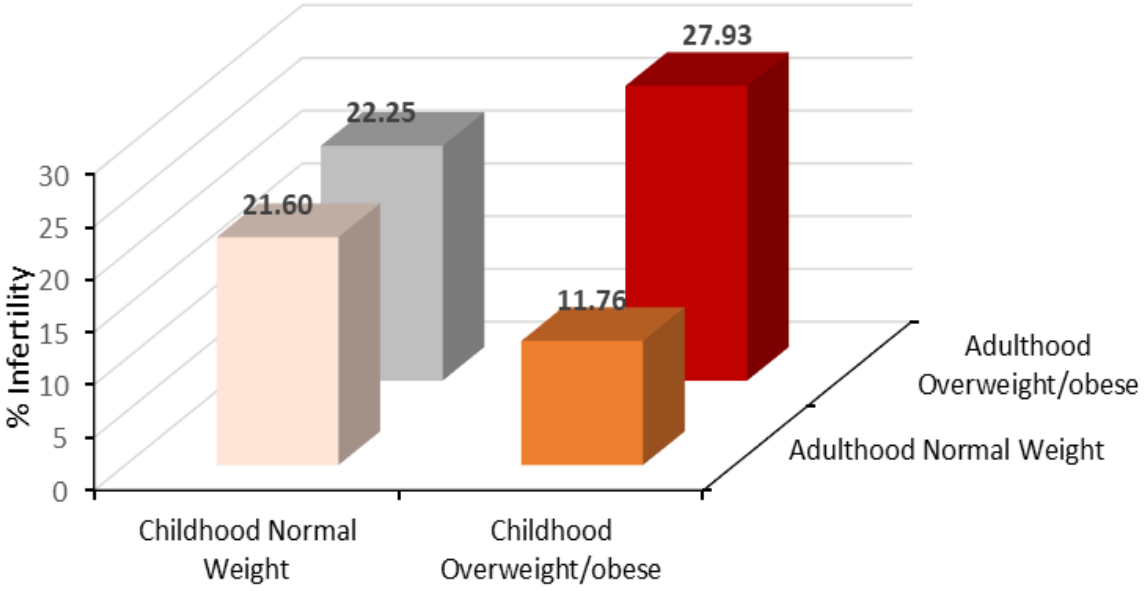
In conclusion, our study of a cohort of Australian women indicated a detrimental impact of childhood obesity before age 12 on infertility later in life. The early prevention of childhood obesity is important for fertility as well as disease prevention.

3.6 Appendix 3 Supplementary material for Chapter 3

Appendix3-1 Diagnoses and investigations in women who had seen a doctor because they were having trouble becoming pregnant, by body mass index category in childhood

	Normal (n=251)	Overweight/obese (n=29)	*P value*
	No. (%)	No. (%)	
Diagnoses			
Ovulatory dysfunction	67 (26.7)	9 (31.0)	0.62
Tubal problem	22 (8.8)	3 (10.3)	0.73
Endometriosis	38 (15.1)	1 (3.5)	0.10
Uterine and other problem	13 (5.2)	3 (6.9)	0.66
Male factor	17 (6.8)	3 (10.3)	0.84
Unexplained	39 (15.5)	4 (13.8)	1.00
No diagnosis	80 (31.9)	10 (34.5)	0.78
Investigations			
Hormone test	206 (82.1)	24 (82.8)	0.93
Laparoscopy	104 (41.4)	11 (37.9)	0.72
Partner's semen analysed	160 (68.8)	15 (51.7)	0.21
No investigation	24 (9.6)	3 (10.3)	0.75

Appendix3-2 Percentage of reported infertility across adiposity status from childhood to adulthood



Appendix3-3 Number of participants by weight status category from childhood to adulthood by adult infertility

Adiposity status from childhood to adulthood	n	Infertility [a]		*P* value
		Yes n (%)	No n (%)	
Normal-normal	852	184 (21.6%)	668 (78.4%)	
Normal-overweight/obese	481	107 (22.3%)	374 (77.8%)	
Overweight/obese-normal	17	2 (11.8%)	15 (88.2%)	
Overweight/obese-overweight/obese	111	31 (27.9%)	80 (72.1%)	0.37

[a] Women answered yes to any one of the two related infertility questions.

Appendix3-4 Relative risks of infertility in adulthood according to changes in weight status from childhood to adulthood

Changes in weight status from childhood to adulthood	n	Infertility [a]			
		Unadjusted		Model 1	
		RR	95% CI	RR	95% CI
Aged 7 to 15 years					
Normal to normal	831	Ref.	—	Ref.	—
Normal to overweight/obese	469	1.00	0.81-1.24	1.07	0.88-1.31
Overweight/obese to normal	17	0.54	0.15-1.99	0.64	0.18-2.28
Overweight/obese to overweight/obese	107	1.24	0.88-1.73	1.23	0.90-1.68
Aged 7-11 years					
Normal to normal	476	Ref.	—	Ref.	—
Normal to overweight/obese	257	1.03	0.75-1.40	1.08	0.80-1.46
Overweight/obese to normal	14	0.38	0.06-2.52	0.42	0.07-2.73
Overweight/obese to overweight/obese	56	1.42	0.88-2.27	**1.60**	**1.04-2.48**
Aged 12-15 years					
Normal to normal	355	Ref.	—	Ref.	—
Normal to overweight/obese	212	0.96	0.72-1.29	1.08	0.82-1.42
Overweight/obese to normal	3	1.29	0.26-6.43	2.29	0.14-36.15
Overweight/obese to overweight/obese	51	1.06	0.66-1.71	1.01	0.64-1.60

Model 1: adjust for age and parental education at baseline, follow-up length, adult education, marital status and alcohol consumption at adulthood.

[a] Women answered yes to any one of the two related infertility questions.

Appendix3-5 Sensitivity analysis using inverse propensity weighting technique. Associations between body composition measures in childhood with fertility problem in adulthood stratified by childhood age, Childhood Determinants of Adult Health Study, 1985–2011

Body Composition	n	Ever tried for≥12 months to become pregnant without succeeding				n	Ever seen a doctor because of trouble becoming pregnant				n	Infertility [a]			
		Unadjusted		Model 1			Unadjusted		Model 1			Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—
Overweight	69	0.78	0.40-1.54	0.84	0.44-1.60	69	1.15	0.68-1.93	1.27	0.79-2.03	69	1.09	0.68-1.75	1.19	0.78-1.82
Obese	8	**2.55**	**1.01-6.40**	**3.77**	**1.93-7.37**	8	2.31	0.92-5.79	**3.53**	**1.88-6.65**	8	1.91	0.76-4.77	**2.86**	**1.46-5.58**
Waist circumference	864	1.01	0.98-1.03	0.99	0.96-1.02	864	1.00	0.98-1.03	1.00	0.97-1.03	864	1.01	0.99-1.23	1.00	0.97-1.02
Waist-to-hip ratio	864	0.90	0.67-1.20	0.97	0.72-1.29	864	0.82	0.60-1.10	0.87	0.65-1.16	864	0.88	0.67-1.16	0.97	0.75-1.25
Waist-to-height ratio															
<0.5	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—
≥0.5	49	0.97	0.47-1.97	1.15	0.59-2.26	49	0.81	0.40-1.65	0.95	0.48-1.88	49	1.00	0.56-1.78	1.23	0.72-2.12
Age 12 to 15 years															
BMI category															
Normal	622	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—
Overweight	47	1.36	0.83-2.24	1.18	0.73-1.91	47	1.13	0.65-1.95	1.03	0.62-1.72	47	1.22	0.78-1.91	1.08	0.69-1.67
Obese	9	1.11	0.32-3.84	1.07	0.31-3.74	9	1.09	0.32-3.77	1.00	0.31-3.24	9	0.87	0.25-2.99	0.87	0.25-3.05
Waist circumference	679	1.01	0.99-1.03	1.01	0.98-1.03	680	1.00	0.97-1.03	1.00	0.98-1.02	680	1.01	0.99-1.02	1.00	0.99-1.02
Waist-to-hip ratio	679	1.16	0.89-1.50	1.15	0.87-1.51	680	1.20	0.93-1.54	1.19	0.91-1.56	680	1.13	0.91-1.39	1.11	0.88-1.40
Waist-to-height ratio															
<0.5	647	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—
≥0.5	31	1.27	0.68-2.37	1.23	0.69-2.17	31	1.07	0.54-2.12	1.04	0.55-1.97	31	1.10	0.62-1.96	1.05	0.62-1.78

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.
Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.
[a] Women answered yes to any one of the two related infertility questions.

Appendix3-6 Associations between childhood obesity and fertility problem in adulthood using USA CDC 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011[a]

Body Composition	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility [b]				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	760	Ref.	—	Ref.	—	760	Ref.	—	Ref.	—	760	Ref.	—	Ref.	—
Overweight	76	0.63	0.30-1.29	0.63	0.31-1.27	76	0.90	0.51-1.59	0.93	0.54-1.60	76	0.87	0.52-1.46	0.90	0.56-1.47
Obese	27	1.51	0.73-3.12	1.60	0.83-3.09	27	**1.85**	**1.01-3.38**	**2.10**	**1.25-3.52**	27	1.52	0.83-2.76	**1.69**	**1.00-2.87**
Age 12 to 15 years															
BMI category															
Normal	611	Ref.	—	Ref.	—	612	Ref.	—	Ref.	—	612	Ref.	—	Ref.	—
Overweight	53	1.33	0.83-2.15	1.21	0.76-1.93	53	1.12	0.66-1.88	1.05	0.64-1.71	53	1.11	0.71-1.74	1.05	0.67-1.63
Obese	14	1.08	0.39-2.99	1.13	0.43-2.94	14	1.06	0.38-2.92	1.10	0.43-2.84	14	1.12	0.48-2.59	1.13	0.52-2.48

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.
Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.
[a] Normal defined as <85th percentile childhood BMI; overweight defined as 85th-94th percentile childhood BMI; obese defined as ≥95th percentile childhood BMI
[b] Women answered yes to any one of the two related infertility questions.

Appendix3-7 Associations between childhood obesity and fertility problem in adulthood using 1985 ASHFS cohort 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011[a]

Childhood BMI	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility [b]				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
Normal	765	Ref.	—	Ref.	—	765	Ref.	—	Ref.	—	765	Ref.	—	Ref.	—
Overweight	67	0.51	0.21-1.19	0.55	0.24-1.27	67	0.64	0.31-1.32	0.71	0.36-1.43	67	0.60	0.31-1.18	0.67	0.35-1.29
Obese	31	1.53	0.78-2.30	1.39	0.76-2.55	31	**1.99**	**1.17-3.40**	**2.20**	**1.40-3.46**	31	**1.80**	**1.10-2.95**	**1.81**	**1.19-2.78**
Age 12 to 15 years															
Normal	601	Ref.	—	Ref.	—	602	Ref.	—	Ref.	—	602	Ref.	—	Ref.	—
Overweight	48	1.10	0.65-1.87	1.05	0.59-1.84	48	0.82	0.43-1.58	0.85	0.45-1.59	48	0.98	0.59-1.64	0.98	0.60-1.60
Obese	29	1.54	0.90-2.66	1.39	0.82-2.35	29	1.53	0.87-2.69	1.37	0.82-2.27	29	1.36	0.81-2.28	1.21	0.75-1.97

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.
Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.
[a] Normal defined as <85th percentile childhood BMI; overweight defined as 85th-94th percentile childhood BMI; obese defined as ≥95th percentile childhood BMI
[b] Women answered yes to any one of the two related infertility questions.

Chapter 4: Associations of childhood adiposity and changes in adiposity status from childhood to adulthood with pregnancy hypertension

The following text in Chapter 4 has been published in *Pregnancy Hypertension-An International Journal of Women's Cardiovascular Health* (*Appendix E 2*)

4.1 Abstract

Objective(s): To investigate the associations between adiposity in childhood, and adiposity change from childhood to adulthood, with pregnancy hypertension.

Study Design: The study followed-up 985 girls from the 1985 Australian Schools Health and Fitness Survey (aged 9-15 years) who were ever pregnant in 2004-2006 and/or 2009-2011. In childhood, overweight and obesity were defined by age-sex-specific international standard for body mass index (BMI) and in adulthood as BMI≥25kg/m^2. Childhood and adult abdominal obesity were defined as waist-to-height ratio (WHtR)≥0.5. A subsample of adults had abdominal obesity measures (n=549).

Main outcome measures: Pregnancy hypertension was self-reported as having had high blood pressure during or due to pregnancy.

Results: Childhood overweight/obesity (relative risk [RR]=1.66, 95% confidence interval [CI]:1.07-2.52) and abdominal obesity (RR=2.55, 95% CI:1.34-4.85) were associated with higher risks of pregnancy hypertension after adjustment for age, socioeconomic status and parity. Further adjustment for adult BMI attenuated the association for childhood overweight/obesity which was no longer statistically significant (RR=1.28, 95% CI: 0.79-2.07). The association with childhood abdominal obesity persisted after adjustment for adult WHtR (RR=2.15, 95% CI: 1.10-4.20). Compared to participants with persistently normal BMI or WHtR, those who were overweight/obese in adulthood only (RR=1.49, 95% CI: 1.10-2.02), persistently overweight/obese (RR=2.06, 95% CI: 1.29-3.29) or persistently abdominally obese (RR=3.09, 95% CI: 1.54-6.20) had increased risks of pregnancy hypertension.

Conclusion(s): Childhood adiposity was associated with increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult

abdominal obesity. Women who were persistently overweight/obese or abdominally obese since childhood had the highest risk of pregnancy hypertension.

4.2 Introduction

Hypertension affects an estimated 10% of all pregnancies and is the most frequently identified medical problem during pregnancy. Hypertensive disorders of pregnancy include both pregnancy-induced (gestational hypertension and preeclampsia) and pre-existing (chronic hypertension) conditions and are associated with a higher risk of cardiovascular events later in life [159].

Being overweight or obese puts a woman at risk of developing pregnancy hypertension. The risk of preeclampsia doubles with each 5-7 unit increase in pre-pregnancy body mass index (BMI) [85]. Abdominal obesity has also been associated with pregnancy hypertension. The results from one Australian cohort indicated that every 1cm increase in waist circumference was associated with a 4% increased risk of pregnancy hypertension [88]. Another case-control study indicated that waist circumference was a better predictor of pregnancy hypertension than BMI [89]. Despite the known detrimental effect of adult adiposity on pregnancy hypertension, the relationship with childhood obesity, especially childhood abdominal obesity with pregnancy hypertension is less well understood.

To our knowledge, only two studies have reported a longitudinal relationship between childhood obesity and pregnancy hypertension, and childhood BMI was the only predictor [77, 91]. The 1958 British birth cohort study included 4,681 girls and reported that being overweight or obese at the age of 7 years increased the risk of self-reported hypertension in pregnancy before age 33, but this risk did not persist after adjustment for adult BMI [77]. More recently, a report based on 703 participants in the USA Bogalusa Heart Study showed that elevated childhood BMI was a significant risk factor for self-reported pregnancy hypertension without considering adult BMI.

Therefore, the aim of our present study was to examine the association between different adiposity measures in childhood and changes in adiposity status from childhood to adulthood, with pregnancy hypertension.

4.3 Materials and Methods

4.3.1 Participants

The Childhood Determinants of Adult Health (CDAH) Study is a follow-up of 8,498 children including 4,191 girls aged 7-15 years who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS), a nationwide sample of Australian school children [160]. In 1985, all children had physical assessments and those aged 9, 12 and 15 years had blood pressure measured. During 2002-2004, a total of 3,412 female participants were traced and 2,734 enrolled to participate in the CDAH Study (enrolment) (Figure 4.1). During 2004-2006, the first follow-up (CDAH-1) of those enrolled was conducted when participants were aged 26-36 years. Of the 1,017 women who reported having ever been pregnant and answered questions about pregnancy hypertension in the questionnaire, 735 attended one of 34 study clinics held around Australia for physical measurements. The second follow-up (CDAH-2) was conducted during 2009-2011 when participants were aged 31-41 years and 901 reported having ever been pregnant women and completed the same questions about pregnancy hypertension. A total of 1,324 women who were ever pregnant and answered the pregnancy hypertension questions at CDAH-1 and/or CDAH-2 were included in the analysis reported here (423 women only participated in CDAH-1, 307 women only participated in CDAH-2 and 594 women participated in both CDAH-1 and CDAH-2).

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

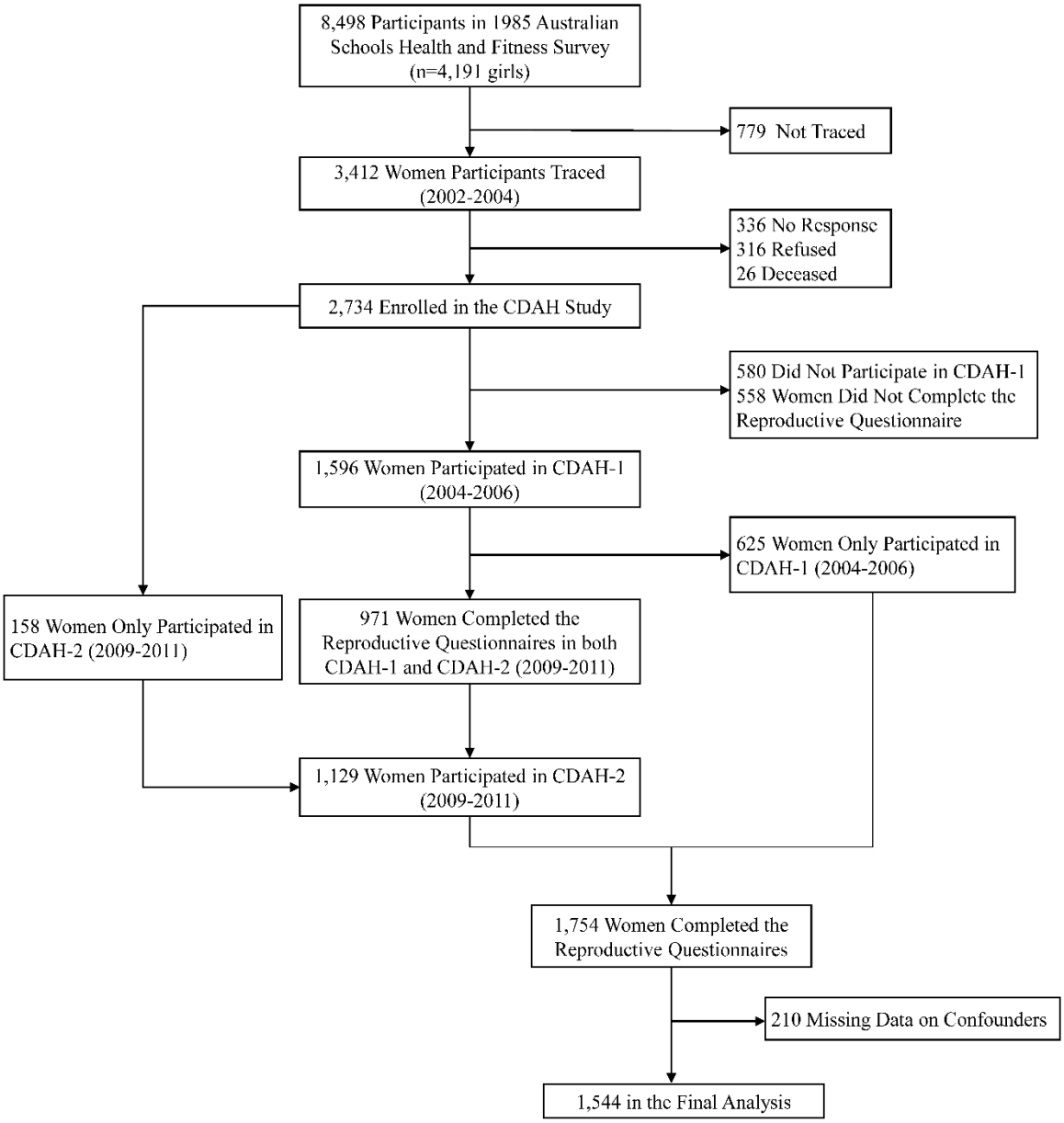


Figure 4.1 Selection of participants for the Childhood Determinants of Adult Health (CDAH) Study

4.3.2 Childhood adiposity measures

BMI, calculated as weight (kg)/height $(m)^2$, was derived from measured height and weight. Overweight and obese were combined for analysis and defined using international age- and sex-specific cut-points for BMI [8]. Waist and hip circumference were measured to the nearest 0.1 cm. Waist-to-hip ratio was calculated by dividing waist by hip circumference. Waist-to-

height ratio (WHtR) was calculated by dividing waist circumference by height. Abdominal obesity was defined as WHtR≥0.5 [133]. Childhood BMI and waist circumference z scores were calculated based on age- and sex-specific standardization of the full childhood cohort.

4.3.3 Adult adiposity measures

At CDAH-1, weight, height, waist circumference and hip circumference were measured at study clinics for most participants. Some participants (n=1,119) also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. Participants who did not visit clinics self-reported their weight and height, and a correction factor was applied to adjust for error [26]. BMI (kg/m^2) was calculated from height and weight. WHtR was calculated from measured waist circumference and height at clinics.

Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the correction factor applied at CDAH-1. Height was self-reported and adjusted 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) [2]. Adult abdominal obesity was defined as WHtR≥0.5 [13].

4.3.4 Pregnancy hypertension

In CDAH-1 and CDAH-2, women were asked to answer ‘yes’ or ‘no’ to the question ‘Have you ever been told that you have high blood pressure during pregnancy or due to pregnancy?’ Pregnancy hypertension was recorded if they responded ‘yes’.

4.3.5 Covariate measures

Information on sociodemographic characteristics was self-reported in childhood and follow-up including childhood age, parental education, parental smoking and childhood smoking experimentation, both childhood and adult area-level disadvantage [161], alcohol consumption, physical activity and adult education level, smoking status, occupation and parity.

4.3.6 Statistical analyses

Taking into account the repeated measures of variables over CDAH-1 and CDAH-2, log-binomial models with generalized estimating equations (GEE) were used to estimate relative risk (RR) for associations between childhood adiposity measures and change in adiposity status from childhood to adulthood with pregnancy hypertension. Subsample analysis was conducted among those with measured adult waist circumference and height at the CDAH-1 clinics.

The independent effects of childhood BMI and childhood abdominal obesity measures on pregnancy hypertension were examined by including corresponding adult BMI and adult abdominal obesity measures (for the subsample only) in the models. In addition, as abdominal obesity had been suggested to be a stronger predictor of cardiovascular disease than BMI [13, 90], in the current study, childhood abdominal obesity measures were further adjusted for childhood and adult BMI to investigate the effects of fat distribution in childhood on pregnancy hypertension more specifically. Covariates remaining in the final model were variables which associated with the exposure and the outcome and resulted in more than 10% change in the coefficient of the study factor.

The following sensitivity analyses were conducted. First, we excluded those who reported 'yes' to ever having pregnancy hypertension in CDAH-1 but 'no' in CDAH-2. Second, since multiple births and high childhood blood pressure may be associated with increased risk of pregnancy hypertension [162, 163], we restricted our sample to women who had singleton pregnancies and those who had measured childhood systolic (SBP) and diastolic blood pressure (DBP). To investigate whether high blood pressure persisted post-pregnancy in those with a history of pregnancy hypertension, we compared blood pressure in a subsample of women (n=609) who had participated in the first follow-up (CDAH-1) clinics and had measured

systolic and diastolic blood pressure. Third, inverse probability weighting was used to account for missing data at follow-up, with multiple imputation of incomplete baseline data [164].

Finally, to examine if there is a difference in risk of pregnancy hypertension associated with adiposity during different time periods of growth, we repeated the analyses by stratifying childhood age before or after 12 years.

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

4.4 Results

4.4.1 Participant characteristics

This study included 1,324 women who had ever been pregnant and completed hypertension questions at follow-ups; 594 of them completed both follow-ups; 423 participated in CDAH-1 only; and 307 women participated in CDAH-2 only. Participants who had missing data on confounders (n=339) were excluded, leaving 985 women for the final analysis. A total of 549 women with measured waist circumference and height at the CDAH-1 clinics were included in the subsample analysis.

Characteristics of participants in childhood and adulthood are shown in Table 4.1. In childhood, 10 (1.0%) girls were obese, 77 (7.8%) were overweight as defined by BMI cutoffs, and 47 (4.8%) had abdominal obesity as defined by WHtR category. The mean age at CDAH-1 was 32.8 years and 37.5 years at CDAH-2. There were 111 (13.8%) and 68 (10.6%) women who reported experiencing pregnancy hypertension in CDAH-1 and CDAH-2. Among them 21 women reported having had pregnancy hypertension in CDAH-1 but not in CDAH-2.

Compared with those who did not participate in CDAH-1 or CDAH-2, those who did participate in CDAH-1 and/or CDAH-2 were older in childhood (12.1 vs 10.5 years; P<0.001),

had greater BMI (18.8 vs 18.2 kg/m^2; *P*<0.001) and waist circumference (64.1 vs 62.1 cm; *P*<0.001), lower WHtR (0.42 vs 0.44; *P*<0.001) and waist-to-hip ratio (0.80 vs 0.82; *P*<0.001), and were less likely to be obese (1.0% vs 1.8%; *P*=0.001) or abdominally obese (4.8% vs 7.9%; *P*=0.001).

Table 4.1 Characteristics of participants in childhood (1985), CDAH-1 (2004-2006) and CDAH-2 (2009-2011), Childhood Determinants of Adult Health study[a]

Characteristics	Childhood (n=985)	CDAH-1 (n=806)	CDAH-2 (n=641)
Age, years, Mean(SD)	12.1(2.0)	32.8(2.0)	37.5(2.0)
BMI, kg/m^2, Mean(SD)	18.8(2.8)	25.0(5.1)	25.2(5.5)
Waist circumference, cm, Mean(SD)	64.1(7.5)	79.3(10.9)	
Waist-to-height ratio, Mean(SD)	0.42(0.04)	0.48(0.07)	
Waist-to-hip ratio, Mean(SD)	0.80(0.06)	0.76(0.06)	
BMI category (%)[b]			
Normal	91.2	60.7	59.9
Overweight	7.8	24.8	22.9
Obese	1.0	14.5	17.2
WHtR category (%)			
<0.5	95.2	69.0	
≥0.5	4.8	31.0	
Area-level disadvantage (%)			
High	26.9	27.3	25.7
Medium-high	28.9	25.0	24.7
Medium-low	38.2	22.5	23.8
Low	6.0	25.2	25.8
Highest parental education (%)			
University education	23.3		
Vocational training	35.0		
High school	41.7		
Childhood smoking experimentation (%)			
None	56.1		
A few puffs	21.7		
<10 cigarettes	8.5		
>10 cigarettes	13.8		
Parental smoking (%)			
None	57.8		
Either parent smoked	26.8		
Both parents smoked	15.4		
Childhood alcohol assumption (%)			
Never	67.6		
Less than once per week	26.3		
More than once per week	6.1		
Physical activity, mins/week, Mean(SD)[c]	406.7(365.7)	784.3(502.0)	819.4(507.0)

Systolic blood pressure, mmHg, Mean(SD)	108.9(12.0)		
Diastolic blood pressure, mmHg, Mean(SD)	66.6(11.0)		
Adulthood smoking status (%)			
Never smoker		49.7	56.1
Ex-smoker		28.0	30.4
Current smoker		22.4	13.5
Highest education attainment (%)			
University education		36.6	46.2
Vocational training		26.8	27.7
High school		36.6	26.1
Adulthood alcohol consumption (%)			
Non-drinkers		23.6	22.6
Light drinkers		56.8	57.8
Moderate drinkers		14.5	14.9
Heavy/very heavy drinkers		5.2	4.7
Occupation (%)			
Professional or manager		38.8	43.7
Nonmanual		28.3	27.6
Manual		5.5	6.1
Not in the labour force		27.4	22.6
Parity, Mean(SD)		1.6(1.0)	2.1(1.0)
Pregnancy hypertension (%)		13.8	10.6

[a] Childhood overweight and obesity were defined according to the international cut-offs; the final sample (n=985) included participants who participated in CDAH-1 (n=806) or CDAH-2 (n=641);
[b] Sample size in Childhood ranges from 415-985, CDAH-1 ranges from 549-806, CDAH-2 ranges from 596-641 due to missing data on some variables;
[c] Childhood physical activity was assessed by Australia Health and Fitness Survey, 1985; CDAH-1 and CDAH-2 physical activity was assessed by International Physical Activity Questionnaire;

Abbreviations: BMI, body mass index; CDAH, Childhood Determinants of Adult Health Study; SD, standard deviation; WHtR, waist-to-height ratio.

4.4.2 Pregnancy hypertension

As shown in Table 4.2, after adjustment for age, area-level disadvantage in childhood, parity and occupation in adulthood, childhood overweight/obese and abdominal obesity measures were all associated with an increased risk of pregnancy hypertension (Model 1). To determine whether childhood abdominal obesity measures contributed to the risks of pregnancy hypertension were independent of childhood BMI, we further adjusted for childhood BMI (Model 2), the associations between childhood abdominal obesity measures and pregnancy hypertension remained significant. Model 3 included additional adjustment for adult BMI to investigate whether associations with childhood overweight/obese and abdominal obesity

measures were independent of adult BMI. Childhood overweight/obese was no longer associated with pregnancy hypertension after adjustment for adult BMI (Model 3). However, associations remained for childhood abdominal obesity measures. In the subsample of participants with measured waist circumference and height at the CDAH-1 clinics (Table 4.3), childhood abdominal obesity measures were associated with increased risk of pregnancy hypertension (Model 1). When further adjusted for corresponding abdominal measures in adulthood (Model 2), although there remained significant associations with childhood WHtR (RR=1.24, 95% CI:1.01-1.54) and childhood abdominal obesity (WHtR≥0.5) (RR=2.15, 95% CI:1.10-4.20), these associations were attenuated with adjustment for adult WHtR.

Table 4.2 Associations between adiposity measures in childhood with pregnancy hypertension, Childhood Determinants of Adult Health study

Body composition	n	Unadjusted model		Model 1		Model 2		Model 3	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI (kg/m^2)	985	**1.06**	**1.01-1.12**	**1.08**	**1.02-1.14**			1.04	0.97-1.11
BMI z score	985	**1.19**	**1.03-1.38**	**1.20**	**1.04-1.40**			1.09	0.92-1.30
BMI category									
Normal	898	Ref.	—	Ref.	—			Ref.	—
Overweight/obese	87	**1.64**	**1.05-2.49**	**1.66**	**1.07-2.57**			1.28	0.79-2.07
Waist circumference (cm)	985	**1.03**	**1.01-1.05**	**1.04**	**1.02-1.06**	**1.04**	**1.01-1.07**	**1.03**	**1.00-1.07**
Waist circumference z score	985	**1.28**	**1.11-1.41**	**1.29**	**1.12-1.49**	**1.28**	**1.01-1.61**	1.25	0.99-1.57
Waist circumference, per SD (7.51 cm)	985	**1.26**	**1.10-1.44**	**1.32**	**1.14-1.54**	**1.33**	**1.04-1.69**	**1.29**	**1.01-1.65**
Waist-to-hip ratio, per SD (0.06)	985	**1.22**	**1.05-1.42**	**1.25**	**1.07-1.47**	**1.22**	**1.04-1.43**	**1.20**	**1.03-1.41**
Waist-to-height ratio, per SD (0.04)	985	**1.33**	**1.17-1.51**	**1.33**	**1.15-1.53**	**1.35**	**1.09-1.67**	**1.24**	**1.06-1.43**
WHtR category									
<0.5	938	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	47	**2.33**	**1.45-3.74**	**2.54**	**1.61-4.01**	**2.14**	**1.18-3.87**	**2.21**	**1.09-4.48**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Model 2: adjusted for age, area-level disadvantage and body mass index at childhood, parity and occupation at adulthood;
Model 3: adjusted for age, area-level disadvantage and body mass index at childhood (for abdominal obesity measures only), parity, occupation and body mass index at adulthood;
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

Table 4.3 Associations between abdominal measures in childhood with pregnancy hypertension in CDAH-1 clinic participants, Childhood Determinants of Adult Health study

Body composition	n	Unadjusted model		Model 1		Model 2	
		RR	95% CI	RR	95% CI	RR	95% CI
Waist circumference (cm)	549	**1.03**	**1.00-1.06**	**1.04**	**1.01-1.07**	1.03	1.00-1.07
Waist circumference z score	549	**1.26**	**1.03-1.55**	**1.33**	**1.08-1.65**	1.22	0.96-1.56
Waist circumference, per SD (7.30 cm)	549	**1.22**	**1.01-1.48**	**1.36**	**1.09-1.69**	1.25	0.97-1.60
Waist-to-hip ratio, per SD (0.06)	549	1.15	0.93-1.42	1.21	0.96-1.52	1.20	0.94-1.52
Waist-to-height ratio, per SD (0.04)	549	**1.32**	**1.10-1.58**	**1.34**	**1.11-1.61**	**1.24**	**1.01-1.54**
WHtR category							
<0.5	526	Ref.	—	Ref.	—	Ref.	—
≥0.5	23	**2.29**	**1.19-4.40**	**2.55**	**1.34-4.85**	**2.15**	**1.10-4.20**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;

Model 2: adjusted for age, area-level disadvantage at childhood, parity, occupation and corresponding abdominal measures at adulthood;

Abbreviations: CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

4.4.3 Influence of adiposity change from childhood to adulthood

The relative risk of pregnancy hypertension by BMI and WHtR category change from childhood to adulthood is displayed in Table 4.4. Compared with participants who had persistently normal BMI in childhood and adulthood, those who became overweight/obese reported a higher risk of pregnancy hypertension with a RR of 1.49 (95% CI 1.10-2.02). The risk was highest for participants who were persistently overweight/obese from childhood into adulthood (RR=2.06; 95% CI 1.29-3.29). In the subsample of participants who had WHtR data in both childhood and adulthood (N=549), 19 (3.5%) were abdominally obese in both childhood and adulthood and 31.6% of them had pregnancy hypertension (Figure 4.2). Compared with those who were not abdominally obese in childhood and adulthood (68.3% of the subset, 11.5% with pregnancy hypertension), those who were persistently abdominally obese had a significantly higher risk of pregnancy hypertension (RR=3.09; 95% CI: 1.54-6.20) (Table 4.4). Subjects who were not abdominally obese in childhood but who developed abdominal obesity in adulthood (27.5%) also had a higher risk of pregnancy hypertension (RR=1.56; 95% CI 1.00-2.43), but the significance of this association was attenuated after adjustment for confounders.

Table 4.4 Relative risk of pregnancy hypertension according to adiposity status from childhood to adulthood, Childhood Determinants of Adult Health Study

Body composition from childhood to adulthood	n (%)[a]	Pregnancy hypertension			
		Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI
BMI category (N=985)					
Persistently normal	860(59.4)	Ref.	—	Ref.	—
Normal to overweight/obese	469(32.4)	**1.49**	**1.11-2.01**	**1.49**	**1.10-2.02**
Overweight/obese to normal	13(0.9)	1.00	0.15-6.53	1.09	0.16-7.29
Persistently overweight/obese	105(7.3)	**2.05**	**1.27-3.29**	**2.06**	**1.29-3.29**
WHtR category [b] (N=549)					
Persistently not abdominally obese	375(68.3)	Ref.	—	Ref.	—
Not abdominally obese to abdominally obese	151(27.5)	**1.56**	**1.00-2.43**	1.43	0.92-2.25
Abdominally obese to not abdominally obese	4(0.7)	2.18	0.39-12.18	2.13	0.40-11.43
Persistently abdominally obese	19(3.5)	**2.75**	**1.34-5.65**	**3.09**	**1.54-6.20**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
[a] n indicated the total number of observations in each BMI category from childhood to CDAH-1 and/or CDAH-2 and the number of participants in each WHtR category from childhood to CDAH-1;
[b] Subgroup analysis which only available in those who participated in 1985 Australian Schools Health and Fitness Survey and CDAH-1 clinics;

Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; WHtR, waist-height ratio.

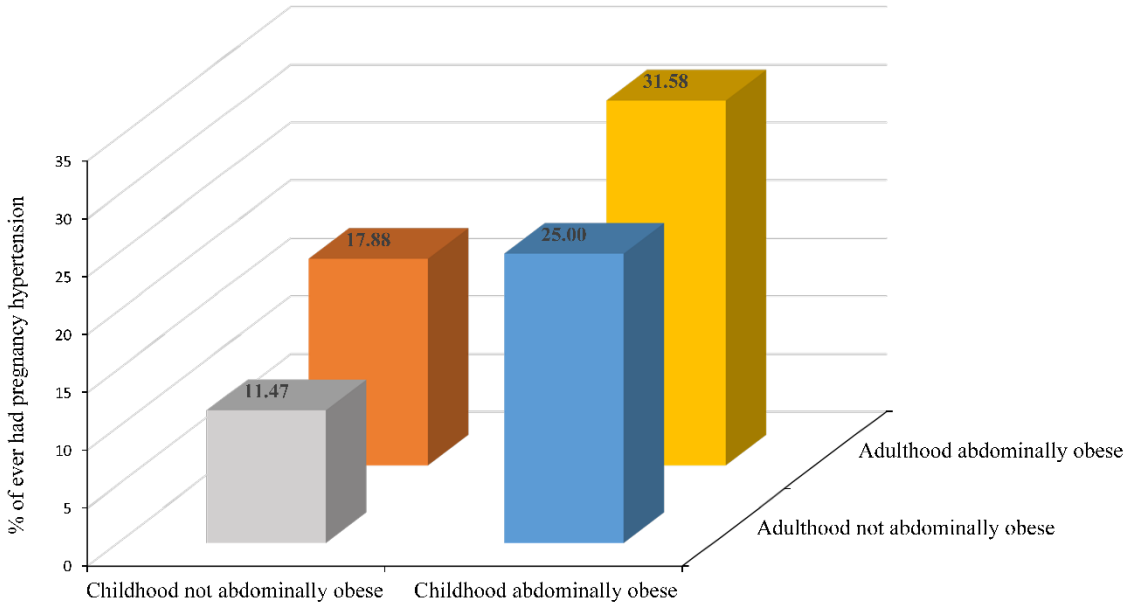


Figure 4.2 Percentage of ever had pregnancy hypertension across abdominal obesity category from childhood to adulthood, Childhood Determinants of Adult Health Study

4.4.4 Sensitivity analysis

Similar results were observed after excluding women who reported they had pregnancy hypertension in CDAH-1 but not in CDAH-2 (n=231). When restricting the sample to women with singleton pregnancies, the risk of pregnancy hypertension (RR=2.55, 95% CI 1.28-5.09) remained significantly higher in those who were abdominally obese in childhood. A total of 415 girls aged 9, 12 and 15 years had blood pressure measured in childhood. The mean childhood SBP and DBP were similar in those with and without self-reported pregnancy hypertension in CDAH-1 (SBP: 110.4±14.8 vs 109.0±11.8, *P*=0.50; DBP: 65.4±12.2 vs 66.8±10.8, *P*=0.43) and CDAH-2 (SBP: 112.6±12.7 vs 108.5±11.8, *P*=0.06; DBP: 67.8±11.1 vs 66.1±10.6, *P*=0.38). Further adjustment for childhood SBP and DBP in these participants did not substantially change the main results: the changes in the magnitude of estimates were within 17.2% (Appendix4-1). In the subsample of women (n=609) who had participated in the first follow-up (CDAH-1) clinics and had measured blood pressure, we found that compared with women who did not report pregnancy hypertension, those who reported ever having had pregnancy hypertension had significantly higher SBP (116.7 vs 110.0mmHg, P<0.001), and DBP (74.7 vs 68.7mmHg, P<0.001) and higher prevalence of hypertension (9.5% vs 1.1%, P<0.001). Sensitivity analyses to address loss to follow-up by using combined multiple imputation and inverse probability weighting produced similar patterns of results as the unweighted analyses: changes in the magnitude of significant associations ranging from -23.5-58.0% (Appendix4-2).

When stratified by age, childhood BMI and BMI z score showed similar associations in 12 to 15 year-olds (RR=1.07, 95% CI:1.00-1.15; RR=1.21, 95% CI:1.00-1.45) to those younger than 12 years (RR=1.09, 95% CI:0.99-1.19; RR=1.20, 95% CI:0.94-1.53). However, the observed statistically significant association in the 12 to 15 year age group did not persist after further adjustment for adult BMI. In a subsample analysis, a stronger association with pregnancy

hypertension was found with abdominal obesity before age 12 (RR=5.38, 95% CI:2.67-10.82) than age 12-15 years (RR=1.48, 95% CI:0.52-4.27). The significant associations with abdominal obesity before age 12 persisted after adjustment for adult WHtR (RR=5.36, 95% CI:2.68-10.73).

4.5 Discussion

To the best of our knowledge, this is the first study to report the long-term associations of childhood abdominal obesity and change in body composition from childhood to adulthood with pregnancy hypertension. We found that childhood abdominal obesity was associated with an increased risk of pregnancy hypertension. This association persisted after adjustment for adult abdominal obesity. Persistent overweight/obesity and abdominal obesity were associated with the highest risk of pregnancy hypertension.

Our finding that the association of childhood BMI with pregnancy hypertension was not independent of adult BMI was consistent with findings from the 1958 British birth cohort study [77] and that overweight/obesity that is proximal to pregnancy is especially important for pregnancy hypertension risk. A higher risk was found for women who were persistently overweight/obese in childhood and adulthood than those who became overweight/obese as adults, even though the difference did not reach statistical significance. This may be explained by the higher BMI in adulthood among those with persistently high adiposity status from childhood to adulthood than in those who had a normal BMI as children and were overweight/obese as adults (33.2 vs 29.5, $P<0.001$).

Although childhood abdominal obesity has been observed in several cross-sectional studies to be associated with cardio-metabolic risk in childhood [13, 165-167], the current understanding of the long-term effect of abdominal obesity on chronic conditions including pregnancy hypertension remains limited. Most studies from childhood have followed participants into

adulthood and collected BMI due to ease of measurement. In our study, one SD of 0.04 unit increase in childhood WHtR was associated with 33% greater likelihood of reporting pregnancy hypertension and was largely unchanged after adjusting for childhood and adulthood BMI. Similar results were found in a subsample with adult abdominal obesity measures, the associations of childhood WHtR persisted with further adjustment for adult WHtR. These results indicated a detrimental impact of childhood abdominal obesity on the risk of pregnancy hypertension, which was not modified by BMI or adult abdominal obesity. It has been suggested that early onset obesity may have higher risks of adverse outcomes in later life [168]. Consistent with this we observed stronger associations with childhood abdominal obesity in girls younger than age 12 than in older girls. In the Bogalusa Heart Study, a stronger association of childhood BMI with pregnancy hypertension was reported between ages 12 to 17 than before age 12. In our study, similar associations of childhood BMI with pregnancy hypertension were found in these younger than age 12 and age 12 to 15 after accounting for adult BMI.

The exact mechanism by which childhood abdominal obesity influences risk of pregnancy hypertension remains unclear. Plausible mechanisms include the long-term adverse effects of excess childhood visceral fat on blood pressure, insulin resistance, inflammation upregulation, oxidative stress and endothelial dysfunction [169-172].

Some potential limitations of our study are acknowledged. The first is the measurement of pregnancy hypertension and that self-report may lead to misclassification [173, 174]. However, the prevalence of pregnancy hypertension in our study is similar to global prevalence [159]. Beyond that, two validation studies to investigate the validity of self-reported pregnancy hypertension show good concordance of self-report with clinical records [173, 175]. Second is the loss to follow-up. We applied inverse probability weighting to account for missingness but these did not appreciably change the results. Third is the potential over adjustment of adult BMI and abdominal obesity measures. Our findings were for ever-pregnant women, but we were unable

to account for their BMI and abdominal measures immediately prior to pregnancy. Women's weight or waist circumference may increase after pregnancy, however, over adjustment of adult anthropometric measures tend to favour our study results. Fourth, we cannot classify the category of pregnancy hypertension exactly. Preeclampsia is a distinct cause of maternal morbidity and mortality and can lead to further systemic disorders [159]. Future studies that address pre-eclampsia specifically are needed. Finally, we did not have information on whether hypertension persisted beyond delivery. However, our finding of subsequent higher blood pressure and more prevalent hypertension in a subsample of women who reported a history of pregnancy hypertension is consistent with the literature [176, 177], indicating that the risk of future chronic hypertension may be increased.

The strengths of our study include the following. Foremost, this is the first prospective study to investigate the long-term association between childhood abdominal obesity measures and pregnancy hypertension. Second, we conducted objective measurement of childhood anthropometrics including childhood BMI and abdominal obesity measures. Third, unlike previous two studies examining childhood BMI and pregnancy hypertension, a range of data on covariates has been collected in our study.

4.6 Conclusion

Childhood adiposity was associated with increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult abdominal obesity. Women with persistently high adiposity from childhood to adulthood had the highest risk of pregnancy hypertension. Childhood abdominal obesity may be considered in addition to BMI, as an indicator of the risk of future cardiometabolic conditions including pregnancy hypertension.

4.7 Appendix 4 Supplementary material for Chapter 4

Appendix4-1 Associations between adiposity measures in childhood with pregnancy hypertension, Childhood Determinants of Adult Health Study (Considering childhood blood pressure)

Body composition	n	Unadjusted model		Model 1		Model 2		Model 3		Model 4	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI (kg/m^2)	415	**1.10**	**1.02-1.18**	**1.12**	**1.03-1.21**			1.03	0.93-1.15	1.04	0.93-1.16
BMI z score	415	**1.29**	**1.04-1.58**	**1.31**	**1.06-1.62**			1.06	0.81-1.40	1.09	0.81-1.44
BMI category											
Normal	380	Ref.	—	Ref.	—			Ref.	—	Ref.	—
Overweight/obese	35	**2.58**	**1.50-4.45**	**2.75**	**1.60-4.73**			1.85	0.95-3.59	1.98	0.91-4.30
Waist circumference (cm)	415	**1.04**	**1.02-1.07**	**1.05**	**1.02-1.08**	**1.05**	**1.00-1.09**	**1.04**	**1.00-1.09**	**1.04**	**1.01-1.09**
Waist circumference z score	415	**1.38**	**1.14-1.67**	**1.41**	**1.17-1.70**	1.36	0.99-1.87	**1.35**	**1.00-1.82**	**1.36**	**1.03-1.80**
Waist circumference, per SD (7.87 cm)	415	**1.38**	**1.15-1.66**	**1.46**	**1.20-1.78**	**1.42**	**1.01-2.01**	**1.41**	**1.04-1.92**	**1.43**	**1.07-1.90**
Waist-to-hip ratio, per SD (0.06)	415	1.26	1.00-1.58	**1.33**	**1.04-1.70**	1.25	0.98-1.60	1.23	0.97-1.57	1.23	0.97-1.56
Waist-to-height ratio, per SD (0.04)	415	**1.43**	**1.20-1.71**	**1.44**	**1.22-1.70**	**1.44**	**1.09-1.90**	**1.41**	**1.10-1.81**	**1.40**	**1.09-1.80**
WHtR category											
<0.5	395	Ref.	—	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	20	**3.24**	**1.81-5.80**	**3.50**	**2.01-6.10**	**2.88**	**1.25-6.59**	**2.75**	**1.11-6.82**	**3.28**	**1.56-6.87**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Model 2: adjusted for age, area-level disadvantage and body mass index at childhood, parity and occupation at adulthood;
Model 3: adjusted for age, area-level disadvantage and body mass index at childhood (for abdominal obesity measures only), parity, occupation and body mass index at adulthood;
Model 4: adjusted for age, area-level disadvantage, body mass index (for abdominal obesity measures only) and systolic and diastolic blood pressure at childhood, parity, occupation and body mass index at adulthood;
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

Appendix4-2 Sensitivity analysis using inverse propensity weighting technique with multiple imputation. Associations between adiposity measures in childhood with pregnancy hypertension, Childhood Determinants of Adult Health Study

Body composition	n	Unadjusted model		Model 1		Model 2		Model 3	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI (kg/m^2)	985	**1.06**	**1.01-1.12**	**1.07**	**1.01-1.13**			1.02	0.96-1.09
BMI z score	985	**1.18**	**1.01-1.38**	**1.19**	**1.02-1.39**			1.04	0.87-1.24
BMI category									
Normal	898	Ref.	—	Ref.	—			Ref.	—
Overweight	77	**1.72**	**1.07-2.77**	**1.76**	**1.10-2.82**			1.22	0.73-2.05
Obese	10	1.22	0.33-4.45	1.26	0.35-4.51			0.50	0.13-1.88
Waist circumference (cm)	985	**1.03**	**1.01-1.05**	**1.04**	**1.02-1.06**	**1.04**	**1.01-1.07**	1.03	1.00-1.07
Waist circumference z score	985	**1.28**	**1.10-1.48**	**1.28**	**1.10-1.48**	**1.28**	**1.02-1.60**	1.21	0.94-1.57
Waist circumference, per SD (7.51 cm)	985	**1.26**	**1.10-1.45**	**1.31**	**1.12-1.52**	**1.32**	**1.05-1.68**	1.26	0.97-1.65
Waist-to-hip ratio, per SD (0.06)	985	**1.22**	**1.04-1.44**	**1.29**	**1.09-1.52**	**1.25**	**1.05-1.49**	**1.26**	**1.05-1.50**
Waist-to-height ratio, per SD (0.04)	985	**1.33**	**1.17-1.51**	**1.33**	**1.18-1.51**	**1.43**	**1.18-1.74**	**1.40**	**1.3-1.72**
WHtR category									
<0.5	938	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	47	**2.36**	**1.46-3.82**	**2.48**	**1.54-4.00**	**2.15**	**1.13-4.08**	**2.50**	**1.43-4.37**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Model 2: adjusted for age, area-level disadvantage and body mass index at childhood, parity and occupation at adulthood;
Model 3: adjusted for age, area-level disadvantage and body mass index (for abdominal obesity measures only) at childhood, parity, occupation and body mass index at adulthood;
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

Chapter 5: 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

The following text in Chapter 5 has been published in *Human Reproduction* *(Appendix E 3)*

5.1 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.

5.2 Introduction

Menstrual irregularity and polycystic ovary syndrome (PCOS) have been associated with higher risk of lower fecundity and cardiovascular diseases [178, 179] as well as some cancers [180, 181]. PCOS is recognized as the most common heterogeneous endocrine disorder, affecting 8-13% of women of reproductive age [101]. 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 [96].

General and abdominal obesity are associated with a greater risk of menstrual irregularity in adult women [182-185]. 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 [182]. 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 [109]. 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 [77, 106] 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 [77]. 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[106]. Two further papers based on the same Northern Finland cohort reported

associations of weight gain [186] and age at adiposity rebound with PCOS [187]. 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 [188].

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).

5.3 Materials and Methods

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

5.3.1.1 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 [143] (Figure 5.1). 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) [182]. 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.

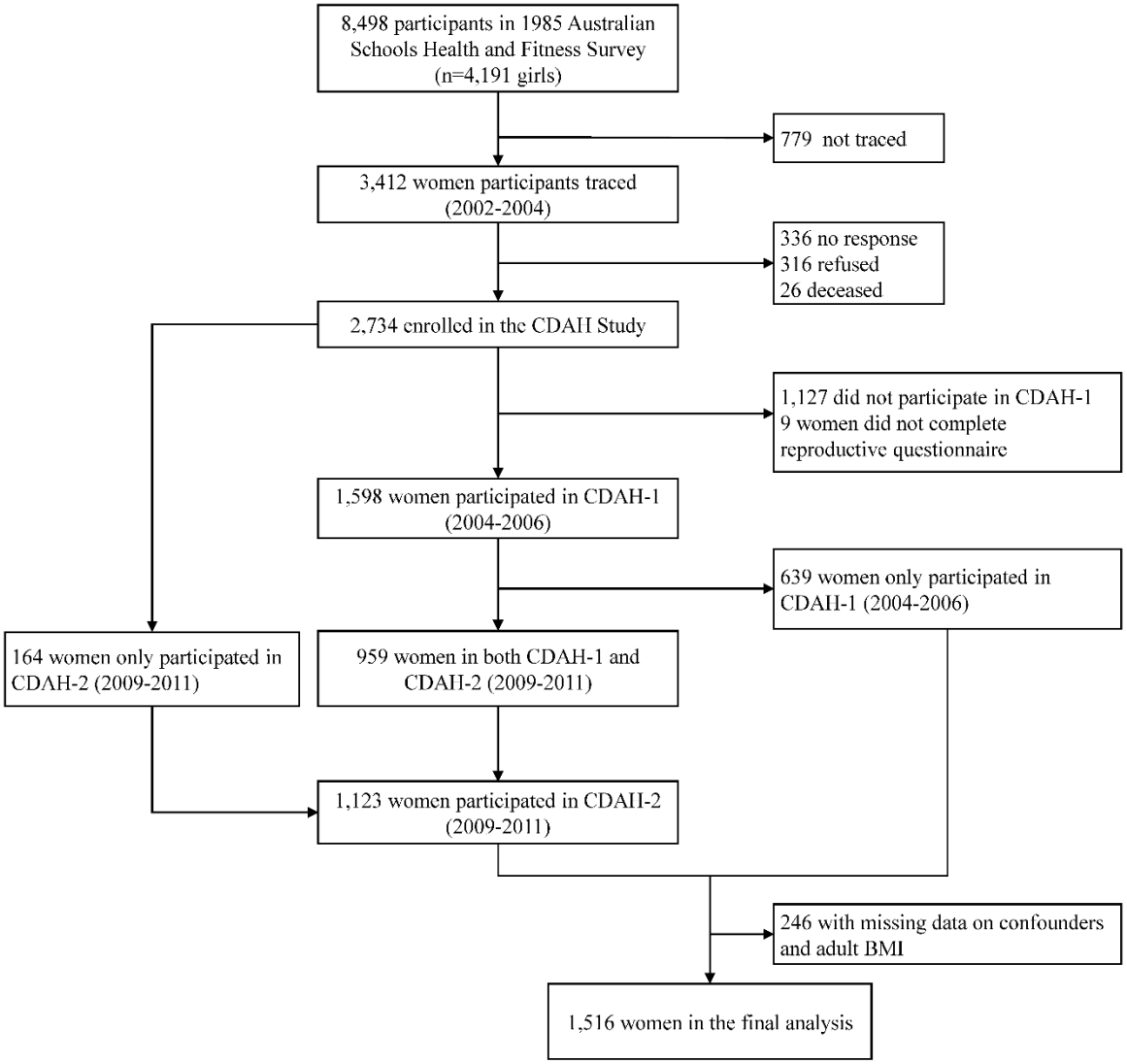


Figure 5.1 Flow chart of the study population for the Childhood Determinants of Adult Health Study in Australia, 1985–2011

CDAH: Childhood Determinants of Adult Health

5.3.1.2 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 [8]. BMI-z score was calculated based on age-sex-specific World Health Organization Child Growth standards [7]. 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 [133].

5.3.1.3 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 [26]. 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) [2].

5.3.1.4 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 [189]. The presence of hirsutism was defined as ever having seen a doctor because of concern about the amount of hair on their face.

5.3.1.5 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 [190].

5.3.2 The Bogalusa Heart Study: a cohort from the USA

5.3.2.1 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 [134]. 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 (Figure 5.2).

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.

5.3.2.2 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.

5.3.2.3 Adult anthropometric measurements

Adult height and weight were recorded in the BBS [136]. Where necessary, height and weight before age 40 years were extracted from records of the BHS [191]. BMI, overweight and obesity were calculated or classified using the same criteria as described in the CDAH study.

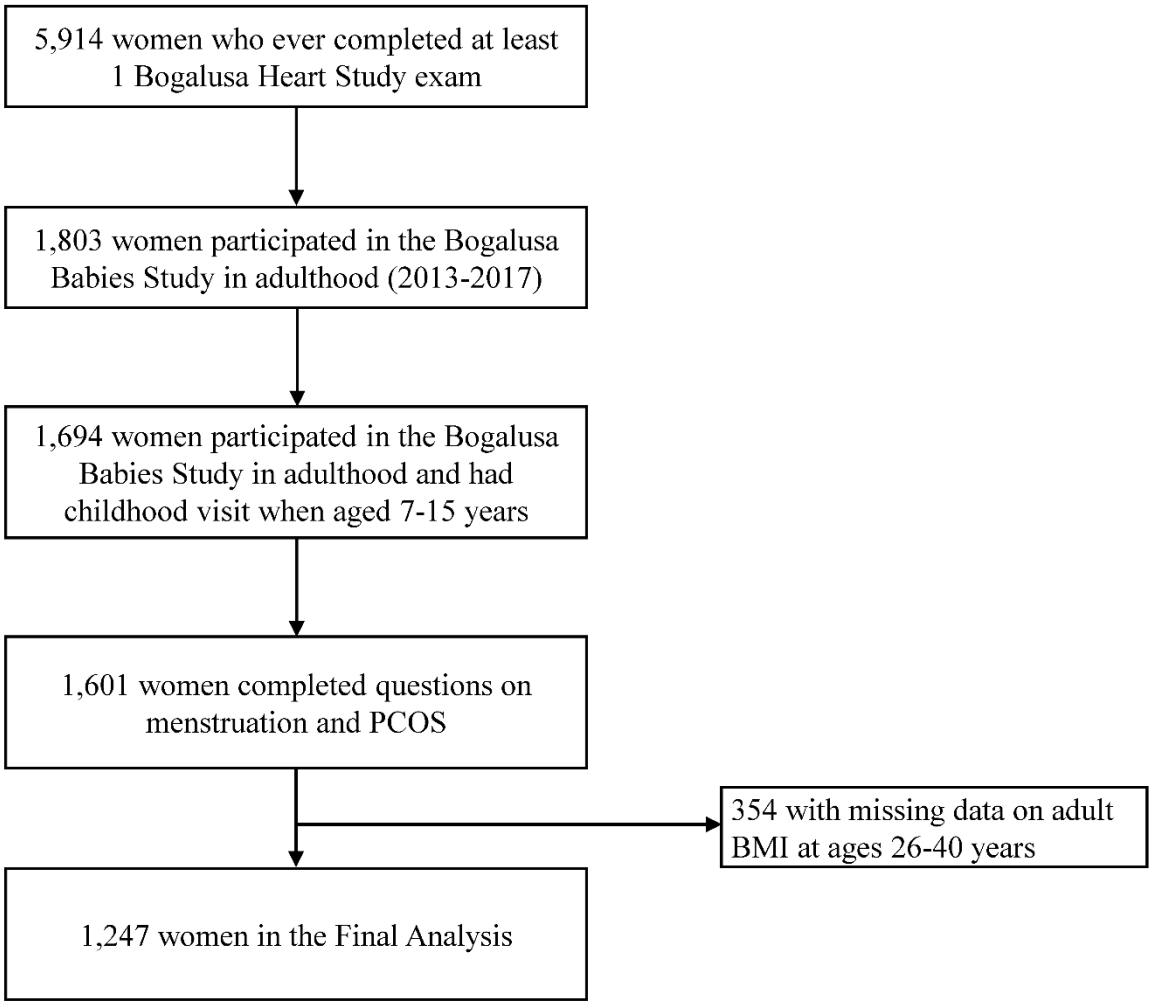


Figure 5.2 Flow chart of the study population for the Bogalusa Heart Study in the USA, 1973–2017

PCOS: polycystic ovary syndrome

5.3.2.4 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.

5.3.2.5 Covariates

Race (white/black) was recorded at the initial BHS visit. As previously described [192], 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).

5.3.3 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 [193].

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 [149]. 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 [194]. 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) [195]. 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.

5.4 Results

5.4.1 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 5.1. 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.

Table 5.1 Participants' characteristics in the Childhood Determinants of Adult Health Study and the Babies sub-study of the Bogalusa Heart Study[a]

Variable	CDAH (n=1,516)			BBS (n=1,247)	
	Childhood	Adulthood		Childhood	Adulthood
		CDAH-1	CDAH-2		BBS
Race, %(n)					
White				58.5(730)	
Black				41.5(517)	
Age, years, Mean(SD) [b]	11.0(2.5)	31.5(2.6)	36.4(2.6)	11.6(2.0)	44.1(7.9)
BMI, kg/m^2, Mean(SD) [b]	18.2(2.8)	24.9(5.2)	25.4(5.5)	19.5(4.0)	29.2(7.8)
BMI z-score, Mean(SD) [b]	0.16(0.90)			0.36(1.24)	
BMI category, %(n) [b]					
Normal	91.2(1383)	62.4(943)	58.7(505)	74.9(934)	36.2(451)
Overweight	7.7(116)	23.7(358)	24.5(211)	17.6(219)	24.9（310）
Obese	1.1(17)	14.0(211)	16.7(144)	7.5(94)	39.0（486）
Waist/height ratio, Mean(SD) [b]	0.43(0.04)			0.46(0.07)	
WHtR category [b]					
<0.5	94.7(1436)			77.6(228)	
≥0.5	5.3(80)			22.5(66)	
Highest parental education, %(n)					
University education	28.0(425)			29.8(334)	
Vocational training	33.5(508)			21.7(234)	
High school	38.5(583)			48.5(543)	
Highest own-education, %(n)					
University education		46.6(704)	54.0(464)		28.1(350)
Vocational training		25.9(392)	25.4(218)		33.4(416)
High school		27.5(416)	20.7(178)		38.6(481)
Smoking, %(n)					
Never smoked	88.2(1035)	54.7(827)	59.2(507)	76.8(763)	53.3(471)
Ever smoked	11.8(1439)	45.3(684)	40.8(350)	23.2(230)	46.7(412)
Alcohol consumption, %(n)					
None, light, moderate drinker	99.1(1166)	93.8(1398)	95.8(800)	98.5(400)	82.9(707)
Heavy and very heavy drinker	0.9(11)	6.2(93)	4.2(35)	1.5(6)	17.1(146)
Age at menarche, years, Mean(SD)	13.1(1.3)			12.6(1.5)	
SHBG, nmol/l, Mean(SD) [c]		52.1(27.4)			
Testosterone, nmol/l, Mean(SD) [c]		1.5(0.6)			
Free testosterone, nmol/l, Mean(SD) [c]		23.9(14.0)			
Hirsutism, %(n)					
Yes		3.5(52)	4.0(34)		6.5(81)
No		96.5(1439)	96.0(820)		93.5(1160)
Menstrual irregularity, %(n)					
Yes		16.6(139)	16.7(87)		24.5(303)
No		83.4(699)	83.3(434)		75.5(935)
PCOS (menstrual irregularity+hirsutism), %(n) [d]					

Yes	1.5(12)	1.4(7)	2.2(27)
No	98.6(817)	98.7(513)	97.8(1211)
Self-reported doctor diagnosed PCOS, %(n)			
Yes	5.8(88)	8.2(70)	6.9(84)
No	94.2(1423)	91.8(785)	93.2(1142)
PCOS, %(n)			
Yes	6.2(93)	8.6(74)	8.0(100)
No	93.9(1419)	91.4(786)	92.0(1147)

[a] Sample size varied [range from 652-1512 for Childhood Determinants of Adult Health (CDAH) and range from 294-1241 for Babies sub-study of the Bogalusa Heart Study (BBS)] because of the missing data

[b] The variables were calculated using the mean values in multiple childhood visits in BBS

[c] Available in a subsample of 622 participants who attended the first follow-up clinic in CDAH

[d] Defined as reporting menstrual cycle≥ 35 days/totally variable and presenting hirsutism

PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; WHtR, waist/height ratio

5.4.2 Childhood adiposity and menstrual irregularity

Table 5.2 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, in the BBS, when further adjusted for race, childhood obesity was associated with nearly twice the risk of having menstrual irregularity.

5.4.3 Childhood adiposity and self-reported PCOS

In CDAH, childhood obesity defined by BMI and childhood abdominal obesity defined by WHtR were significantly associated with an increased risk of self-reported PCOS (Table 5.3). A 0.01 unit increase in childhood WHtR was associated with a 5% increased likelihood of self-reported PCOS. In the BBS sample overall, results were consistent with CDAH: childhood obesity was associated with a higher risk of self-reported PCOS and every 0.01 unit increase in WHtR was associated with 8% greater likelihood of PCOS (Table 5.3).

Table 5.2 Associations of adiposity in childhood with menstrual irregularity in adulthood in CDAH and BBS

Childhood adiposity	CDAH				BBS			
	Unadjusted model (n=1,010)		Model 1 (n=1,010)		Unadjusted model (n=1,238)		Model 1[a] (n=1,238)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.11	0.94-1.31	1.13	0.96-1.34	**1.09**	**1.00-1.18**	1.09	1.00-1.19
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	1.50	0.99-2.28	**1.62**	**1.06-2.48**	1.07	0.88-1.29	1.07	0.88-1.30
Obese	**2.72**	**1.60-4.64**	**2.84**	**1.63-4.96**	**1.43**	**1.08-1.89**	**1.44**	**1.08-1.92**
WHtR, per 0.01 unit [b]	1.03	1.00-1.06	1.03	0.99-1.06	1.03	1.00-1.06	1.03	0.99-1.06
WHtR category [b]								
<0.5	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	1.44	0.87-2.39	1.47	0.89-2.45	**1.62**	**1.06-2.46**	1.56	1.00-2.45

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education

[a] Model 1 further adjust for race in the BBS

[b] n=293 in BBS

RR, relative risk

Table 5.3 Associations of adiposity in childhood with PCOS in adulthood in CDAH and BBS.

Childhood adiposity	CDAH				BBS			
	Unadjusted model (n=1,516)		Model 1 (n=1,516)		Unadjusted model (n=1,247)		Model 1[a] (n=1,247)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.25	0.98-1.58	1.26	0.98-1.62	**1.31**	**1.10-1.56**	**1.42**	**1.19-1.69**
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	**2.33**	**1.30-4.15**	**2.28**	**1.25-4.16**	**1.73**	**1.21-2.46**	**1.96**	**1.35-2.83**
Obese	3.08	0.85-11.21	**4.05**	**1.10-14.83**	1.68	1.00-2.83	**1.95**	**1.19-3.29**
WHtR, per 0.01 unit [b]	**1.06**	**1.01-1.10**	**1.06**	**1.01-1.11**	1.05	0.98-1.11	**1.06**	**1.01-1.11**
WHtR category [b]								
<0.5	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	**2.22**	**1.11-4.42**	**2.26**	**1.16-4.42**	0.99	0.34-2.91	1.09	0.39-3.07

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education

[a] Model 1 further adjust for race in BBS

[b] n=294 in BBS

5.4.4 Racial differences in the associations of self-reported PCOS in BBS

Significant racial differences were observed in the associations of childhood adiposity with self-reported PCOS, but not with menstrual irregularity, in BBS white and black participants (Table 5.4). Childhood obesity and a 0.01 unit increase in WHtR were both associated with an increased risk of PCOS in BBS white participants, but no significant associations of childhood obesity or WHtR with PCOS were found in BBS black participants.

Table 5.4 Associations of adiposity in childhood with PCOS in adulthood in BBS, by race

Race and childhood adiposity	n	PCOS			
		Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI
White	730				
BMI z-score		**1.50**	**1.25-1.79**	**1.54**	**1.28-1.87**
BMI category					
Normal		Ref.	–	Ref.	–
Overweight		**2.07**	**1.38-3.11**	**2.19**	**1.42-3.35**
Obese		**2.82**	**1.63-4.86**	**2.93**	**1.65-5.22**
WHtR, per 0.01 unit [a]		**1.08**	**1.04-1.11**	**1.11**	**1.05-1.17**
WHtR category [a]					
<0.5		Ref.	–	Ref.	–
≥0.5		2.00	0.66-6.07	2.00	0.64-6.27
Black	517				
BMI z-score		1.00	0.70-1.43	1.03	0.72-1.47
BMI category					
Normal		Ref.	–	Ref.	–
Overweight		1.36	0.59-3.13	1.43	0.64-8.26
Obese		0.29	0.04-2.35	0.19	0.03-2.78
WHtR, per 0.01 unit [a]		0.89	0.76-1.04	0.88	0.76-1.02
WHtR category [a]					
<0.5		Ref.	–	Ref.	–
≥0.5		N/A		N/A	

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education
[a] n=109 in white race and n=185 in black race in BBS

5.4.5 Influence of weight status from childhood into adulthood

The relative risk of menstrual irregularity by change of weight status from childhood to adulthood is displayed in Table 5.5. Compared with participants who had persistently normal BMI in childhood and adulthood, those who became overweight or obese in adulthood reported a higher risk of menstrual irregularity in BBS. Participants who were persistently

overweight/obese since childhood had significantly higher risks of menstrual irregularity in 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 5.6). 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 5.6).

5.4.6 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 (Appendix5-1, Appendix5-2 and Appendix5-3). 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 (Appendix5-4).

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) (Appendix5-5), 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.

Table 5.5 Associations of weight status change from childhood to adulthood with menstrual irregularity in CDAH and the BBS

Weight status from childhood to adulthood	CDAH					BBS				
	n	Cases (%)[a]	Unadjusted model		Model 1	n	Cases (%)[a]	Unadjusted model		Model 1[a]	
			RR	95% CI	RR 95% CI			RR	95% CI	RR	95% CI
	1010					1238					
Persistently normal		786 (57.9)	Ref.	—	Ref. —		850 (36.4)	Ref.	—	Ref.	—
Normal to overweight/obese		447 (32.9)	0.97	0.93-1.30	1.04 0.77-1.39		889 (38.0)	**1.26**	**1.01-1.57**	**1.29**	**1.03-1.61**
Overweight/obese to normal		16 (1.2)	1.57	0.65-3.81	1.65 0.70-3.89		44 (1.9)	1.47	0.89-2.43	1.47	0.88-2.46
Persistently overweight/obese		108 (8.0)	**1.63**	**1.09-2.45**	**1.76** **1.15-2.71**		554 (23.7)	**1.36**	**1.01-1.83**	**1.39**	**1.01-1.90**

Model 1: adjust for age at menarche, highest parental education and own-education

[a] indicated the total number of observations in each weight status category from childhood to adulthood

Table 5.6 Associations of weight status change from childhood to adulthood with PCOS in CDAH and BBS

Weight status from childhood to adulthood	CDAH					BBS				
	n	Cases (%)[a]	Unadjusted model		Model 1		n	Cases (%)[a]	Unadjusted model		Model 1[b]	
			RR	95% CI	RR	95% CI			RR	95% CI	RR	95% CI
Overall	1516						1247					
Persistently normal		1414 (59.7)	Ref.	—	Ref.	—		855 (36.2)	Ref.	—	Ref.	—
Normal to overweight/obese		455 (31.9)	1.19	0.81-1.73	1.34	0.93-1.94		900 (38.1)	0.80	0.52-1.22	1.00	0.65-1.53
Overweight/obese to normal		31 (1.3)	0.92	0.13-6.40	1.02	0.15-6.93		46 (2.0)	1.99	0.78-5.05	**2.69**	**1.10-6.62**
Persistently overweight/obese		169 (7.1)	**2.93**	**1.65-5.18**	**3.66**	**2.05-6.56**		560 (23.7)	**2.55**	**1.47-4.43**	**3.72**	**2.12-6.54**
White							730					
Persistently normal								651 (44.9)	Ref.	—	Ref.	—
Normal to overweight/obese								489 (33.7)	1.03	0.67-1.60	1.06	0.69-1.63
Overweight/obese to normal								25 (1.7)	**4.00**	**1.66-9.62**	**4.70**	**1.93-11.43**
Persistently overweight/obese								286 (19.7)	**4.66**	**2.62-8.28**	**5.41**	**2.98-9.83**
Black							517					
Persistently normal								204 (22.4)	Ref.	—	Ref.	—
Normal to overweight/obese								411 (45.2)	0.43	0.13-1.42	0.46	0.15-1.43
Overweight/obese to normal								21 (2.3)		N/A		N/A
Persistently overweight/obese								274 (30.1)	0.75	0.21-2.65	0.88	0.28-2.80

Model 1: adjust for age at menarche, highest parental education and own-education

[a] indicated the total number of observations in each BMI category from childhood to adulthood

[b] Model 1 further adjust for race in the overall BBS

5.5 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 [77]. Though some studies have suggested that the distribution of body fat in adult women may be a risk factor of menstrual irregularity cross-sectionally [182, 185], 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 [141, 196]. 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 [96], 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 [109, 197]. 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. [198] 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 [199-201]. 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 [202]. 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 [203, 204], 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 [205]. Familial trends in PCOS are reported, but no specific genetic association has been reported and more research is necessary to define the genetic basis [206]. Environmental factors, including health-related behaviours or lifestyles and economic disadvantage, are potentially involved in the aetiology, prevalence, and modulation of PCOS [202]. 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 [106]. 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 significantly higher risk of PCOS, suggesting independent effects of childhood adiposity that need to be confirmed in larger studies.

There are several limitations in our study. First, menstrual cycle characteristics and PCOS were self-reported by questionnaire. Previous studies have suggested that women's retrospective self-report of menstrual length can be prone to error [95] and the agreement between diary records and retrospectively recalled menstrual cycle length was moderate [207]. Self-reported PCOS likely tends to underestimate prevalence [208, 209]. Also, if the accuracy of self-reported menstrual cycle length and PCOS differed by obesity status, then our effect estimates might have been biased. However, previous studies have shown no evidence of this [95, 106, 207].

A second potential limitation of this study was the exclusion of women using hormonal contraception (28.4%) in the analysis of menstrual irregularity in CDAH. Since hormonal contraception is commonly prescribed for menstrual irregularity [210], we may have under-estimated the prevalence of menstrual irregularity. Third, we have limited information on the

age at which PCOS was diagnosed in the two cohorts. Only in the second follow-up in CDAH were participants asked to report the age when their PCOS was diagnosed (ages ranged from 14-36 years with only four participants reporting the diagnosis of PCOS before age 18 years). It has been suggested that adolescents with characteristics of PCOS should be reassessed at or before full reproductive maturity, at 8 years post menarche [96] to confirm a diagnosis. In this study, participants reporting a diagnosis of PCOS during adolescence may have been misclassified. Fourth, the diagnostic criteria for PCOS have recently changed [96] and there may have been differences in how PCOS was diagnosed in Australia compared to the USA. Despite all of these limitations, we showed that the prevalence of menstrual irregularity and PCOS in the two cohorts was consistent with the literature [98, 101].

Finally, some characteristics of those continuing in the study differed from those lost to follow-up, and this might limit the generalizability of the findings. In CDAH, non-participants had higher BMI and WHtR values, on average, in childhood than the participants, indicating the current sample may have comprised healthier participants. However, if non-participants were also more likely to have menstrual irregularity and PCOS in adulthood than participants, the effect of this bias would be to underestimate the magnitude of the associations observed. Participants in the BBS were more likely to be black (41% versus 34%) compared with the rest of the study cohort, but childhood BMI was similar among participants and non-participants [208].

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

In conclusion, greater childhood BMI was associated with an increased risk of menstrual irregularity in adulthood in both CDAH and BBS. Greater childhood BMI and WHtR were associated with an increased risk of PCOS in adulthood in CDAH, and in BBS white participants. These risks were significantly higher in women with persistent overweight/obesity since childhood. No significant association of adiposity with PCOS was found in BBS black participants, suggesting there are racial differences in childhood adiposity associating with the development of PCOS, and other environmental or genetic 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.

5.6 Appendix 5 Supplementary material for Chapter 5

Appendix5-1 Associations of childhood obesity with menstrual irregularity in adulthood in the Childhood Determinants of Adult Health Study and the Babies sub-study of the Bogalusa Heart Study[a]

Childhood obesity	CDAH				BBS			
	Unadjusted model (n=1,010)		Model 1 (n=1,010)		Unadjusted model (n=1,238)		Model 1[b] (n=1,238)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.09	0.91-1.31	1.13	0.93-1.36	1.09	0.99-1.20	1.10	0.99-1.21
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	1.45	0.96-2.20	**1.54**	**1.01-2.33**	1.03	0.85-1.26	1.04	0.85-1.27
Obese	**2.14**	**1.28-3.56**	**2.23**	**1.31-3.81**	**1.38**	**1.06-1.81**	**1.38**	**1.05-1.83**

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education.
[a] Use definition of US Centres for Disease Control and Prevention (CDC) growth reference to calculate BMI-z score and to classify childhood weight status of overweight and obesity.
[b] Model 1 further adjust for race in the Babies sub-study of Bogalusa Heart Study (BBS).
CDAH: Childhood Determinants of Adult Health Study, RR: relative risk.

Appendix5-2 Associations of childhood obesity with PCOS in CDAH and BBS[a]

Childhood obesity	CDAH				BBS			
	Unadjusted model (n=1,516)		Model 1 (n=1,516)		Unadjusted model (n=1,247)		Model 1[b] (n=1,247)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.22	0.93-1.60	1.25	0.94-1.65	**1.35**	**1.10-1.66**	**1.49**	**1.21-1.83**
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	1.68	0.91-3.12	1.78	0.96-2.30	**1.49**	**1.04-2.13**	**1.67**	**1.15-2.41**
Obese	**3.51**	**1.58-7.79**	**3.91**	**1.76-8.67**	**2.14**	**1.36-3.38**	**2.57**	**1.60-4.43**

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education.
[a] Use definition of US CDC growth reference to calculated BMI-z score and to classify childhood weight status of overweight and obesity.
[b] Model 1 further adjust for race in BBS.
PCOS, polycystic ovary syndrome

Appendix5-3 Associations of childhood obesity with PCOS in BBS, by race[a]

Race and childhood obesity	n	PCOS			
		Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI
White	730				
BMI z-score		**1.57**	**1.25-1.97**	**1.63**	**1.29-2.06**
BMI category					
Normal		Ref.	—	Ref.	—
Overweight		**1.80**	**1.18-2.75**	**1.91**	**1.22-2.97**
Obese		**3.10**	**1.81-5.29**	**3.27**	**1.86-5.73**
Black	517				
BMI z-score		1.01	0.68-1.49	1.05	0.71-1.57
BMI category					
Normal		Ref.	—	Ref.	—
Overweight		0.99	0.43-2.30	1.07	0.49-2.32
Obese		1.21	0.44-3.35	1.25	0.44-3.57

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education.
[a] Use definition of US CDC growth reference to calculated BMI-z score and to classify childhood weight status of overweight and obesity.

Appendix5-4 Associations of the z-score change from weight-at-birth to BMI-in-childhood in BBS

The z-score change from weight-at-birth to BMI-in-childhood	n	Menstrual irregularity				n	PCOS			
		Unadjusted model		Model 1			Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Overall	780					788				
Δ birth weight-BMI (z-score)		**1.11**	**1.02-1.22**	**1.13**	**1.03-1.25**		**1.26**	**1.03-1.55**	**1.43**	**1.18-1.73**
White race	467					471				
Δ birth weight-BMI (z-score)		**1.15**	**1.02-1.30**	**1.17**	**1.03-1.33**		**1.37**	**1.11-1.68**	**1.46**	**1.18-1.80**
Black race	313					317				
Δ birth weight-BMI (z-score)		1.07	0.93-1.24	1.08	0.94-1.25		1.29	0.82-2.02	1.28	0.85-1.93

Model 1: adjusted for age at menarche, highest parental education and own-education.

Appendix5-5 Associations of adiposity in childhood with menstrual irregularity in adulthood in BBS in women under aged 40 years at follow-up

Childhood adiposity	BBS					
	Unadjusted model (n=431)		*P value*	Model 1[a] (n=431)		*P value*
	RR	95% CI		RR	95% CI	
BMI z-score	1.10	0.96-1.27	*0.166*	1.09	0.94-1.27	*0.237*
BMI category						
Normal	Ref.	—	—	Ref.	—	—
Overweight	1.03	0.70-1.53	*0.873*	1.03	0.70-1.52	*0.874*
Obese	1.51	0.97-2.36	*0.070*	1.50	0.94-2.41	*0.090*
WHtR, per 0.01unit [b]	1.03	1.00-1.06	*0.075*	1.03	0.99-1.06	*0.124*
WHtR category [b]						
<0.5	Ref.	—	—	Ref.	—	—
≥0.5	**1.60**	**1.05-2.43**	*0.028*	1.55	0.99-2.41	*0.055*

Model 1: adjust for childhood age, age at menarche, race, highest parental education and own-education;
[b] n=291;

WHtR, waist/height ratio.

Chapter 6: The associations of childhood adiposity with menopausal symptoms in women aged 45-49 years: an Australian cohort study

The following text in Chapter 6 has been accepted for publication in *Maturitas-An international journal of midlife health and beyond*

6.1 Abstract

Objectives: To examine the associations of childhood adiposity with menopausal symptoms in women aged 45-49 years.

Study design: National population-based cohort study of 334 girls prospectively followed from childhood (aged 11-15) through to midlife (aged 45-49). Childhood overweight and obesity were defined by international age-sex-specific standards for BMI and abdominal obesity was defined as waist/height ratio≥0.5.

Main outcome measures: Vasomotor Symptoms (VMS), vaginal dryness, total menopausal symptoms and domain-specific symptoms (somatic, psychological and urogenital) were measured during 2018-19 using the Menopause Rating Scale (MRS) and classified as none, mild, moderate or severe.

Results: The prevalence of mild, moderate and severe VMS was 24.0%, 9.0% and 3.9% and 12.6%, 4.8% and 2.4% for vaginal dryness. No significant associations of childhood overweight/obesity or abdominal obesity with VMS or vaginal dryness were found after adjustment for childhood age, follow-up length, smoking, socioeconomic status and diet quality. Childhood overweight/obesity was associated with increased risks of more severe total (RR:1.17, 95% CI:1.02-1.36), psychological (RR:1.19, 95% CI:1.04-1.35) and urogenital (RR:1.29, 95% CI:1.14-1.46) symptoms measured using the MRS. Associations with childhood abdominal obesity were mostly stronger with more severe total (RR:2.19, 95% CI:1.48-3.23), somatic (RR:1.52, 95% CI:1.15-2.02), psychological (RR:1.21, 95% CI:1.04-1.42) and urogenital (RR:2.11, 95% CI:1.39-3.20) symptoms.

Conclusions: Childhood adiposity was not associated with increased risks of more severe VMS or vaginal dryness in women aged 45-49 years. Childhood adiposity, especially abdominal obesity, was associated with more severe total, somatic, psychological and

urogenital symptoms. However, the association between these symptoms and menopause is not established.

6.2 Introduction

Menopause is a normal reproductive stage in women. The early menopausal transition is characterized by increased variability in menstrual cycle length and changes in circulating gonadotrophins. This proceeds into the late menopause transition which is characterized by the onset of vasomotor symptoms (hot flushes and night sweats), usually occurring around age 47 years [110]. The reduction in circulating oestradiol during postmenopausal years is commonly associated with genitourinary symptoms including vaginal dryness. The nature and severity of menopausal symptoms varies substantially within women over time, between women and by ethnicity and geographical locations [211]. For example, African American women are most likely, and women of Asian background least likely, to report VMS. There are several standardized scales used to collect data on the nature and severity of menopausal symptoms. The Menopause Rating Scale (MRS) is a self-administered scale designed to (a) assess symptoms/complaints of aging women under different conditions, (b) evaluate the severity of symptoms over time, and (c) measure changes pre- and post- hormone therapy (HT) treatment [116]. The MRS has three independent dimensions: Somatic, psychological and urogenital domains.

Adiposity is a known risk factor for VMS during the menopausal transition and early postmenopause [117]. The mechanisms underlying this association are poorly understood but may include insulation due to greater body fat that prevents heat dissipation with VMS [120]. Adipose tissue is an active endocrine organ and secretes multiple cytokines and inflammatory factors that may be related to VMS occurrence [212] and/or ovarian function [124]. Evidence on the associations between adiposity and vaginal dryness are limited. Several studies have reported no significant association of high body mass index (BMI) in adulthood with vaginal dryness [127, 213]. Symptoms associated with ageing that are not definitively attributable to menopause including joint pain, urinary incontinence, psychological symptoms and other symptoms have

been associated with adiposity in adulthood. However, most of these studies are cross-sectional [127, 214]. Until now, no studies have reported the long-term association of childhood adiposity with menopausal symptoms.

We utilized an Australian population-based cohort followed from childhood through to midlife. We aimed to 1) investigate the associations of childhood adiposity with VMS and vaginal dryness and, 2) examine the associations of childhood adiposity with total menopausal symptoms and domain-specific symptoms as measured by the MRS in women aged 45-49 years.

6.3 Materials and Methods

6.3.1 Participants

The Childhood Determinants of Adult Health (CDAH) Study is a follow-up of a nationwide sample of 8,498 children including 4,191 girls aged 7-15 years who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS) [143]. The study participants were predominantly white with race inferred from the childhood questionnaire on father's and mother's country of birth and language spoken at home. Between 2018-19, 1,153 women aged 39-49 years participated in the third follow-up of the study (CDAH-3). Because the normal menopause transition characteristically starts in the mid-to-late 40s [215], only participants age 45 and above were included. Therefore, we restricted our sample to 441 women aged ≥45 years (herein referred to "midlife"), 318 of whom attended clinics for physical measurements. We further excluded those who did not complete the MRS (n=30), had previous hysterectomy (n=35), were pregnant (n=2), had missing data on anthropometrics (n=4) or missing data on confounders (n=36). A total of 334 women were included in the final analysis (Figure 6.1) (313 white, 1 black, 14 other race and 6 had no information). A subsample of 247 women with measured waist circumference in ASHFS and CDAH-3 clinics were included in the analyses to measure abdominal adiposity.

The study was approved by the Human Research Ethics Committee (Tasmania) Network. Written informed consent was obtained in childhood from parents and obtained at follow-up from participants.

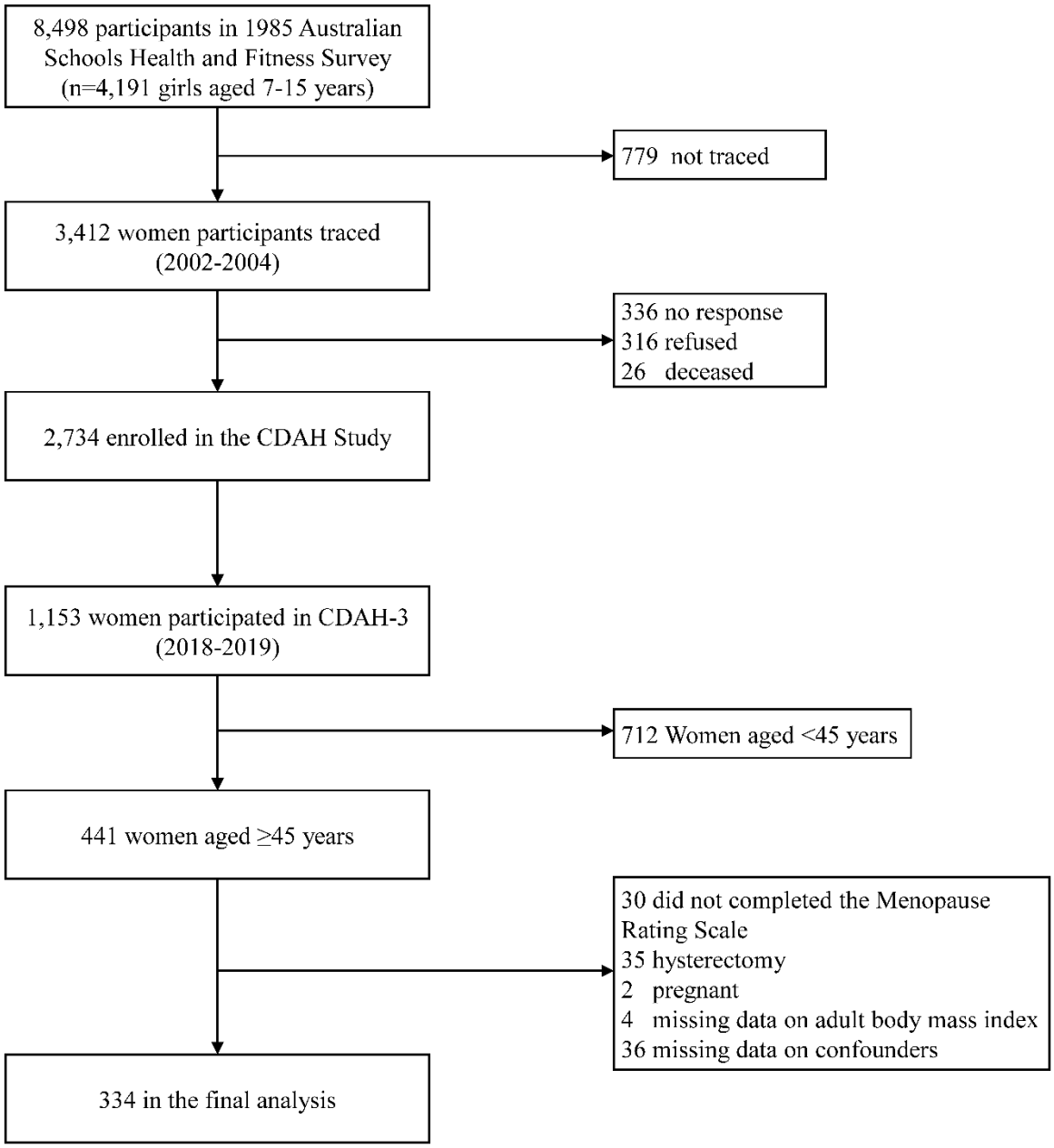


Figure 6.1 Selection of participants for the Childhood Determinants of Adult Health (CDAH) Study

6.3.2 Childhood adiposity

Measures of childhood adiposity included BMI, waist circumference and waist/height ratio (WHtR). Waist circumference and WHtR were the indicators of abdominal obesity. BMI, calculated as weight (kg)/height $(m)^2$, was derived from measured height and weight with weight status defined using international age-and sex-specific cut-points [8]. Waist circumference was measured to the nearest 0.1 cm. WHtR was calculated by dividing waist circumference by height. Abdominal obesity was defined as WHtR≥0.5 [133]. Childhood BMI and waist circumference z-scores were calculated based on age- and sex-specific standardization of the full childhood cohort.

6.3.3 Adult adiposity

At CDAH-3, weight, height and waist circumference were measured at study clinics for most participants (n=832). Some participants (n=790) also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. Participants who did not visit clinics (n=291) self-reported their weight and height, and a linear regression model was used to obtain a correction factor to adjust for error of self-reported BMI. BMI (kg/m^2) was calculated from height and weight. WHtR was calculated from measured waist circumference and height at clinics.

Adult BMI was classified into three categories as normal (BMI<25 kg/m^2), overweight (25.0≤BMI≤29.9 kg/m^2) or obese (BMI≥30 kg/m^2). Adult abdominal obesity was defined as WHtR≥0.5 [13].

6.3.4 Symptoms measured by the MRS

Menopausal symptoms were measured using the MRS. This scale contains 11 questions relating to three domains of symptoms: Somatic (hot flushes and sweating, heart discomfort,

sleep problems, and muscle and joint pains), psychological (depression, irritability, anxiety, and physical and mental exhaustion), and urogenital symptoms (sexual problems, bladder problems and vaginal dryness). Each question is assigned a score for symptom intensity: 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe). VMS and vaginal dryness were evaluated from the corresponding single questions. Because very few participants reported "very severe VMS" (n=1) or "very severe vaginal dryness" (n=1), these measures were combined with "severe" symptoms.

Scores on total, somatic, psychological and urogenital symptom domains are categorized as no or little, mild, moderate and severe according to their corresponding cut points [116].

6.3.5 Covariate measures

Information on sociodemographic characteristics and other relevant covariates was self-reported in childhood and at follow-up including childhood age, parental education, parental smoking, childhood smoking, age at menarche; alcohol consumption, physical activity and diet quality in both childhood and midlife. Duration of follow-up from childhood to midlife, level of completed education, smoking status, marital status, occupation, hormonal contraceptive use and parity in midlife were collected. Diet quality was indicated by a dietary guidelines index (DGI) which was derived as a valid measure of diet quality according to 2013 Australian Dietary Guidelines, with higher scores reflecting better diet quality [216].

6.3.6 Statistical analyses

The log ordinal regression model, which estimated relative risks (RRs) and 95% confidence intervals (CIs) [217] was used to estimate the association of adiposity with the severity of VMS, vaginal dryness, total, somatic, psychological, urogenital symptoms.

Covariates remaining in the final models were variables that were associated with the outcome, unbalanced between the exposures and resulted in more than 10% change in the coefficient of the principal study factor when added to the model.

The following sensitivity analyses were conducted. First, hormonal contraceptive use might affect menopausal symptoms, so we repeated the analyses of the associations of childhood adiposity with VMS and vaginal dryness in midlife women who were not using hormonal contraception. Second, as underweight may also be associated with increased risk of menopausal symptoms [218] (potentially due to lower circulating estrogens from adipose tissue) and earlier age at menopause, we excluded those who were underweight in childhood (according to international definitions of thinness for children and adolescents [219] and adulthood (BMI<18.5) in the analyses of VMS and vaginal dryness. Third, to examine whether the associations of childhood abdominal obesity were independent of corresponding adult abdominal obesity measures, childhood abdominal obesity measures were further adjusted for abdominal obesity measures in midlife in a subsample (n=247). Fourth, given overweight and obesity may have different associations with age at menopause, analyses of childhood BMI category with menopausal symptoms were separated by childhood overweight and childhood obesity. Fifth, inverse probability weighting was used to account for missing data at follow-up.

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

6.4 Results

6.4.1 Participant characteristics

Table 6.1 shows the sociodemographic characteristics of participants and their adiposity measures in childhood and midlife. In childhood, 8.4% of participants were overweight/obese,

and 5.1% of participants were abdominally obese. The mean age at follow-up was 46.9 years. Most participants (63.2%) did not report VMS. Around one quarter (24.0%) reported mild VMS, 9.0% reported moderate VMS and 3.9% reported severe VMS. Most (80.2%) did not report vaginal dryness: 12.6% reported mild vaginal dryness, 4.8% reported moderate vaginal dryness and 2.4% reported severe vaginal dryness.

Using baseline (1985 ASHFS) characteristics, compared with all other non-participants, those who participated in the follow-up study had an older mean age in childhood(13.5 vs 10.6 years; $P<0.001$), had lower WHtR (0.42 vs 0.43; $P<0.001$) and were less likely to be overweight/obese in childhood (8.4% vs 12.7%; $P=0.022$).

Table 6.1 Characteristics of participants in childhood (1985) and midlife (2018-2019), Childhood Determinants of Adult Health study, Australia[a]

Characteristics (n=334)	**Childhood**	**Midlife**
Age (years), Mean (SD)	13.5 (1.2)	46.9 (1.1)
BMI z score, Mean (SD)	-0.07 (1.00)	
BMI (kg/m^2), Mean (SD)	19.8 (2.9)	27.8 (6.1)
BMI category, % (n)		
Normal	91.6 (306)	38.0 (127)
Overweight	6.6 (22)	32.9 (110)
Obese	1.8 (6)	29.0 (97)
WC z score, Mean (SD)	-0.06 (1.03)	
WC (cm), Mean (SD)	67.0 (7.7)	85.3 (13.1)
WHtR, Mean (SD)	0.42 (0.04)	0.52 (0.08)
WHtR category, % (n)		
<0.5	94.9 (317)	47.4 (117)
≥0.5	5.1 (17)	52.6 (130)
Age at menarche (years), Mean (SD)	13.2 (1.2)	
Highest own-education attainment, % (n)		
University education		53.3 (178)
Vocational training		31.1 (104)
High school		15.6 (52)
Smoking status, % (n)		
Never smoker		57.5 (192)
Ex-smoker		31.1 (104)
Current smoker		11.4 (38)
Occupation, % (n)		
Professional or manager		52.1 (174)
Nonmanual		29.6 (99)
Manual		5.7 (19)
Not in the labour force		12.6 (42)
Current hormonal contraceptive users, %(n)		
No		72.1 (238)

Yes	27.9 (92)
Diet guidelines index, Mean (SD)	58.2 (11.2)
Menopause rating scale	
Total score (0-44), %(n)	
No, little (0-4)	39.2 (131)
Mild (5-8)	27.5 (92)
Moderate (9-16)	26.7 (89)
Severe (17+)	6.6 (22)
Somatic domain (0-16), % (n)	
No, little (0-1)	54.2 (181)
Mild (2-3)	28.1 (94)
Moderate (4-6)	15.9 (53)
Severe (7+)	1.8 (6)
Psychological domain (0-16), % (n)	
No, little (0-2)	37.1 (124)
Mild (3-4)	30.2 (101)
Moderate (5-8)	20.4 (68)
Severe (9+)	12.3 (41)
Urogenital domain (0-12), % (n)	
No, little (0)	42.2 (141)
Mild (1)	20.7 (69)
Moderate (2-3)	22.8 (76)
Severe (4+)	14.3 (48)
Severity of vasomotor symptoms, % (n)	
None	63.2 (211)
Mild	24.0 (80)
Moderate	9.0 (30)
Severe/very severe	3.9 (13)
Severity of vaginal dryness, % (n)	
None	80.2 (268)
Mild	12.6 (42)
Moderate	4.8 (16)
Severe/very severe	2.4 (8)

[a] Sample size ranges from 330-332 due to missing data on some variables;
Abbreviations: BMI, body mass index; SD, standard deviation; WC, waist circumference; WHtR, waist/height ratio.

6.4.2 Vasomotor symptoms and vaginal dryness

In childhood, no significant associations of any childhood adiposity measures with the severity of VMS and vaginal dryness were observed (Table 6.2 Model 1) after adjustment for childhood age, follow-up length, smoking status, occupation, highest own-education, and DGI in midlife.

Table 6.2 Associations of childhood adiposity with vasomotor symptoms and vaginal dryness measured by the MRS in midlife

Childhood adiposity	n (%)	Vasomotor symptoms		Vaginal dryness	
		Unadjusted model	Model 1	Unadjusted model	Model 1
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI z score	334	1.05 (0.97-1.14)	1.03 (0.95-1.11)	1.00 (0.87-1.14)	1.00 (0.87-1.15)
BMI category					
Normal	306 (91.6)	Ref.	Ref.	Ref.	Ref.
Overweight/obese	28 (8.4)	1.09 (0.82-1.45)	1.02 (0.77-1.35)	1.08 (0.69-1.70)	1.09 (0.68-1.74)
WC z score	334	1.08 (1.00-1.17)	1.04 (0.96-1.12)	1.04 (0.92-1.18)	1.04 (0.92-1.18)
WHtR, per SD (0.04)	334	1.06 (0.98-1.13)	1.03 (0.95-1.11)	1.05 (0.93-1.19)	1.05 (0.93-1.19)
WHtR category					
<0.5	317 (94.9)	Ref.	Ref.	Ref.	Ref.
≥0.5	17 (5.1)	**1.34 (1.03-1.75)**	1.20 (0.88-1.62)	1.47 (0.98-2.21)	1.53 (0.96-2.44)

Model1: adjusted for childhood age, follow-up length from childhood to midlife, smoking status, occupation, highest own-education and dietary guidelines index in midlife;

Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk; SD, standard deviation; WHtR, waist/height ratio; WC, waist circumference.

6.4.3 Total symptoms and domain-specific symptoms measured by the MRS

Table 6.3 presents the associations of childhood adiposity with total symptoms and domain-specific symptoms measured by the MRS. Higher childhood BMI z-score and childhood overweight and obesity were positively associated with more severe total, psychological and urogenital symptoms after adjustment for confounders (Table 6.3 Model 1). Higher childhood waist circumference z-score, WHtR and childhood abdominal obesity were associated with increased risks of more severe total symptoms in all three domains (Table 6.3 Model 1). When examining each individual urogenital symptom (urinary symptoms, sexual problems and vaginal dryness), significant associations with childhood adiposity were only present for urinary symptoms (data not shown). To determine whether the above associations were independent of adult BMI, we further adjusted for BMI in midlife (Table 6.3 Model 2). Here, the associations with higher childhood BMI z-score remained significant for psychological and urogenital symptoms, and the associations with childhood overweight and obesity remained significant for urogenital symptoms. The above associations with abdominal obesity measures

all persisted after adjustment for BMI in midlife except for the association of childhood abdominal obesity with psychological symptoms.

Table 6.3 Associations of childhood adiposity with total menopausal symptoms and domain-specific symptoms measured by the MRS in midlife

Childhood adiposity		Total score			Somatic			Psychological			Urogenital		
	n (%)	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI z score	334	**1.06 (1.01-1.17)**	**1.08 (1.03-1.14)**	1.06 (0.99-1.13)	1.06 (0.99-1.13)	1.06 (0.99-1.14)	1.01 (0.92-1.10)	**1.07 (1.03-1.10)**	**1.08 (1.03-1.12)**	**1.08 (1.02-1.14)**	**1.08 (1.03-1.13)**	**1.07 (1.02-1.13)**	**1.11 (1.04-1.19)**
BMI category													
Normal	306 (91.6)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight/obese	28 (8.4)	1.13 (0.99-1.30)	**1.17 (1.02-1.36)**	1.07 (0.89-1.28)	1.19 (0.95-1.49)	1.18 (0.95-1.48)	1.02 (0.79-1.30)	**1.17 (1.04-1.31)**	**1.19 (1.04-1.35)**	1.13 (0.96-1.33)	**1.22 (1.11-1.35)**	**1.29 (1.14-1.46)**	**1.48 (1.23-1.78)**
WC z score	334	**1.09 (1.03-1.15)**	**1.11 (1.04-1.17)**	**1.09 (1.02-1.16)**	**1.08 (1.02-1.13)**	**1.11 (1.04-1.17)**	1.06 (0.98-1.15)	**1.07 (1.03-1.11)**	**1.08 (1.03-1.13)**	**1.08 (1.03-1.14)**	**1.08 (1.03-1.13)**	**1.09 (1.03-1.15)**	**1.10 (1.04-1.16)**
WHtR, per SD (0.04)	334	**1.08 (1.03-1.14)**	**1.10 (1.04-1.17)**	**1.08 (1.02-1.15)**	**1.07 (1.03-1.12)**	**1.10 (1.04-1.16)**	1.06 (0.99-1.13)	**1.06 (1.02-1.09)**	**1.07 (1.03-1.12)**	**1.06 (1.01-1.12)**	**1.09 (1.05-1.13)**	**1.10 (1.05-1.16)**	**1.12 (1.06-1.18)**
WHtR category													
<0.5	317 (94.9)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥0.5	17 (5.1)	**1.32 (1.21-1.43)**	**2.19 (1.48-3.23)**	**2.11 (1.41-3.14)**	**1.44 (1.18-1.75)**	**1.52 (1.15-2.02)**	1.34 (1.00-1.79)	**1.18 (1.03-1.34)**	**1.21 (1.04-1.42)**	1.16 (0.98-1.39)	**1.31 (1.21-1.41)**	**2.11 (1.39-3.20)**	**2.22 (1.45-3.40)**

Model1: adjusted for childhood age, follow-up length, smoking status, occupation, highest own-education and dietary guidelines index in midlife;
Model2: Model1 + body mass index in midlife;
Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk; SD, standard deviation; WHtR, waist/height ratio; WC, waist circumference.

6.4.4 Adiposity from childhood to midlife

The relative risks of more severe VMS and vaginal dryness by adiposity status from childhood to midlife are displayed in Table 6.4 No significant associations of BMI categories from childhood to midlife with VMS and vaginal dryness were found. In the subsample of participants who had WHtR data in both childhood and midlife, compared with those who were not abdominally obese in both childhood and midlife, those with persistent abdominal obesity (n=8) had significantly higher risks of more severe VMS and vaginal dryness (Table 6.4 Model 1).

For total symptoms and the three domain-specific symptoms, compared with women with persistently normal BMI since childhood, those who were persistently overweight/obese had significantly higher risks of more severe total and somatic, psychosocial and urogenital symptoms after adjustment for confounders (Table 6.5 Model 1). In the subsample of participants who had WHtR data in both childhood and midlife, those who were abdominally obese in midlife but not in childhood had significantly higher risks of more severe total and somatic symptoms (Table 6.5 Model 1). Those who were persistently abdominally obese since childhood had the highest risks of more severe total symptoms and all the domain-specific symptoms (Table 6.5 Model 1).

6.4.5 Sensitivity analysis

Similar associations of childhood adiposity with VMS and vaginal dryness were observed after excluding 92 women who were using hormonal contraception at midlife (n=242) (data not shown). In the subsample of participants with adult abdominal obesity measures (n=247) (Appendix6-1), the associations of childhood abdominal obesity with more severe total symptoms and domain-specific symptoms persisted after further adjustment for corresponding abdominal obesity measures in midlife. The observed associations of adiposity with VMS and

vaginal dryness did not change after excluding those who were underweight in childhood (n=5) and in midlife (n=2) (data not shown). When analyses were performed by separating childhood overweight (n=22) and obesity (n=6), no association was found with VMS and vaginal dryness (Appendix6-2). Childhood obesity was associated with increased risks of urogenital symptoms and total score independent of BMI in midlife (Appendix6-3). Reanalysis of the data with inverse probability weighting produced results consistent with unweighted analyses, with the direction of the associations remaining the same and the changes in β coefficient of significant associations ranging from -3.5% to 81.6%.

Table 6.4 Associations of adiposity status from childhood to midlife with vasomotor symptoms and vaginal dryness measured by the MRS

Adiposity status from childhood to midlife	n (%)	Vasomotor symptoms		Vaginal dryness	
		Unadjusted model	Model 1	Unadjusted model	Model 1
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI category					
Persistently normal	126 (37.8)	Ref.	Ref.	Ref.	Ref.
Normal to overweight/obese	180 (54.1)	1.14 (0.93-1.40)	1.05 (0.85-1.29)	1.09 (0.81-1.46)	1.05 (0.78-1.40)
Persistently overweight/obese	27 (8.1)	1.21 (0.88-1.65)	1.13 (0.82-1.55)	1.16 (0.71-1.89)	1.17 (0.72-1.92)
WHtR category					
Persistently not abdominally obese	116 (47.2)	Ref.	Ref.	Ref.	Ref.
Not abdominally obese to abdominally obese	122 (49.6)	1.24 (0.95-1.63)	1.08 (0.81-1.44)	1.33 (0.90-1.95)	1.19 (0.80-1.76)
Persistently abdominally obese	8 (3.3)	**1.89 (1.30-2.75)**	**2.36 (1.42-3.93)**	**2.31 (1.34-3.99)**	**2.34 (1.13-4.84)**

Model1: adjusted for smoking status, occupation, highest own-education and dietary guidelines index in midlife;
Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk; WHtR, waist/height ratio.

Table 6.5 Associations of adiposity status from childhood to midlife with total menopausal symptoms and domain-specific symptoms measured by the MRS

Adiposity status from childhood to midlife	n (%)	Total score		Somatic		Psychological		Urogenital	
		Unadjusted model	Model 1	Unadjusted model	Model 1	Unadjusted model	Model 1	Unadjusted model	Model 1
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI category									
Persistently normal	126 (37.8)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Normal to overweight/obese	180 (54.1)	**1.15 (1.02-1.29)**	1.12 (0.99-1.26)	**1.28 (1.06-1.55)**	1.19 (0.98-1.45)	**1.12 (1.00-1.25)**	1.08 (0.96-1.21)	1.07 (0.96-1.19)	1.06 (0.95-1.18)
Persistently overweight/obese	27 (8.1)	**1.22 (1.03-1.44)**	**1.22 (1.04-1.44)**	**1.36 (1.03-1.80)**	**1.34 (1.02-1.75)**	**1.25 (1.09-1.44)**	**1.20 (1.04-1.40)**	**1.27 (1.12-1.44)**	**1.34 (1.16-1.53)**
WHtR category									
Persistently not abdominally obese	116 (47.2)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Not abdominally obese to abdominally obese	122 (49.6)	**1.34 (1.12-1.61)**	**1.39 (1.14-1.69)**	**1.64 (1.25-2.15)**	**1.57 (1.19-2.05)**	**1.18 (1.04-1.33)**	1.13 (0.99-1.30)	**1.20 (1.01-1.42)**	1.12 (0.95-1.32)
Persistently abdominally obese	8 (3.3)	**2.42 (1.88-3.11)**	**9.40 (4.92-17.94)**	**3.16 (1.96-5.09)**	**3.03 (1.92-4.80)**	**1.35 (1.13-1.60)**	**1.32 (1.06-1.64)**	**1.76 (1.42-2.17)**	**3.23 (2.13-4.91)**

Model1: adjusted for smoking status, occupation, highest own-education and dietary guidelines index in midlife;

Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk; WHtR, waist/height ratio.

6.5 Discussion

This study is the first to report the associations of childhood adiposity with menopausal symptoms in midlife women aged 45-49 years. We found no association between childhood adiposity and VMS or vaginal dryness. However, childhood adiposity was associated with more severe "other" menopausal symptoms as measured by the MRS. Childhood overweight/obesity was associated with more severe psychological and urogenital symptoms and total score, with the associations with urogenital symptoms persisting after adjustment for adult BMI. Childhood abdominal obesity measures, including waist circumference and WHtR, were positively associated with more severe somatic, psychological and urogenital symptoms and total score, with the associations with psychological and urogenital symptoms and total score persisting after adjustment for adult BMI. Women with persistently high adiposity since childhood had the highest risks of somatic, psychological and urogenital symptoms and total score.

There is a lack of consensus about precisely which symptoms are attributable to menopause. The 2005 National Institutes of Health (NIH) State of the Science report concluded that VMS, vaginal dryness and possibly sleep disturbance were attributable to menopause [220]. Subsequently, cross-sectional and prospective studies have reported changes in psychological, sexual, and urogenital symptoms in addition to changes in metabolic, cardiovascular and musculoskeletal function [221]. However, it is uncertain whether these are due to ageing or the endocrine changes at menopause.

Although widely used, the MRS includes measures which are poorly defined, such as "heart discomfort" and "bladder problems" and symptoms such as irritability and anxiety that are not consistently associated with menopause. The association between childhood adiposity and total

MRS score in the current study was largely accounted for by symptoms in these nonspecific domains.

Multiple cross-sectional and longitudinal studies have reported positive associations of adult adiposity with VMS in midlife [118] but others have not [222, 223]. The inconsistency of these study results may reflect various factors, including differences in participants' race/ethnicity, sample size, menopausal status, the measurement of VMS, and other environmental factors. In our study, no association of childhood adiposity with VMS and vaginal dryness was found. It is possible that most women were in their pre-menopause or in the early menopause transition with a low prevalence of VMS and vaginal dryness. Since overweight and obesity have been associated with later age at natural menopause and later inception of menopause transition, this might dilute the associations observed.

The long-term associations of childhood adiposity, especially abdominal obesity, with psychological and urinary symptoms remain understudied. Psychological symptoms including depression and anxiety are twice as common in women than men with a prevalence of 25-50% at midlife [224]. Our team have previously reported that childhood overweight and obesity are associated with an increased risk of mood disorder in women aged 26-36 years, but this association was largely explained by overweight/obesity in adulthood [44]. Urinary incontinence affects 30-40% of women at midlife and almost 50% of older women [225]. Epidemiological studies have shown that adult obesity is a major modifiable risk factor for urinary incontinence at midlife [226]. Our findings that childhood adiposity was associated with psychological symptoms and "urinary problems" in midlife independently of adult BMI are novel and suggest that early prevention of childhood adiposity may modify or help prevent these conditions. The explanation for why all adiposity measures were associated with urogenital symptoms but mainly abdominal obesity measures were associated with psychological symptoms and total score, independent of adult BMI, are unclear. High BMI is an established risk factor for urinary

incontinence, which may explain the association with urogenital symptoms. The associations between psychological symptoms and menopause are uncertain and vary considerably between women, so the observed association with psychological symptoms may have been spurious.

Those at greatest risk for high total MRS scores and the three domain-specific symptoms were women with persistently high adiposity since childhood. This may reflect the cumulative burden of high adiposity over the life-course or a greater severity of excess adiposity. However, the associations with VMS and vaginal dryness in women with persistent abdominal obesity should be interpreted with caution as there were only 8 participants in this group and the finding therefore needs to be confirmed in larger studies.

We acknowledge the limitations of our study. Reproductive stage was not defined according to Stages of Reproductive Aging Workshop (STRAW) criteria. Our finding that most women did not report VMS or vaginal dryness suggests that they were either pre-menopausal or in the early menopause transition. In addition, because the MRS includes symptoms that may not be attributable to menopause, we cannot be certain that our findings reflect a true association between childhood adiposity and menopausal symptoms. In reproductive age women, higher MRS scores may reflect the known adverse consequences of adiposity rather than menopause. However, in our study, we have separately analyzed the associations with VMS and vaginal dryness that are consistently associated with menopause, though they are not specific to menopause and are commonly reported by premenopausal women as well [227, 228]. A further limitation was the loss to follow-up. We applied inverse probability weighting to account for missingness, and this did not appreciably change our results. Third, the prevalence of high adiposity in our cohort was substantially less than that reported in more contemporary children. The low prevalence of high adiposity in childhood and relatively small sample size may account for the lack of statistically significant associations. Furthermore, whether the associations between childhood adiposity and menopausal symptoms persist when high

adiposity resolves between childhood and midlife is unclear because too few participants (n=1) demonstrated this trajectory. Larger prospective studies including greater numbers of children with high adiposity followed up through the menopause transition are needed to confirm our findings and help better understand whether childhood adiposity, adult adiposity, or both contribute to different types and severities of menopausal symptoms. Finally, this study is an Australian cohort comprised of mainly white women. Whether these findings extend to other geographical regions and races is unknown.

The strengths of our study include that it is the first prospective study to investigate the long-term associations between various childhood adiposity measures and menopausal symptoms using a validated instrument. Second, a wide range of potential confounders was considered in our study.

6.6 Conclusion

Childhood adiposity was not associated with significantly increased risks of vasomotor symptoms or vaginal dryness at midlife in women aged 45-49 years; symptoms that are consistently associated with menopause. Associations of childhood adiposity, especially childhood abdominal obesity, with more severe somatic, psychological and urogenital symptoms were observed and the associations for psychological and urogenital symptoms were independent of adult BMI. However, the association between these symptoms and menopause is not established and needs to be clarified in future studies.

6.7 Appendix 6 Supplementary material for Chapter 6

Appendix6-1 Associations of childhood abdominal obesity measures with total menopausal symptoms and domain-specific symptoms measured by the MRS in midlife

Childhood abdominal obesity measures	n (%)	Total score			Somatic			Psychological			Urogenital		
		Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
WC z score	247	**1.09 (1.01-1.16)**	**1.13 (1.04-1.22)**	**1.10 (1.01-1.21)**	**1.21 (1.09-1.35)**	**1.29 (1.15-1.45)**	**1.23 (1.07-1.41)**	**1.09 (1.03-1.15)**	**1.10 (1.03-1.17)**	**1.11 (1.02-1.21)**	**1.07 (1.01-1.14)**	**1.11 (1.03-1.19)**	**1.25 (1.13-1.39)**
WHtR, per SD (0.04)	247	**1.10 (1.02-1.18)**	**1.12 (1.03-1.23)**	**1.10 (1.00-1.21)**	**1.28 (1.14-1.43)**	**1.35 (1.19-1.56)**	**1.28 (1.11-1.48)**	**1.07 (1.02-1.13)**	**1.07 (1.01-1.14)**	**1.08 (1.00-1.15)**	**1.11 (1.04-1.18)**	**1.13 (1.05-1.22)**	**1.13 (1.04-1.22)**
WHtR category													
<0.5	238 (96.4)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
≥0.5	9 (3.6)	**2.07 (1.67-2.58)**	**3.13 (2.09-4.70)**	**2.83 (1.82-4.40)**	**2.18 (1.40-3.41)**	**2.09 (1.31-3.33)**	**1.99 (1.28-3.10)**	**1.24 (1.08-1.42)**	**1.21 (1.01-1.46)**	1.18 (0.98-1.42)	**1.58 (1.33-1.88)**	**2.50 (1.84-3.40)**	**3.71 (2.34-5.89)**

Model1: adjusted for childhood age, follow-up length, smoking status, occupation, highest own-education and dietary guidelines index in midlife;
Model2: Model1 + corresponding abdominal obesity measures in midlife;
Abbreviation: CI, confidence interval; MRS, menopause rating scale; RR, relative risk; SD, standard deviation; WHtR, waist/height ratio; WC, waist circumference.

Appendix6-2 Associations of childhood weight status with vasomotor symptoms and vaginal dryness measured by the MRS in midlife.

Childhood weight status	n (%)	Vasomotor symptoms		Vaginal dryness	
		Unadjusted model	Model 1	Unadjusted model	Model 1
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI category					
Normal	306 (91.6)	Ref.	Ref.	Ref.	Ref.
Overweight	22 (6.6)	1.05 (0.75-1.46)	1.02 (0.73-1.42)	1.06 (0.64-1.77)	1.09 (0.64-1.84)
Obese	6 (1.8)	1.26 (0.79-2.02)	1.02 (0.62-1.67)	1.15 (0.47-2.85)	1.08 (0.62-2.73)

Model1: adjusted for childhood age, follow-up length, smoking status, occupation, highest own-education and dietary guidelines index in midlife;

Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk.

Appendix6-3 Associations of childhood weight status with total menopausal symptoms and domain-specific symptoms measured by the MRS in midlife.

Childhood weight status	n (%)	Total score			Somatic			Psychological			Urogenital		
		Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2	Unadjusted model	Model 1	Model 2
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
BMI category													
Normal	306 (91.6)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Overweight	22 (6.6)	1.12 (0.88-1.42)	1.17 (0.91-1.51)	1.03 (0.77-1.37)	1.14 (0.87-1.49)	1.12 (0.85-1.47)	0.97 (0.72-1.30)	1.14 (0.90-1.44)	1.14 (0.89-1.47)	1.03 (0.79-1.34)	**1.24 (1.03-1.50)**	**1.40 (1.13-1.75)**	**1.64 (1.26-2.14)**
Obese	6 (1.8)	1.71 (1.33-2.19)	**2.06 (1.40-3.05)**	**2.12 (1.30-3.44)**	1.35 (0.97-1.89)	1.41 (0.96-2.06)	1.17 (0.78-1.74)	**1.46 (1.00-2.13)**	1.20 (0.76-1.91)	1.19 (0.75-1.88)	**1.39 (1.02-1.87)**	1.37 (0.96-1.96)	**1.65 (1.01-2.69)**

Model1: adjusted for childhood age, follow-up length, smoking status, occupation, highest own-education and dietary guidelines index in midlife;

Model2: Model1 + body mass index in midlife;

Abbreviation: BMI, body mass index; CI, confidence interval; MRS, menopause rating scale; RR, relative risk.

Chapter 7: Summary and future directions

7.1 Preamble

Over the past three decades, the worldwide prevalence of childhood obesity has increased dramatically, and its related health burden has been of great concern, particularly the long-term health consequences. Although a large number of investigations has helped to fill a growing list of the potential long-term risks from childhood adiposity, women's reproductive health remains understudied and poorly understood. By using original data from two population-based cohorts, CDAH and BBS, I aimed in this thesis to contribute to current knowledge in this area by investigating the associations of childhood adiposity with infertility, pregnancy hypertension, menstrual irregularity, PCOS and menopausal symptoms in adulthood. By addressing these questions, the long-term consequences of childhood adiposity for women's reproductive health will be better understood. The present work may, therefore, be helpful in making the case for greater emphasis on timely prevention and interventions of childhood adiposity that will benefit the health of the current and future generations including their reproductive health.

The following sections provide a summary of the principal findings of this thesis, their public health implications and an overview of future research directions.

7.2 Summary of findings and public health implications

7.2.1 Childhood obesity before age 12 was associated with an increased risk of infertility

The negative impact of adult adiposity on fertility has been primarily thought to be due to functional alteration of the HPO axis resulting in irregular menstrual cycles and anovulation,

leading to infertility [70, 229]. As childhood and adolescence are the important periods for HPO axis development [230], adiposity during this critical window could have a persistent association with reproductive capacity. In Chapter 3, we showed a U-shaped association of childhood BMI z-score before 12 years of age with infertility and identified an increased risk of later infertility among women with obesity as defined by BMI before 12 years. Our findings of the associations of child obesity with infertility were only observed in the younger age group of 7-11 years but not in 12-15 years age group and were supported by earlier findings from the Bogalusa Heart Study that had similar results [78]. This suggests a differential risk of infertility based on exposure to adiposity during various time periods of growth and the pre-pubertal time window may be a sensitive period where the effects of excess body weight on infertility are more significant and profound than post-pubertal stages. Measures of abdominal adiposity (WC, WHtR and waist-to-hip ratio) in our study were not found to be associated with infertility.

Infertility can be a devastating condition for couples who want to have children, especially for women who have a limited time window for childbearing. Impaired human fertility may arise from many conditions caused by genetic disorders, delayed childbearing, infectious or environmental factors, behaviours and certain diseases [231]. Awareness of the potential risks may lead some people to adopt corrective behaviours and protect fertility. Our study provides evidence of the association of early childhood obesity with infertility making it a potentially modifiable risk factor for infertility and providing further incentives for the early prevention of childhood obesity.

7.2.2 Childhood adiposity was associated with an increased risk of pregnancy hypertension

Although the important role of childhood abdominal obesity in cardiometabolic diseases has been recognised in many previous studies [13, 90, 167], no study has yet reported the association of

childhood abdominal obesity with pregnancy hypertension. In Chapter 4, I extended the findings of two previous longitudinal studies in childhood which examined childhood BMI [77, 91]. Our study explored the associations of different childhood adiposity measures including abdominal obesity with pregnancy hypertension and further determined whether these associations were independent of adult adiposity. It revealed that childhood adiposity was associated with an increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult abdominal obesity.

The results of our study suggest that higher childhood BMI has adverse consequences for pregnancy hypertension, but largely mediated through its association with adult BMI. This is consistent with previous systematic reviews [232, 233] and meta-analysis [234] showing that the associations of childhood BMI with adult cardiovascular diseases were not independent of adult BMI. As adiposity tracks between childhood and adulthood [25], targeting childhood for prevention and treatment of adiposity could have lasting benefits. Furthermore, the independent contribution of childhood abdominal obesity to pregnancy hypertension in our study highlighted that childhood WHtR has the potential to be used as an indicator to identify those at increased risk of future cardiometabolic conditions including pregnancy hypertension.

7.2.3 Childhood adiposity was positively associated with a higher risk of menstrual irregularity in both white and black women, however a higher risk of PCOS was only present in white women

Adult adiposity has long been considered as a risk factor for menstrual irregularity. The association with adiposity, however, remains unclear for PCOS, although PCOS is strongly related to menstrual irregularity. Both environmental and genetic factors have been suggested to influence the development of PCOS [105]. For both disorders, their long-term associations with childhood adiposity remain understudied. By using two cohorts from Australia (CDAH) and

USA (BBS) with different populations and races, Chapter 5 showed childhood adiposity as measured by BMI and WHtR was associated increased risk of menstrual irregularity and PCOS in adulthood, whereas there were racial difference in the associations of adiposity with PCOS, with the association for PCOS only present in white but not in black participants.

Collectively, these findings suggest long-term implications of childhood adiposity on menstrual irregularity in adulthood that are present consistently in different populations and races. The potential biological plausibility includes a series of hormonal factors (increased concentrations of testosterone, LH, insulin, and reduced concentrations of SHBG) caused by childhood adiposity [141]. In addition, increased adipokines produced in adipose tissue can directly inhibit ovarian function [235]. However, the finding of the racial differences in childhood adiposity associating with PCOS highlights that PCOS is a complex trait with contributions from both heritable and nonheritable factors. Though childhood adiposity is not expected to be a single cause of PCOS, it is a risk factor for promoting the development of PCOS in white women. This study has also called for more future investigations into reproductive health across varied races and populations to enhance understanding of reproductive health across diverse societies.

7.2.4 Childhood adiposity was not associated with VMS and vaginal dryness but was associated with other symptoms that are not clearly attributable to menopause at 45-49 years

Whether childhood adiposity is associated with menopausal symptoms in women's midlife is unknown in the current literature. In Chapter 6, menopausal symptoms were measured by the MRS in women aged 45-49 years. We found that childhood adiposity was not associated with VMS and vaginal dryness, symptoms that are consistently associated with menopause, in women aged 45-49 years. However, childhood adiposity, especially abdominal obesity, was

associated with total menopausal symptoms and three domain-specific symptoms (somatic, psychological and urogenital) in midlife that are not clearly attributable to menopause. The associations with psychological and urinary symptoms in particular were independent of adult BMI.

Taken together, our findings suggest childhood adiposity was more likely to be associated with 'other' menopausal symptoms in women aged 45-49 years rather than VMS and vaginal dryness which are most consistently associated with menopause. Therefore, the prevention of childhood adiposity may help reduce the severity of total menopausal symptoms, especially psychological and urinary symptoms during the early stage of menopause transition. However, it is important to note that at this stage, we are not sure whether these 'other' symptoms are attributable to menopause or may be secondary to childhood adiposity in this age group of women. More than one third and less than 20% of women reported having VMS and vaginal dryness in our study suggesting most of the women were in their pre-menopause and early menopause transition. As women proceed into late stages of the menopause transition and experience symptoms that are more clearly attributable to menopause, there will be a further opportunity for our team to investigate whether childhood adiposity is associated with menopausal symptoms in women of more advanced age.

7.2.5 Childhood abdominal obesity was associated with increased risks of women's reproductive health problems

This thesis has filled a gap in current knowledge on the effect of childhood abdominal obesity on women's reproductive health. The results from this thesis support the simple public health message for children and adolescents to 'keep your waist circumference to less than half your height' and this message can be extended to reproductive health. The general population and health professionals need to become better educated about the potential health risks, including

reproductive disorders, of childhood abdominal obesity. Therefore, efforts should be made to promote a healthy childhood weight but also to prevent childhood abdominal obesity.

7.2.6 There are cumulative risks of childhood adiposity across the life course on reproductive health

All the risks of adverse reproductive outcomes in the studies in this thesis were significantly highest in women with persistently high adiposity since childhood. These cumulative higher risks may be explained by the longer duration of adiposity and a more severe adiposity pattern for those with persistently high adiposity since childhood.

There are two major implications for this finding. Firstly, keeping a healthy adiposity status since childhood is of great importance. As adiposity tracks between childhood and adulthood [236], promoting normal adiposity status in childhood could have a lasting effect on future adiposity status. Secondly, prevention of persistently high adiposity trajectories will potentially help reduce the burden of adverse reproductive health outcomes.

Overall, the findings from this thesis add impetus to improving the current efficacy of interventions to reduce the prevalence of childhood obesity, which will help mitigate long-term diseases including women's reproductive health problems.

7.2.7 Potential interpretations and mechanisms for the associations of childhood adiposity with women's reproductive health

Although longitudinal associations between childhood adiposity and later reproductive outcomes were observed in our studies, it is problematic to make causal inferences. Drawing causal inferences from observational epidemiology can be challenging because of complex confounding effects (such as residual confounding and socially patterned behaviours affecting exposure), potential reverse causation (e.g. the relationship between childhood adiposity and

PCOS in our study), chance findings and the results of bias (for example due to considerable loss to follow-up) [237, 238]. The mechanisms for how childhood adiposity may influence later reproductive health are not completely understood, however, multiple factors may play a role and current evidence suggests there may be complex endocrinological mechanisms. Dysregulation of the HPO axis is one hypothesis often used to explain the association between adiposity and reproductive disorders in women. Excess body fat is associated with increased concentrations of insulin, androgens and estrogens, and decreased SHBG levels, which in turn leads to negative feedback on the hypothalamic pituitary axis, decreased gonadotropin-releasing hormone (GnRH) production, less follicle stimulating hormone (FSH) secretion and luteinizing hormone (LH) pulse amplitude [229, 239]. These affect ovarian follicular recruitment and ovulation. Additionally, adipokines and cytokines secreted by adipose tissue (such as leptin and adiponectin), as well as higher levels of insulin and inflammatory markers (e.g. C-reaction protein) may have direct impacts on endometrium receptivity, oocyte and embryo quality, and association with pregnancy complications [240]. However, it is also possible that childhood adiposity is an epiphenomenon (or by-product) of an underlying endocrine-related condition (for example insulin resistance) which is related to reproductive disorders in later life. Taking PCOS as an example, although the aetiology of PCOS is uncertain, childhood adiposity is not likely the cause and increasing evidence suggests a genetic or intra-uterine origin. Therefore, childhood adiposity may be a result of PCOS related endocrine dysregulation in early life, and may amplify the symptoms of PCOS in later life. This may explain why the recent increase in the prevalence of childhood adiposity will not necessarily lead to an increase in the prevalence of adverse reproductive health outcomes.

7.3 Future directions

The work presented in this thesis has broadened knowledge of the long-term associations of childhood adiposity with women's reproductive health. It highlights the need for and importance of studies that use a life course approach to conduct these investigations. Directions for future research include the following:

- **Exploring the associations of childhood adiposity with a more comprehensive spectrum of reproductive outcomes in both men and women**

Although CDAH is a population-based cohort study, it was not initially designed specifically for observing reproductive health outcomes. Therefore, the studies in this thesis have been limited to several reproductive health outcomes in adult females that were available in the follow-ups from CDAH. Similarly, although BBS aimed to examine the role of cardiovascular risk factors in childhood on reproductive outcomes in women, it is a sub-study of BHS which was not initially designed for the observations of reproductive outcomes and was only conducted among female participants. Furthermore, when BBS commenced most women were already in late midlife. It also should be noted that there is rising evidence in the literature demonstrating adverse influences of adult adiposity on male reproductive health, however this research area is still in its infancy. Future cohorts that specifically target reproductive health in both men and women will help extend our knowledge of the associations of childhood adiposity with more areas of reproductive health.

- **Improving the accuracy of reproductive outcome measures**

The reproductive outcomes in the current studies were self-reported. This may lead to potential under- or over-estimation of the prevalence of adverse reproductive outcomes. However, in general, the prevalence of the reproductive outcomes presented in this thesis is consistent with the prevalence in the literature. More accurate definitions from clinical diagnosis, biomedical

markers or validated questionnaires in future studies will provide more precise and convincing results.

- **Investigating whether the findings can be generalised to different countries and races**

Most of the available evidence of the associations of childhood adiposity with reproductive health comes from cohorts from western countries. Future studies should come from a series of diverse cohorts and races to provide external validity to the findings of this thesis.

- **Examining the associations in contemporary cohorts and understanding the associations with growth patterns from infancy to adolescence**

The prevalence of childhood overweight (10.1%), obesity (1.6%) and abdominal obesity (7.3%) in CDAH was relatively low in 1985 compared to the prevalence in present-day children in whom more extreme adiposity and earlier onset of adiposity is observed. Contemporary cohorts with greater numbers of children with high adiposity will add statistical power to examine these associations, making results more robust. Furthermore, contemporary cohorts will help verify whether associations observed in historical cohorts are consistently observed or if there are changes in the strength of associations due to changes in the characteristics of childhood adiposity.

The CDAH study had only a single time point of adiposity measures in childhood, which cannot adequately reflect the complex and dynamic adiposity changes that vary over time during a child's development. Future studies with multiple time points of adiposity measures in early life, for example from infancy to adolescence, could help understand the different risks of diverse adiposity patterns in early life for later reproductive health. They would also help identify potential sensitive periods during early life when exposure to adiposity might have more pronounced associations with later reproductive disorders and help better understand the potential biological mechanisms for the associations.

- **Exploring the role of genetics and epigenetics in the association between childhood adiposity and reproductive health**

It has been suggested that about 30% to 49% of the variation in BMI can be attributed to genetics and 60% to 70% to environment [241]. The patterns of body fat distribution also appear to be partly under genetic control [242, 243]. For example, fat distribution in men is more likely to be abdominal or upper-body whereas in women is more likely to be peripheral or lower-body. Furthermore, there is also growing evidence for the role of epigenetic factors (e.g. parental and intrauterine exposures, dietary, lifestyle and environmental factors) in the development of adiposity. The associations between genetics of adiposity and reproductive health have been explored in recent times. Studies have shown that the genes implicated in the development of adiposity, for example the fat mass and obesity-associated gene (FTO), are associated with susceptibility to PCOS, fertility problems and pregnancy complications [244-246]. The role of epigenetics in obesity and later metabolic disease has been increasingly explored in recent years [247], but little attention has been paid to reproductive health yet. Future research attempting to better understand how genetic factors and epigenetic changes are associated with adiposity and how they influence reproductive health will not only increase our understanding of the pathogenesis of adiposity and the mechanisms behind these associations, but might also help tailor proper therapeutic strategies for those at risk of childhood adiposity and its associated reproductive disorders.

7.4 Conclusion

The studies presented in this thesis together reveal that childhood adiposity has important implications for long-term risks of reproductive health outcomes including infertility, pregnancy hypertension, menstrual irregularity and PCOS in women of reproductive age and some menopausal symptoms. Cumulative exposure to higher levels of adiposity across the life

course was associated with higher risks of adverse reproductive consequences in adulthood. Collectively, the results of these studies provide a better understanding of the long-term consequences of childhood adiposity, especially childhood abdominal obesity, for reproductive health in women. The work undertaken in this thesis suggests that the prevention of childhood adiposity is important for women's reproductive health as well as other disease prevention, adding impetus to strategies aimed at prevention and treatment of childhood adiposity.

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Appendices

Appendix A Reproductive health questions for female participants in CDAH-1 and CDAH-2

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SECTION D: This section is for **WOMEN ONLY.**

If you are MALE please skip to SECTION E (page 15). The answers to the following questions will help us investigate the influence of hormones on the cardiovascular system.

1. **Are you currently using any of the following hormonal contraceptives, even if you are using them for reasons other than contraception?**

   O Oral contraceptive pill

   O Minipill (progesterone only pill)

   O Weekly contraceptive patch

   O Progestagen (e.g., Implanon)

   O Progestagen injection (e.g., Depo Provera)

   O Progestin injection (e.g. , Noristerat)

   O Progestin releasing intrauterine device (e.g. , Mirena, Copper T380A)

   O Progestin releasing implant (e.g. , Norplant)

   O Other (please specify) ☐

2. **How old were you when you had your first menstrual period?**

   Years ☐☐ Months ☐☐

3. **Have you had a hysterectomy; that is, an operation to remove your uterus?**

   O No **-->Skip to Question 4**

   O Yes

   IF YES

   3a) What age were you when you had the hysterectomy? ☐☐ **Years**

   3b) Were your ovaries removed as well?

   O Yes, both ovaries removed

   O Yes, only one ovary removed

   O No

   O Don't know

   SKIP TO Question 5

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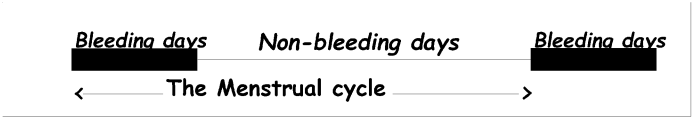
4. The menstrual cycle is the time from the <u>first day</u> of one period to the <u>first day</u> of the next.



4a) How long is your usual <u>menstrual cycle</u>?
In other words, how many days are there from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT?

☐☐☐ Days

4b) What is the longest <u>menstrual cycle</u> you have had in the last 12 months? Again count from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT.

☐☐☐ Days

4c) What is the shortest <u>menstrual cycle</u> you have had in the last 12 months? Again count from the FIRST DAY OF ONE PERIOD to the FIRST DAY OF THE NEXT.

☐☐☐ Days

5. Thinking about the most recent time when you were having periods and were NOT using hormonal contraceptives (e.g., the pill) and were not pregnant or breastfeeding:

5a) Would you describe your periods as:

O Very regular
O Fairly regular
O Irregular
O Very irregular

5b) How old were you at this time?
That is, at the most recent time when you were having periods and were NOT using hormonal contraceptives (e.g., the pill) and were not pregnant or breastfeeding.

☐☐ Years

5c) During this time, approximately how many periods did you have in the space of 12 months?

O More than 13
O 11-13
O 6-10
O 1-5
O None

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6. Have you ever seen a doctor because of irregular periods?

O No **-->Skip to Question 7**

O Yes

IF YES

6a) How old were you when you first saw your doctor about irregular periods?

☐☐ **Years**

6b) Have you ever taken prescribed hormone medications for irregular periods?

O Yes O No

6c) Has a doctor ever told you that you have polycystic ovaries or polycystic ovary syndrome?

O Yes O No

7. Have you ever seen a doctor because of concern about the amount of hair on your face?

O No **-->Skip to Question 8**

O Yes

IF YES

7a) Were you prescribed any treatment for this?

O No

O Yes ☐

(please specify)

8. Has a doctor ever told you that you have acne?

O No **-->Skip to Question 9**

O Yes

IF YES

8a) Were you prescribed any treatment for this?

O No

O Yes ☐

(please specify)

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9. Have you ever tried to become pregnant for 12 months or more without succeeding?

O Yes O No

10. Have you ever seen a doctor because you were having trouble becoming pregnant?

O No **-->Skip to Question 11**

O Yes

IF YES

10a) Did you have any of the following fertility investigations?

O Test of blood or urine hormone levels

O Laparoscopy (incision in your stomach to look at your reproductive organs)

O Your partner's semen analysed

10b) Did a doctor ever tell you that you or your partner had:

O An ovulatory problem?

O A tubal problem?

O Any other female fertility problem?

- please specify ☐

O Semen abnormalities?

O An unexplained fertility problem?

11. Have you ever been pregnant?

O No **-->Skip to SECTION E (Page 15)**

O Yes

12. How many times have you been pregnant? ☐☐ **times**

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13. How many live births have you had?

13a) When were these babies born?

	Baby	Month	Year
First baby	1		
Second baby	2		
Third baby	3		
Fourth baby	4		
Fifth baby	5		

If you have had more than 5 live births please continue at the end of this section.

14. When you were pregnant were you ever tested for diabetes?
That is, did you have a blood or urine sugar test? This may have involved drinking a very sugary drink.

O Yes O No

15. Were you ever told that you had gestational diabetes or pregnancy related diabetes?

O Yes O No

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8. Which of the following describes your current employment status? You can pick more than one.

- O Working full-time
- O Working part-time
- O Not working (but not retired)
- O Home duties
- O Full-time student
- O Part-time student
- O Retired
- O Permanently unable to work / Ill
- O Other ☐ (please specify)

SECTION B: This section is about your health and your medical history

1. Have you <u>ever</u> been told that you have high blood pressure?

O No **-->Skip to Question 2**

O Yes

<u>IF 'YES'</u>

1a) When were you first told this? ☐☐☐☐ (Year)

1b) Was this during pregnancy? O Yes O No O Not applicable

1c) Are you currently taking medication prescribed by a doctor to lower your blood pressure?

O Yes O No

1d) Has a doctor in the past year recommended you change your way of life, in order to lower your blood pressure?

O Yes O No

Appendix B Protocols for anthropometric measurements in CDAH-1 and CDAH-3 clinics

CDAH
CHILDHOOD
DETERMINANTS
of ADULT HEALTH

HEIGHT & WEIGHT MEASUREMENT PROTOCOL

Equipment: Stadiometer
Heine portable scales
Baseboard for scales

Eligibility: Participants who are chairbound should not have their height and weight taken. Similarly, if after discussion with a participant it becomes clear that they are too unsteady on their feet for these measurements, do not attempt to take them. In addition, pregnant women are not eligible for weight as this is clearly affected by their condition.

Procedure:

Height Measurement

Diagram 1

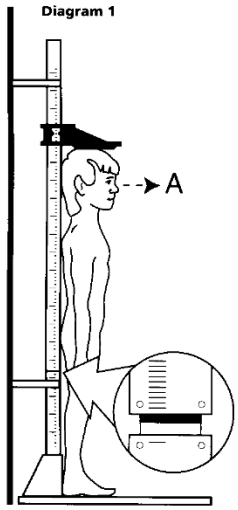
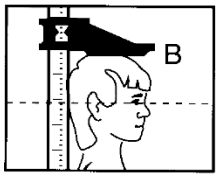


Diagram 2



Installing the Leicester Height Measure

Slot the white upright sections firmly together and ensure that the bottom section locks into the blue base. Slide on the measuring arm and position the 2 white stabilizers as required (see diagram 1).

Ensure the stabilizers stay clear of the joins. The base should be placed on a firm uncarpeted surface with the stabilizers resting against a wall/door to give the Leicester rigidity.

N.B. The metric and imperial scales are calibrated to take account of the 3cm difference between the black measurement arrow and the flat surface of the measuring arm.

1. Stand subject on the "feet" preferably barefoot with his/her heels together and touching the backstop. The spine at pelvis and shoulder level should touch the upright. Shoulders should be relaxed, arms to the side. Remove headgear (bows, ribbon etc.) where possible.
2. Lower the measuring arm onto the head and position the head so that an imaginary horizontal line runs between the ear hole and the lower border of the eye socket (see diagram 2).
3. Ask the subject to stand up straight.
4. Read off the metric height to the last completed millimeter. Do not round up! Measure with care.
5. Record the height in the boxes provided on the Data Record Form.

Additional points:

- If the subject cannot stand upright with their back against the stadiometer and have their heels against the rod (e.g., those with protruding bottoms) then give priority to standing upright.
- If the subject has a hairstyle which stands well above the top of their head, bring the head plate down until it touches the hair. With some hairstyles you can compress the hair to touch the head. If it is a hairstyle that can be altered, e.g., a bun, if possible, ask the subject to change/undo it.
- If the subject is tall, it can be difficult to line up the Frankfort Plane. When you think that the plane is horizontal, take one step back to check from a short distance that this is the case.

Weight Measurement

1. Turn scales on before subject steps on. Scales will automatically re-zero.

2. Ask subject to remove shoes and any heavy clothing, such as jacket etc., and to remove any heavy articles from pockets such as keys, wallets. It is acceptable to leave socks on.

3. Ask subject to step onto scales, look forward (not down) with their hands by their side, and to keep as still as possible.

4. Write down reading, recording to the nearest 0.1 kg.

WAIST & HIP MEASUREMENT PROTOCOL
(Version 3)

Equipment: Lufkin steel (non-stretch) tape measure

Eligibility: All subjects will have waist and hip circumference measurements performed except those who:

- are pregnant
- are chairbound or
- have a colostomy / ileostomy.

Procedure:

a) If possible, without embarrassing the subject, ensure that the following items of clothing are removed:
   - All outer layers of clothing, such as jackets, heavy or baggy jumpers, cardigans and waistcoats.
   - Shoes with heels.
   - Tight garments intended to alter the shape of the body, such as corsets, lycra body suits and support tights.
   - If the subject is wearing a belt, ask them if it would be possible to remove it or loosen it for the measurement (if necessary).
   - Ask subject to empty pockets of heavy items (e.g. keys).

b) Ensure that the subject is standing erect in a relaxed manner and breathing normally. Weight should be balanced evenly on both feet.

c) If possible, either kneel or sit on a chair to the side of the subject.

d) If the subject is large, ask him/her to pass the tape around rather than having to 'hug' them.

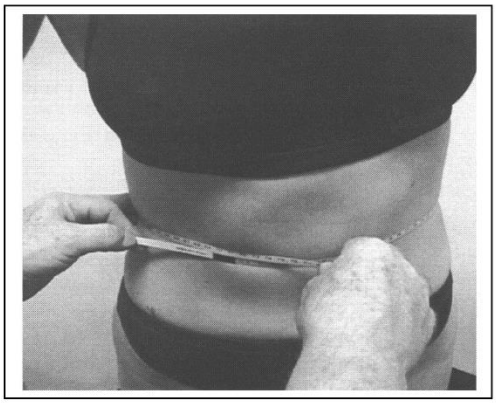
e) Measure and record the waist circumference, followed by the hip circumference. Repeat each 3 times. If the first two scores are the same, it is not necessary to take the third measurement.

Waist Circumference

The waist girth is taken at the level of **the narrowest point** between the lower costal (10^{th} rib) border and the iliac crest. An approximate indicator of this level may be ascertained by asking the subject to bend sideways.

Do not try to avoid the effects of waistbands by measuring the circumference at a different position or by lifting or lowering clothing items. For example, if the subject has a waistband at the correct level of the waist (midway between the lower rib margin and the iliac crest), then ask the subject to move the waistband, or measure the waist circumference over the waistband. If you believe that clothing, posture or any other factor is significantly affecting the waist measurement, record this on the data record form.

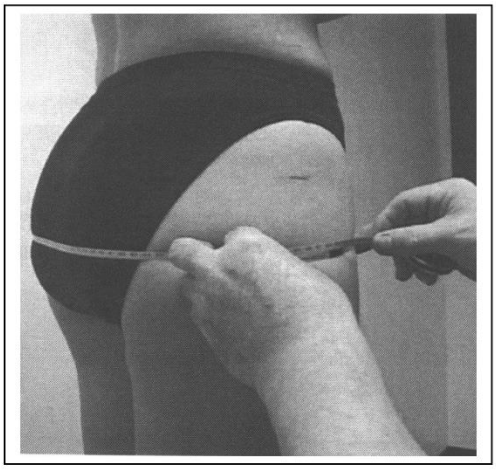
1. Ask the subject to assume a relaxed standing position with the arms folded across the thorax.
2. Stand in front of the subject, while the subject abducts (lifts) the arms slightly, allowing the tape to be passed around the subject's abdomen.
3. The stub of the tape and the housing are then both held in the right hand while you adjust the level of the tape at the back to ensure that it is level with the adjudged level of the narrowest point, with your left hand. (This will be easier if you are kneeling or sitting on a chair to the side of the subject).
4. Instruct the subject to lower their arms to the relaxed position. Readjust the tape to ensure that it has not slipped and is not too tight on the skin (i.e., does not indent the skin).
5. Ask the subject to breathe out normally and to look straight ahead (to prevent holding of one's breath). Take the measurement at the end of a normal expiration, recording measurement to the nearest 0.5 centimetres.



Hip Circumference

The hip girth is taken at the level of the greatest posterior protuberance of the buttocks which usually corresponds anteriorly to about the level of the symphysis pubis.

1. Ask the subject to assume a relaxed standing position with the arms folded across the thorax. The subject's **feet should be together** and the **gluteal muscles relaxed**.
2. Pass the tape around the hips from the side. The stub of the tape and the housing are then held in the right hand while you use your left hand to adjust the level of the tape at the back to the adjusted level of the greatest posterior protuberance of the buttocks.
3. Position the tape in front and the sides so that the tape is held in a horizontal plane at the target level.
4. Readjust the tape if necessary, to ensure that it has not slipped and does not cause indentation of the skin.
5. If clothing is significantly affecting the measurement, record this on the data record sheet.



Appendix C The Menopause Rating Scale for measuring menopausal symptoms in CDAH-3

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark 'none'.

	Symptoms:	none	mild	moderate	severe	very severe
	Score =	0	1	2	3	4
1.	Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2.	Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3.	Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)	☐	☐	☐	☐	☐
4.	Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5.	Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6.	Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7.	Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8.	Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9.	Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10.	Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11.	Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Appendix D Diagnosis of menstrual irregularity and PCOS in BBS

Question	Criteria to attain score value	Score value
Have you ever been told by a doctor that you had PCOS? • Yes • No		
Between the ages of 16 and 40, about how long was your average menstrual cycle (time from first day of one period to the first day of the next period)? (select ONE only) • <25 d • 25-34 d • 35-60 d • More than 60 d • Totally variable	Participant indicates any one of • <25 d • 35-60 d • more than 60 d • totally variable	1
During your menstruating years (not including during pregnancy), did you have a tendency to grow dark, coarse hair on your (circle ALL that apply) • upper lip? • chin? • breasts? • chest between the breasts? • back? • belly? • upper arms? • upper thighs?	Participant indicates 3 or more sites	1
A diagnosis of menstrual irregularity	If participant attained a score value of 1 for the second question;	
A diagnosis of hirsutism	If participant attained a score value of 1 for the third question;	
A diagnosis of PCOS	If participant answered "Yes" to the first question; or total score value ≥ 2.	

Appendix E Publications of Chapter 3, Chapter 4 and Chapter5

Appendix E 1 Publication of Chapter 3

SEMINAL CONTRIBUTION

Association of childhood obesity with female infertility in adulthood: a 25-year follow-up study

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Objective: To evaluate whether childhood obesity is associated with infertility in women's reproductive-aged life.
Design: Prospective longitudinal study.
Setting: Not applicable.
Intervention(s): None.
Patient(s): A total of 1,544 girls, aged 7–15 years in 1985, and who completed questionnaires at follow-up in 2004-2006 and/or 2009-2011.
Main Outcome Measure(s): Infertility was defined as having difficulty conceiving (had tried for ≥12 months to become pregnant without succeeding) or having seen a doctor because of trouble becoming pregnant.
Result(s): At ages from 7–11 years, girls at both the lower and upper end of the body mass index (BMI) *z* score had increased risk of infertility. Compared with normal weight girls, those with obesity at ages 7–11 years were more likely in adulthood to report infertility (adjusted relative risk [aRR] = 2.94, 95% confidence interval [CI] 1.48–5.84), difficulty conceiving (aRR = 3.89, 95% CI 1.95–7.77), or having seen a doctor because of trouble becoming pregnant (aRR = 3.65, 95% CI 1.90–7.02) after adjusting for childhood age, follow-up length, highest parental education, and marital status.
Conclusion(s): Childhood obesity before 12 years of age appears to increase the risk of female infertility in later life. (Fertil Steril® 2018;110:596-604. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Childhood, body mass index, infertility, body composition, waist-to-height ratio

The increase in obesity among children and adolescents is of great concern around the world (1). In Australia, one in four children aged 5–17 years were overweight or obese in 2014-2015, which is twice the recorded prevalence in 1986 (2). Substantial evidence suggests that obesity in women is associated with a wide range of gynecological disorders including infertility (3, 4). Obesity during childhood and adolescence has been linked with early puberty, menstrual disorders, and polycystic ovarian syndrome (PCOS) (5). From the life course perspective of female reproductive health, it is important to determine whether childhood obesity has long-term effects on infertility in adulthood, typically defined clinically as a failure to conceive after regular unprotected intercourse or attempting pregnancy for ≥12 months (6).

Few studies have investigated the association of childhood obesity with female infertility and the findings were not consistent. In a study of 3,327 British girls, Lake and colleagues (7) reported little impact of childhood body mass index (BMI) at the age of 7 years on infertility 26 years later (defined by achieving a pregnancy after ≥12 months). However, participants were restricted to women with a live birth from their first pregnancy. The BMI cutpoints were defined using an index of relative weight (weight expressed as a percentage of the standard weight for age, height, and sex). More recently, a report (8) based on 1,061 participants in the Bogalusa Heart Study in the United States showed that girls with obesity before 12 years of age were more likely in later life to have tried to become pregnant without success. Weight status was defined according to age and gender specific BMI percentiles and based on US Centers for Disease Control and Prevention statistics (e.g., ≥95th percentile for obesity). A

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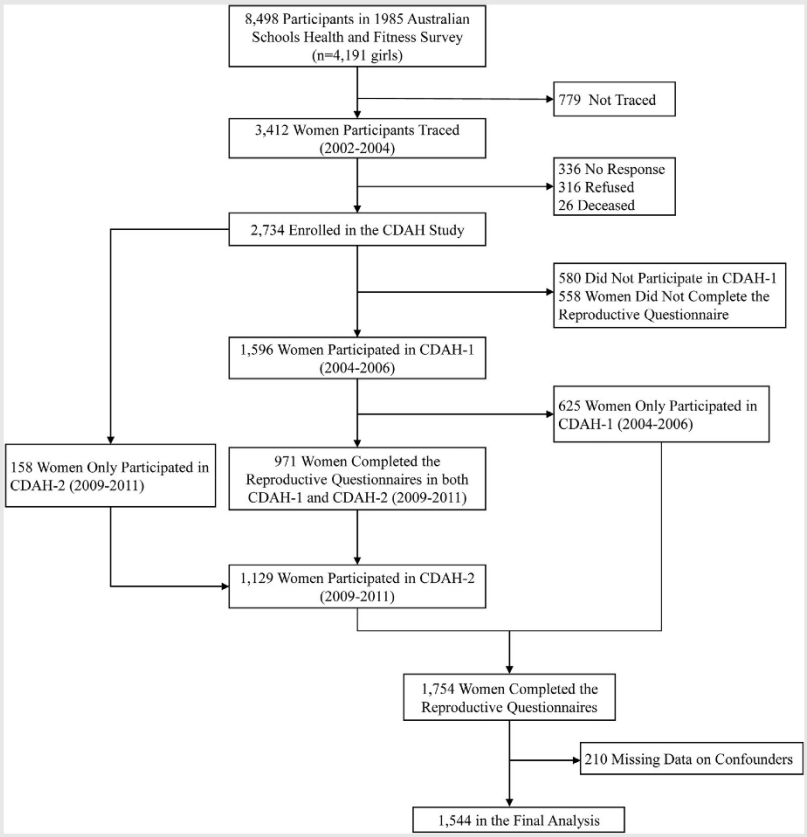
FIGURE 1



Selection of participants for the Childhood Determinants of Adult Health (CDAH) study, Australia, 1985–2011.

He. Childhood obesity and infertility. Fertil Steril 2018.

limitation of this study is that it determined whether participants had "ever tried to become pregnant and were unable to" but did not specify a time interval and may have resulted in misclassification of infertility. In addition, male factors (e.g., poor semen quality) are commonly reported causes of infertility (9) and not the outcome of interest. Neither of these studies was able to exclude them. The aim of the present study was to examine the association between different measures of body composition at ages 7–15 years and infertility at ages 26–41 years in a large population-based sample of Australian women with consideration of a wide range of potential confounders.

MATERIALS AND METHODS

Participants

The Childhood Determinants of Adult Health (CDAH) study is a follow-up of 8,498 children, which included 4,191 girls who participated in the 1985 Australian Schools Health and Fitness Survey, a nationally representative sample of Australian school children aged 7–15 years (herein referred to as "baseline") (10). At baseline, all children had physical assessments and those aged 9–15 years completed questionnaires. During 2002-2004, 3,412 women participants were traced and 2,734 women agreed to participate in the CDAH study (Fig. 1). During 2004-2006, when the participants were aged 26–36 years, 1,596 women completed questions on reproductive health (CDAH-1). The second follow-up (CDAH-2) was conducted during 2009-2011, when participants were aged 31–41 years and 1,129 women completed questions on reproductive health. After combining the two follow-ups, a total of 1,754 women who answered reproductive health questions at CDAH-1 or CDAH-2 or both were eligible for the study.

The study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee. Written informed consent was obtained at both time points.

Childhood Body Composition Measurement

The BMI, calculated as weight (in kilograms)/height (in meters)^2, was derived from measured height and weight with weight status defined using international age- and sex-specific cutpoints (11) and was transformed into BMI *z* scores based on age- and sex-specific standardization of the full childhood cohort (n = 4,189 girls). Waist circumference was taken at the level of the umbilicus to the nearest 0.1 cm. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Waist-to-hip ratio was calculated by dividing waist by hip circumference. Waist-to-height ratio (WHtR) was calculated by dividing the waist circumference by height and the dichotomized into <0.5 or ≥ 0.5. Abdominal obesity was defined as WHtR ≥ 0.5 (12).

Adult Body Composition Measurement

At CDAH-1, weight and height were measured at study clinics. A subsample of these participants also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. The difference between clinic and self-reported weight and height was used to calculate a correction factor from a linear regression model. Participants who did not visit a study clinic self-reported their weight and height, and a correction factor was applied to adjust for error (13). The BMI (in kilograms per meter squared) was calculated from height and weight.

Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the correction factor applied at CDAH-1. The BMI was calculated using measured height at CDAH-1, adjusted self-reported height at CDAH-1, or at enrolment.

Adult BMI was categorized into three groups (<25, 25–30, and ≥ 30 kg/m^2). Overweight was defined as 25 kg/m^2 $\leq$ BMI $\leq$29.9 kg/m^2 and obesity was defined as BMI $\geq$30 kg/m^2 (14).

Adult Infertility Measurement

In the reproductive questionnaire of CDAH-1 and CDAH-2, women were asked to answer yes or no to questions "Have you ever tried to become pregnant for 12 months or more without succeeding?" and "Have you ever seen a doctor because you were having trouble becoming pregnant?" Infertility was recorded if they responded "yes" to either of the two questions. Women were further asked whether any of the following investigations had been undertaken if they reported having seen a doctor because of difficulty conceiving: hormone test, laparoscopy, and partner's semen test. Participants were also asked about any diagnosis they had been given including ovulatory problem, tubal problem, male factor, unexplained fertility problem, or any other female problem with a written specified reason. We categorized the answers into tubal, male, ovulatory (including ovulatory problem, PCOS, hyperprolactinemia, hypogonadotrophic, hypergonadotrophic, and premature ovarian failure), endometriosis, unexplained, other, and uterine factors.

Covariate Measures

Childhood factors considered as covariates included age, age at menarche (self-reported in adulthood), socioeconomic position based on area of residence (high, medium high, medium low, or low), highest parental education (reported in adulthood as high school only, vocational training, any university education), smoking experimentation (none, a few puffs, <10 cigarettes in their life, and ≥ 10 cigarettes in their life), alcohol consumption (never, less than once per week, more than once per week), and total physical activity (minutes/week). Sociodemographic characteristics were self-reported at follow-ups. Adult covariates included highest level of education attained (classified as for childhood), socioeconomic position based on area of residence (classified as for childhood), marital status (single, married/living as married, separated/divorced/widowed), smoking status (never, exsmoker, current smoker), alcohol consumption (nondrinker, light drinker, moderate drinker, heavy/very heavy drinker), and total physical activity (minutes/week). Follow-up length was also considered as a potential confounder.

Statistical Analyses

Subgroup analyses by child age (7–11 years and 12–15 years) were undertaken because of reported differences in the association of onset of obesity in childhood with later infertility (8). Univariable and multivariable log-binomial regression was used to derive risk ratio (RR) estimates for the association between body composition and infertility before and after adjustment for potential confounders. If the log binomial model failed to converge, RRs were estimated using Poisson regression with robust standard errors to correct for the misspecification of the binomial errors (15–18). Covariates kept in the final model were variables associated with the exposure and the outcome, and resulted in $>10\%$ change in the coefficient of the principal study factor when added into the model.

Restricted cubic regression splines based on 4 knot points were used to present associations between childhood BMI *z* score and infertility (19). The x-axis on the graph goes from the 5th to the 95th percentile of childhood BMI *z* score.

The following sensitivity analyses were conducted. First, we excluded those who reported male factor infertility to examine whether it had biased the observed association between childhood obesity and having ever seen a doctor because of trouble becoming pregnant. Second, we restricted our sample to women who were married or living as married. Third, we considered the effect of loss to follow-up using inverse probability weighting. The completed factors available at baseline used to determine the weights were childhood age, school type, and state of residence. Fourth, childhood BMI was classified alternatively as normal ($<$85th percentile), overweight (85th–94th percentile), or obese ($\geq$95th percentile) based on age- and sex-specific US Centers for Disease Control and Prevention norms (20) and age- and sex-specific childhood BMI in our 1985 Australian Schools Health and Fitness Survey cohort.

All analyses were performed using STATA software, version 14.2 (Stata Corp.). A P value of $<.05$ was considered statistically significant.

RESULTS

Participant Characteristics

This study included 1,754 women who reported fertility outcomes. Of these participants, 971 completed both follow-up surveys, 625 participated in only the first follow-up, and 158 women participated in only the second follow-up. Participants who had missing data on confounders (210 women) were excluded, leaving 1,544 women for the final analysis.

The anthropometric and sociodemographic characteristics of participants at childhood and adulthood are shown in Table 1. At baseline, 17 (1.1%) children were obese, 116 (7.5%) were overweight, and 80 (5.2%) children had abdominal obesity as defined by BMI cutpoints and WHtR category. The mean age at follow-up was 34 years (range, 26-41 years). There were 346 (22.4%) women who reported experiencing infertility in adulthood, including 264 (17.1%) who reported having tried for ≥12 months to become pregnant without succeeding and 281 (18.2%) who had seen a doctor because of trouble becoming pregnant. Participants with lower parental education in childhood and those who were married or living as married in adulthood were more likely to report infertility. Compared with those who did not participate in the follow-up, those who did participate were slightly older (11.0 vs. 10.8 years; $P=.003$), had marginally lower BMI (18.2 vs. 18.4 kg/m^2; $P=.009$), and were less likely to have abdominal obesity (5.2% vs. 8.3%; $P<.001$) at baseline.

Infertility

After adjustment for age, follow-up length, parental education, and marital status, compared with women with normal childhood weight between 7 and 11 years (Table 2), those who were obese as children were more likely to report infertility (adjusted relative risk [aRR] = 2.94, 95% confidence interval [CI] 1.48–5.84), having ever tried for >12 months to become pregnant without succeeding (aRR = 3.89, 95% CI 1.95–7.77), and having seen a doctor because of trouble becoming pregnant (aRR = 3.65, 95% CI 1.90–7.02). This association was not evident for the group aged 12–15 years at baseline. No significant association was found between other adiposity indicators (waist circumference, waist-to-hip ratio, and WHtR ≥0.5) in childhood and infertility in adulthood, including when abdominal adiposity measures were adjusted for childhood BMI.

The association between childhood BMI z score and relative risk of infertility in adulthood is shown in Figure 2. There was a U-shaped association of BMI z score with infertility in the 7- to 11-year-old group (Fig. 2A), with the risk significantly higher in children with z scores >1.05 or < -0.80. No significant association was observed for those in the 12- to 15-year-old group (Fig. 2B).

Cause of Infertility

Most women who had seen a doctor because of trouble becoming pregnant reported one or more infertility causes and infertility investigations (Supplemental Table 1, available online). Endometriosis was a less common cause of infertility in those who were overweight or obese in childhood (15.1% in normal vs. 3.3% in overweight/obese; $P=.10$). Similar proportions of women had infertility investigations irrespective of their childhood BMI category (Supplemental Table 1).

Influence of Adiposity from childhood into Adulthood

The proportions and the number of women who reported infertility by adiposity status from childhood to adulthood are displayed in Supplemental Figure 1 and Supplemental Table 2, both available online. For consistently normal weight participants (normal weight in childhood and adulthood), the prevalence of infertility was 21.6%, and for consistently overweight/obese participants (overweight/obese from childhood to adulthood), the corresponding figure was 27.9%. Although a higher prevalence of reported infertility was observed in the persistently overweight and obese group, it did not reach statistical significance ($P=.37$). After adjustment for childhood age and parental education at baseline, length of follow-up, adult education, marital status, and alcohol consumption in adulthood, the risk of infertility was significantly higher in women who were persistently overweight or obese from childhood (ages 7–11 years) into adulthood than those who had consistently healthy weight (Supplemental Table 3, available online).

Sensitivity Analysis

Similar results were observed after excluding women who reported infertility due to male factor (n = 20) and endometriosis (n = 39). Compared with those of normal weight in childhood, the risk of having ever seen a doctor because of trouble becoming pregnant in the obese group was 3.69 (95% CI 1.94–6.99) and 4.16 (95% CI 2.14–8.06) for those aged 7–11 years at baseline. When restricting the sample to women who were married or living as married (and who it might be assumed would have a greater likelihood of becoming pregnant), the risks of infertility (aRR = 3.15, 95% CI 1.37–7.25), having ever tried for >12 months to become pregnant without succeeding (aRR = 4.12, 95% CI 1.78–9.50) and having ever seen a doctor because of trouble becoming pregnant (aRR = 3.84, 95% CI 1.78–8.25) remained significantly higher in those who were obese at ages 7–11 years. Sensitivity analyses conducted by reanalyzing the data with inverse probability weighting produced similar patterns of results as the unweighted analyses and the changes in the magnitude of significant associations were small, ranging from 1.5%–3.3% (Supplemental Table 4, available online). Further analysis using US Centers for Disease Control and Prevention and our cohort internal cutpoints of 85th and 95th childhood BMI percentiles showed similar significant associations of childhood obesity and infertility in the 7- to 11-year-old group (Supplemental Tables 5 and 6, available online).

TABLE 1

Characteristics of women in childhood (1985) and adulthood (2004–2011).[a]

Characteristic	Tried for ≥12 mo to become pregnant without succeeding		Seen a doctor because of trouble becoming pregnant		Any fertility problem[b]	
	Yes (n = 264)	No (n = 1,279)	Yes (n = 281)	No (n = 1,263)	Yes (n = 346)	No (n = 1,198)
Childhood						
Age (y), mean ± SD	11.5 ± 2.4[c]	10.9 ± 2.5	11.4 ± 2.5[c]	10.9 ± 2.5	11.4 ± 2.4[c]	10.9 ± 2.5
SEIFA disadvantage, %						
High	24.3	27.5	28.9	26.4	25.8	27.2
Medium-high	30.3	28.7	27.6	29.4	29.7	28.8
Medium-low	37.2	38.1	36.9	38.2	37.8	38.0
Low	8.3	5.7	6.7	6.1	6.7	6.0
Waist circumference (cm), mean ± SD	63.2 ± 8.1[c]	61.9 ± 7.7	62.9 ± 8.1	62.0 ± 7.7	63.0 ± 8.0[c]	61.9 ± 7.7
Waist-to-hip ratio, mean ± SD	0.81 ± 0.06	0.81 ± 0.06	0.81 ± 0.06	0.81 ± 0.06	0.81 ± 0.06	0.82 ± 0.06
Body mass index (kg/m^2), mean ± SD	18.4 ± 3.0	18.1 ± 2.7	18.4 ± 3.0	18.1 ± 2.7	18.4 ± 3.0	18.1 ± 2.7
BMI category, %						
Normal	90.1	91.6	89.6	91.8	89.9	91.8
Overweight	8.0	7.4	8.6	7.3	8.7	7.2
Obese	1.9	0.9	1.8	1.0	1.5	1.0
Smoking experimentation, %						
None	55.7	59.2	57.9	58.7	57.1	59.0
A few puffs	20.8	21.9	19.7	22.2	20.2	22.2
<10 cigarettes	8.6	7.2	8.8	7.1	8.7	7.0
>10 cigarettes	14.9	11.7	13.6	12.0	13.9	11.8
Parental education, %						
University education	20.1[c]	29.1	23.8	28.4	22.5	29.0
Vocational training	37.1	33.0	34.9	33.5	35.3	33.3
High school	42.8	37.9	41.3	38.2	42.2	37.7
Alcohol assumption, %						
Never	72.9	69.5	70.2	70.0	72.5	69.3
<1 per wk	22.6	24.6	25.0	24.1	22.3	24.9
>1 per wk	4.5	5.9	4.8	5.9	5.2	5.8
Physical activity (min/wk), mean ± SD	384 ± 342	398 ± 376	396 ± 378	395 ± 368	388 ± 353	398 ± 375
Age at menarche (y), mean ± SD	13.1 ± 1.3	13.2 ± 1.3	13.1 ± 1.3	13.2 ± 1.3	13.1 ± 1.3	13.1 ± 1.3
Adulthood						
Age (y), mean ± SD	33.5 ± 2.9[c]	34.2 ± 3.5	33.4 ± 2.9[c]	34.3 ± 3.5	33.4 ± 2.8[c]	34.2 ± 3.5
SEIFA disadvantage, %						
High	26.9	24.1	25.6	24.9	26.0	24.4
Medium-high	25.4	22.9	19.9	23.5	23.4	23.2
Medium-low	23.9	25.2	24.9	25.2	24.0	25.3
Low	23.9	27.8	29.5	26.3	26.0	27.1
BMI (kg/m^2), mean ± SD	25.7 ± 5.8	25.2 ± 5.4	25.4 ± 5.6	25.3 ± 5.5	25.5 ± 5.6	25.3 ± 5.4
BMI category, %						
Normal	56.2	60.2	58.1	59.7	57.5	60.1
Overweight	23.7	24.1	22.3	24.2	23.1	24.1
Obese	20.1	15.7	19.6	16.1	19.4	15.8
Smoking status, %						
Never smoker	54.2	55.3	55.7	55.2	55.4	55.2
Exsmoker	25.0	26.9	26.4	26.5	25.8	26.7
Current smoker	20.8	17.8	17.9	18.3	18.8	18.1
Self-education, %						
University education	45.1[c]	47.1	46.4	46.8	45.2[c]	47.2
Vocational training	22.4	28.2	24.3	28.0	23.8	28.4
High school	32.6	24.7	29.3	25.2	31.0	24.5
Marital status, %						
Single	2.7[c]	22.4	2.5[c]	22.5	2.9[c]	23.5
Married/living as married	93.2	72.7	94.0	72.7	93.4	71.5
Separated/divorced/widowed	4.2	4.9	3.6	4.8	3.8	4.9
Alcohol consumption, %						
Nondrinkers	29.5[c]	21.4	24.5	22.3	27.2[c]	21.5
Light drinkers	57.9	56.9	59.7	56.5	57.4	56.8
Moderate drinkers	10.3	16.2	13.2	15.8	12.4	16.2
Heavy/very heavy drinkers	2.3	5.6	2.6	5.4	3.0	5.5
Physical activity (min/wk), mean ± SD	755 ± 512	766 ± 495	732 ± 500	770 ± 497	743 ± 488	769 ± 501
Follow-up length (y), mean ± SD	22.6 ± 2.5		22.6 ± 2.5		22.5 ± 2.5	

Note: Childhood overweight and obesity were defined according to the international cutpoints. BMI = body mass index; SD = standard deviation; SEIFA = Socio-Economic Indexes for Areas.

[a] Sample size ranges from 873–1,543 due to missing data on some covariates.

[b] Women who answered yes to any one of the two related infertility questions.

[c] $P < .05$.

He. Childhood obesity and infertility. Fertil Steril 2018.

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TABLE 2

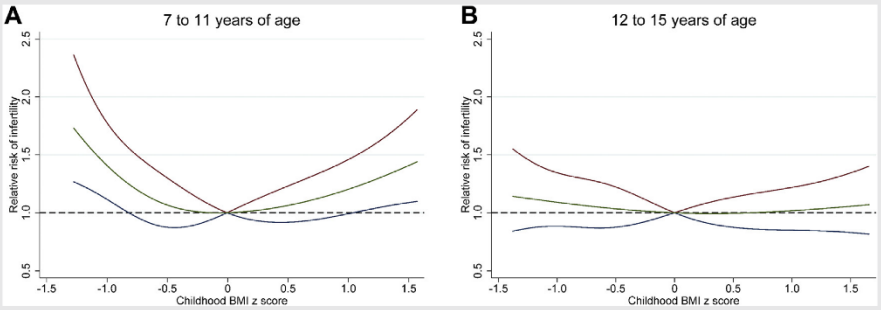
Associations between body composition measures in childhood with fertility problem in adulthood, stratified by childhood age.

	Tried for ≥12 mo to become pregnant without succeeding					Seen a doctor because of trouble becoming pregnant					Infertility[a]				
		Unadjusted		Model 1			Unadjusted		Model 1			Unadjusted		Model 1	
Body composition	n	RR	95% CI	RR	95% CI	n	RR	95% CI	RR	95% CI	n	RR	95% CI	RR	95% CI
Age, 7–11 y															
BMI category															
Normal	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—
Overweight	69	0.80	0.41–1.57	0.85	0.45–1.61	69	1.18	0.71–1.98	1.30	0.82–2.07	69	1.12	0.70–1.80	1.21	0.80–1.84
Obese	8	2.59	1.04–6.43	3.89	1.95–7.77	8	2.36	0.95–5.85	3.65	1.90–7.02	8	1.94	0.78–4.80	2.94	1.48–5.84
Waist circumference	864	1.01	0.98–1.03	0.99	0.97–1.02	864	1.01	0.98–1.03	1.00	0.97–1.03	864	1.01	0.99–1.03	1.00	0.97–1.02
Waist-to-hip ratio	864	0.90	0.67–1.20	0.97	0.72–1.29	864	0.82	0.63–1.09	0.88	0.67–1.16	864	0.88	0.69–1.13	0.98	0.77–1.24
Waist-to-height ratio															
<0.5	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—
>0.5	49	0.99	0.49–2.00	1.17	0.60–2.27	49	0.87	0.43–1.75	1.02	0.52–1.99	49	1.04	0.59–1.84	1.29	0.76–2.18
Age, 12–15 y															
BMI category															
Normal	622	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—
Overweight	47	1.40	0.86–2.28	1.18	0.75–1.87	47	1.16	0.67–1.99	1.06	0.64–1.76	47	1.26	0.81–1.95	1.11	0.72–1.70
Obese	9	1.12	0.33–3.85	1.05	0.33–3.37	9	1.10	0.32–3.77	1.03	0.32–3.27	9	0.88	0.26–3.00	0.90	0.26–3.12
Waist circumference	679	1.01	0.99–1.03	1.01	0.99–1.03	680	1.01	0.99–1.03	1.00	0.98–1.02	680	1.01	0.99–1.02	1.00	0.99–1.02
Waist-to-hip ratio	679	1.18	0.91–1.53	1.18	0.90–1.53	680	1.23	0.95–1.58	1.23	0.95–1.59	680	1.15	0.92–1.43	1.14	0.91–1.43
Waist-to-height ratio															
<0.5	647	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—
≥0.5	31	1.28	0.69–2.38	1.24	0.70–2.18	31	1.11	0.57–2.16	1.07	0.57–2.01	31	1.13	0.64–2.00	1.09	0.65–1.82

Note: Model 1: adjusted for age and parental education at baseline, follow-up length, and marital status at adulthood. BMI = body mass index; CI = confidence interval; RR = risk ratio.
[a] Women answered yes to any one of the two related infertility questions.

He. Childhood obesity and infertility. Fertil Steril 2016.

FIGURE 2



Relative risk (RR) of infertility and childhood body mass index (BMI) *z* score, adjusting for age, parental status at baseline, follow-up length, and marital status at adulthood. **(A)** 7- to 11-year-old group; **(B)** 12- to 15-year-old group. The *dashed line* indicates an RR of 1. The *green lines* indicate the RR for the association between childhood BMI *z* score and adult infertility. The *blue and red lines* indicate the upper and lower bounds of the 95% confidence interval for the association. The axes on the graph go from 5th to 95th percentile of the childhood BMI *z* score distribution, which range from -1.28 to 1.57 in 7–11 years age group **(A)** and from -1.38 to 1.69 in 12–15 years age group **(B)**.

Hc. Childhood obesity and infertility. Fertil Steril 2018.

DISCUSSION

Our findings indicate that being obese before the age of 12 years is associated with impaired fertility in later life and a U-shaped relationship between childhood BMI *z* score and infertility. A previous study (21) also suggested an inverted U-shaped between BMI in adolescence and the number of children conceived. Some evidence suggests that body fat distribution in women may have more impact on fertility than obesity (22), but our results did not support this association in relation to children's WHtR. No appreciable differences in the associations of waist circumference, waist-to-hip ratio, and abdominal obesity in childhood were found with later infertility in adulthood.

Current evidence on the association of childhood obesity and adult infertility is not consistent. Similar to our finding, a study from the United States (8) reported that obesity before age 12 years was associated with an increased likelihood of having ever tried to become pregnant without success. In contrast, the analysis from a British cohort study (7) showed that weight during childhood did not predict subsequent fecundity, but it did find that obesity at the age of 7 years was associated with increased menstrual irregularities by age 33 years. The reasons for the inconsistent results may be the use of different methods to sample study populations (e.g., the British cohort study was limited to women with a live birth from their first pregnancy).

The explanation for the difference in associations by age group is unclear but there may be cumulative impacts of childhood obesity on adult infertility whereby girls who are obese at a younger age (i.e., 7–11 years in this study) have more impaired fertility, and/or that the prepubertal phase is a more sensitive window for the effects of high BMI on the development of reproductive capacity than later pubertal or postpubertal stages of development. A recent study (23) in rodents suggests that early-onset obesity induces reproductive deficits in adult female rats by reducing the number of oocyte and preantral follicles and inhibiting the LH surge. In humans, early-onset obesity is associated with the earlier puberty and earlier maturation of the hypothalamopituitary axis, which may impact on the development of the reproductive system in girls (24). Increased estrogen (E) produced by more body fat and accelerated aromatization of adrenal and ovarian androgens in adipose tissue promotes earlier adrenarche, pubarche, and thelarche, which may have unfavorable influences on the hypothalamopituitary axis, ovarian function, oocyte quality, endometrial receptivity, or any combination of these factors in the long-term (25). In addition, obesity in childhood is an important factor contributing to the presence and severity of PCOS in adolescents, which may increase the risk of subsequent anovulatory infertility (26–28). In our study, we failed to detect an association between elevated level of childhood adiposity and infertility due to ovulatory dysfunction. It is plausible that obesity disrupts endocrine homeostasis with long-term effects on infertility. However, the mechanisms involved in reducing reproductive potential are still poorly understood.

Our finding that endometriosis as a cause of infertility was less common in those in the childhood overweight/obese group (3.5%) than in the normal weight group (15.1%) was similar to findings from a recent meta-analysis (29), which pooled 11 studies of participants with ages ranging from 16–65 years and reported that more elevated BMI was associated with a lower risk of endometriosis in adulthood. Furthermore, results from our sensitivity analysis suggest that male factor infertility did not bias the observed association between childhood obesity and infertility in adulthood.

The strengths of our study are a relatively contemporary cohort with childhood body composition measurements taken in 1985 and follow-ups conducted during women's reproductive years. Although the Bogalusa Heart Study measured

skinfolds in childhood, to our knowledge our study is the first to have reported the associations of various abdominal obesity indicators in childhood with adult infertility including waist circumference, waist-to-hip ratio, and WHtR. In addition, our definition of having difficulty conceiving specified a time interval of having tried for ≥12 months and is more consistent with definitions used in clinical practice (30). In addition, we demonstrated associations with infertility of BMI *z* score as a continuous variable as well as obesity defined by age- and sex-specific BMI ≥95th percentile.

Some limitations should be acknowledged. First, the sample size in the childhood obese group is small. The prevalence of obesity in girls using international BMI cutpoints was only 1.1%. However, similar findings were shown with continuous BMI *z* scores and sensitivity analyses in our study. Second, we could not distinguish primary infertility (no prior pregnancies) and secondary infertility (infertility after at least one prior conception), which is important for evaluating women's ability to have children and exploring the etiology of infertility. Third, our measure of infertility relied on self-reported problems. However, the prevalence of infertility in our study is consistent with Australian estimates of approximately one in six couples experiencing a delay of ≥12 months to achieve a planned pregnancy during their reproductive life (31, 32). Although infertility diagnoses and investigations are self-reported, these are likely to be important events for women, and women should be able to recall specific diagnoses and investigations that have been undertaken.

In conclusion, our study of a cohort of Australian women indicated a detrimental impact of childhood obesity before age 12 years on infertility later in life. The early prevention of childhood obesity is important for fertility, as well as disease prevention.

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SEMINAL CONTRIBUTION

Asociación de obesidad infantil con infertilidad femenina en la edad adulta: Un estudio de 25 años de seguimiento

Objetivo: Evaluar si la obesidad infantil se asocia a infertilidad en mujeres en edad reproductiva.

Diseño: Estudio prospectivo longitudinal.

Entorno: No aplica.

Intervención(es): Ninguna.

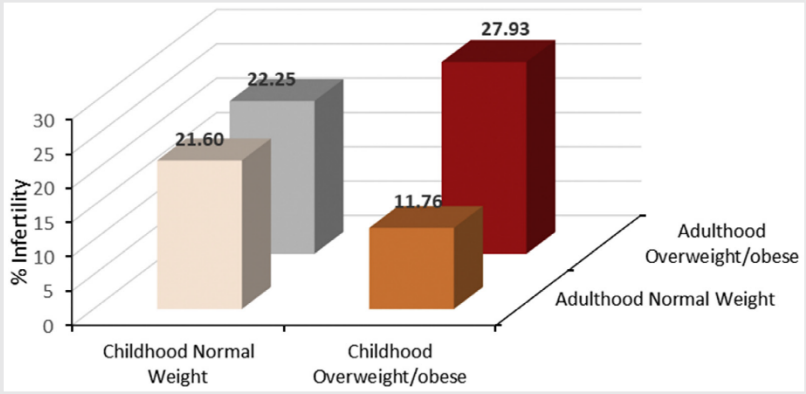
Paciente(s): Un total de 1544 niñas, con edades entre 7-15 años en 1985, y que completaron cuestionarios en seguimientos en 2004-2006 y/o 2009-2011.

Principales medidas de resultados: La infertilidad fue definida como tener dificultad para concebir (haber intentado conseguir embarazo durante ≥ 12 meses sin éxito), o haber visitado al médico por problemas para conseguir embarazo).

Resultado(s): A las edades de 7-11 años, las niñas en los límites inferior y superior del índice de masa corporal (IMC) tuvieron un riesgo incrementado de infertilidad. Comparadas con las niñas con peso corporal normal, aquellas con obesidad a las edades de 7-11 años fueron más propensas a reportar infertilidad en la edad adulta (riesgo relativo ajustado [aRR] = 2,94, 95% intervalo de confianza [IC] 1,48-5,84), dificultad para concebir (aRR = 3,89, 95% IC 1,95-7,77), o haber visitado a un médico por problemas para conseguir embarazo (aRR = 3,65, 95% IC 1,90-7,02) después de ajustar para edad infantil, duración del seguimiento, mayor educación de los padres y estado civil.

Conclusión: La obesidad infantil antes de los 12 años parece aumentar el riesgo de infertilidad femenina en la vida posterior.

SUPPLEMENTAL FIGURE 1



Percentage of reported infertility across adiposity status from childhood to adulthood.

He. Childhood obesity and infertility. Fertil Steril 2018.

Appendix E 2 Publication of Chapter 4

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Associations of childhood adiposity and changes in adiposity status from childhood to adulthood with pregnancy hypertension☆

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ABSTRACT

Objective(s): To investigate the associations between adiposity in childhood, and adiposity change from childhood to adulthood, with pregnancy hypertension.
Study Design: The study followed-up 985 girls from the 1985 Australian Schools Health and Fitness Survey (aged 9–15 years) who were ever pregnant in 2004–2006 and/or 2009–2011. In childhood, overweight and obesity were defined by age-sex-specific international standard for body mass index (BMI) and in adulthood as BMI ≥ 25 kg/m^2. Childhood and adult abdominal obesity were defined as waist-to-height ratio (WHtR) ≥ 0.5. A subsample of adults had abdominal obesity measures (n = 549).
Main outcome measures: Pregnancy hypertension was self-reported as having had high blood pressure during or due to pregnancy.
Results: Childhood overweight/obesity (relative risk [RR] = 1.66, 95% confidence interval [CI]:1.07–2.52) and abdominal obesity (RR = 2.55, 95% CI:1.34–4.85) were associated with higher risks of pregnancy hypertension after adjustment for age, socioeconomic status and parity. Further adjustment for adult BMI attenuated the association for childhood overweight/obesity which was no longer statistically significant (RR = 1.28, 95% CI:0.79–2.07). The association with childhood abdominal obesity persisted after adjustment for adult WHtR (RR = 2.15, 95% CI:1.10–4.20). Compared to participants with persistently normal BMI or WHtR, those who were overweight/obese in adulthood only (RR = 1.49, 95% CI:1.10–2.02), persistently overweight/obese (RR = 2.06, 95% CI:1.29–3.29) or persistently abdominally obese (RR = 3.09, 95% CI:1.54–6.20) had increased risks of pregnancy hypertension.
Conclusion(s): Childhood adiposity was associated with increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult abdominal obesity. Women who were persistently overweight/obese or abdominally obese since childhood had the highest risk of pregnancy hypertension.

1. Introduction

Hypertension affects an estimated 10% of all pregnancies and is the most frequently identified medical problem during pregnancy. Hypertensive disorders of pregnancy include both pregnancy-induced (gestational hypertension and preeclampsia) and pre-existing (chronic hypertension) conditions and are associated with a higher risk of cardiovascular events later in life [1].

Being overweight or obese puts a woman at risk of developing pregnancy hypertension. The risk of preeclampsia doubles with each 5–7 unit increase in pre-pregnancy body mass index (BMI) [2]. Abdominal obesity has also been associated with pregnancy hypertension. The results from one Australian cohort indicated that every 1 cm increase in waist circumference was associated with a 4% increased risk of pregnancy hypertension [3]. Another case-control study indicated that waist circumference was a better predictor of pregnancy hypertension than BMI [4]. Despite the known detrimental effect of adult adiposity on pregnancy hypertension, the relationship with childhood

Abbreviations: ASHFS, Australian Schools Health and Fitness Survey; BMI, Body Mass Index; CI, Confidence Interval; CDAH, Childhood Determinants of Adult Health; DBP, Diastolic Blood Pressure; GEE, generalized estimating equations; RR, Relative Risk; WHtR, Waist-to-height Ratio; SBP, Systolic Blood Pressure; SD, Standard Deviation

☆ **Previous presentation:** The abstract was presented at the XXIII Annual Congress of Perinatal Society of Australian and New Zealand from 17th-20th March 2019 in Gold Coast, Australia.

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Appendices

obesity, especially childhood abdominal obesity with pregnancy hypertension is less well understood.

To our knowledge, only two studies have reported a longitudinal relationship between childhood obesity and pregnancy hypertension, and childhood BMI was the only predictor [5–6]. The 1958 British birth cohort study included 4,681 girls and reported that being overweight or obese at the age of 7 years increased the risk of self-reported hypertension in pregnancy before age 33, but this risk did not persist after adjustment for adult BMI [5]. More recently, a report based on 703 participants in the USA Bogalusa Heart Study showed that elevated childhood BMI was a significant risk factor for self-reported pregnancy hypertension without considering adult BMI.

Therefore, the aim of our present study was to examine the association between different adiposity measures in childhood and changes in adiposity status from childhood to adulthood, with pregnancy hypertension.

2. Materials and methods

2.1. Participants

The Childhood Determinants of Adult Health (CDAH) Study is a follow-up of 8,498 children including 4,191 girls aged 7–15 years who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS), a nationwide sample of Australian school children. [7] In 1985, all children had physical assessments and those aged 9, 12 and 15 years had blood pressure measured. During 2002–2004, a total of 3,412 female participants were traced and 2,734 enrolled to participate in the CDAH Study (enrolment) (Fig. 1). During 2004–2006, the first follow-up (CDAH-1) of those enrolled was conducted when participants were aged 26–36 years. Of the 1,017 women who reported having ever been pregnant and answered questions about pregnancy hypertension in the questionnaire, 735 attended one of 34 study clinics held around Australia for physical measurements. The second follow-up (CDAH-2) was conducted during 2009–2011 when participants were aged 31–41 years and 901 reported having ever been pregnant women and completed the same questions about pregnancy hypertension. A total of 1,324 women who were ever pregnant and answered the pregnancy hypertension questions at CDAH-1 and/or CDAH-2 were included in the analysis reported here (423 women only participated in CDAH-1, 307 women only participated in CDAH-2 and 594 women participated in both CDAH-1 and CDAH-2).

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

2.2. Childhood adiposity measures

BMI, calculated as weight (kg)/height $(m)^2$, was derived from measured height and weight. Overweight and obese were combined for analysis and defined using international age- and sex-specific cut-points for BMI [8]. Waist and hip circumference were measured to the nearest 0.1 cm. Waist-to-hip ratio was calculated by dividing waist by hip circumference. Waist-to-height ratio (WHtR) was calculated by dividing waist circumference by height. Abdominal obesity was defined as WHtR $\geq$ 0.5 [9]. Childhood BMI and waist circumference z scores were calculated based on age- and sex-specific standardization of the full childhood cohort.

2.3. Adult adiposity measures

At CDAH-1, weight, height, waist circumference and hip circumference were measured at study clinics for most participants. Some participants (n = 1,119) also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. Participants who did not visit clinics self-reported their weight and height, and a correction factor was applied to adjust for error [10]. BMI (kg/m^2) was calculated from height and weight. WHtR was calculated from measured waist circumference and height at clinics.

Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the correction factor applied at CDAH-1. Height was self-reported and adjusted as described above.

Adult BMI was categorized as normal (BMI $<$ 25 kg/m^2), overweight (25.0 $\leq$ BMI $\leq$ 29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) [11]. Adult abdominal obesity was defined as WHtR $\geq$ 0.5 [12].

2.4. Pregnancy hypertension

In CDAH-1 and CDAH-2, women were asked to answer 'yes' or 'no' to the question 'Have you ever been told that you have high blood pressure during pregnancy or due to pregnancy?' Pregnancy hypertension was recorded if they responded 'yes'.

2.5. Covariate measures

Information on sociodemographic characteristics was self-reported in childhood and follow-up including childhood age, parental education, parental smoking and childhood smoking experimentation, both childhood and adult area-level disadvantage [13], alcohol consumption, physical activity and adult education level, smoking status, occupation and parity.

2.6. Statistical analyses

Taking into account the repeated measures of variables over CDAH-1 and CDAH-2, log-binomial models with generalized estimating equations (GEE) were used to estimate relative risk (RR) for associations between childhood adiposity measures and change in adiposity status from childhood to adulthood with pregnancy hypertension. Subsample analysis was conducted among those with measured adult waist circumference and height at the CDAH-1 clinics.

The independent effects of childhood BMI and childhood abdominal obesity measures on pregnancy hypertension were examined by including corresponding adult BMI and adult abdominal obesity measures (for the subsample only) in the models. In addition, as abdominal obesity had been suggested to be a stronger predictor of cardiovascular disease than BMI [12,14], in the current study, childhood abdominal obesity measures were further adjusted for childhood and adult BMI to investigate the effects of fat distribution in childhood on pregnancy hypertension more specifically. Covariates remaining in the final model were variables which associated with the exposure and the outcome and resulted in more than 10% change in the coefficient of the study factor.

The following sensitivity analyses were conducted. First, we excluded those who reported 'yes' to ever having pregnancy hypertension in CDAH-1 but 'no' in CDAH-2. Second, since multiple births and high childhood blood pressure may be associated with increased risk of pregnancy hypertension [15–16], we restricted our sample to women who had singleton pregnancies and those who had measured childhood systolic (SBP) and diastolic blood pressure (DBP). Third, to investigate whether high blood pressure persisted post-pregnancy in those with a history of pregnancy hypertension, we compared blood pressure in a subsample of women (n = 609) who had participated in the first follow-up (CDAH-1) clinics and had measured systolic and diastolic blood pressure. Fourth, inverse probability weighting was used to account for missing data at follow-up, with multiple imputation of incomplete baseline data [17].

Finally, to examine if there is a difference in risk of pregnancy hypertension associated with adiposity during different time periods of growth, we repeated the analyses by stratifying childhood age before or after 12 years.

Appendices

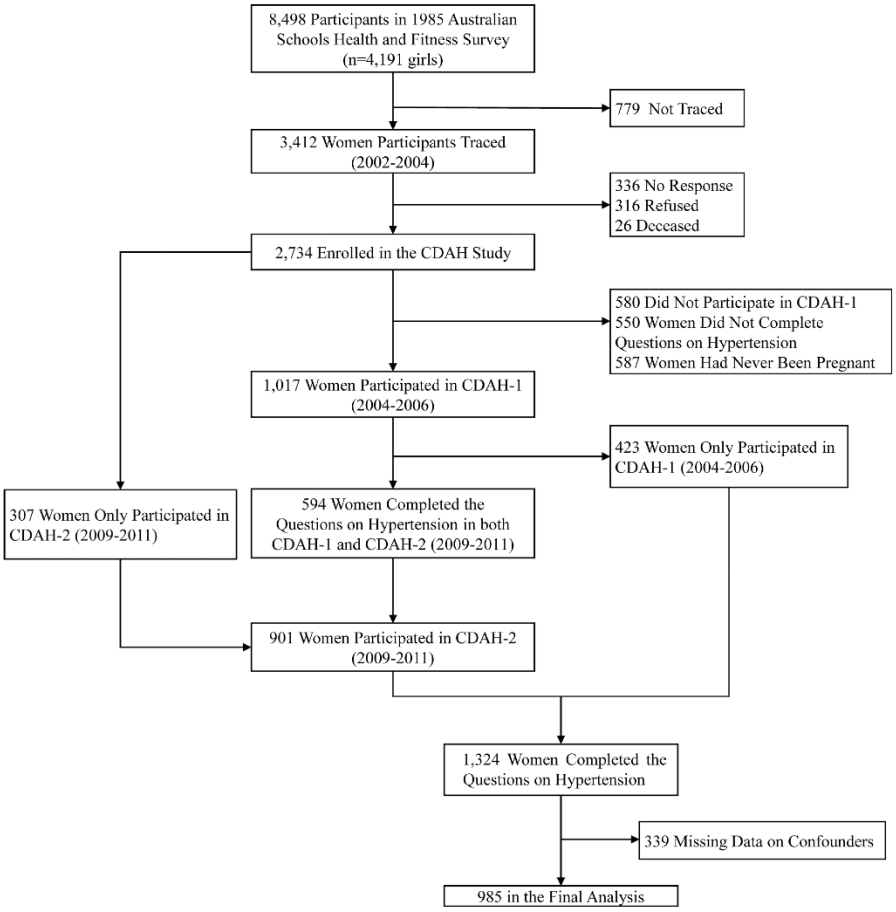

Fig. 1. Selection of participants for the Childhood Determinants of Adult Health (CDAH) Study.

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

3. Results

3.1. Participant characteristics

This study included 1,324 women who had ever been pregnant and completed hypertension questions at follow-ups; 594 of them completed both follow-ups; 423 participated in CDAH-1 only; and 307 women participated in CDAH-2 only. Participants who had missing data on confounders (n = 339) were excluded, leaving 985 women for the final analysis. A total of 549 women with measured waist circumference and height at the CDAH-1 clinics were included in the subsample analysis.

Characteristics of participants in childhood and adulthood are shown in Table 1. In childhood, 10 (1.0%) girls were obese, 77 (7.8%) were overweight as defined by BMI cutoffs, and 47 (4.8%) had abdominal obesity as defined by WHtR category. The mean age at CDAH-1 was 32.8 years and 37.5 years at CDAH-2. There were 111 (13.8%) and 68 (10.6%) women who reported experiencing pregnancy hypertension in CDAH-1 and CDAH-2. Among them 21 women reported having had pregnancy hypertension in CDAH-1 but not in CDAH-2.

Compared with those who did not participate in CDAH-1 or CDAH-2, those who did participate in CDAH-1 and/or CDAH-2 were older in childhood (12.1 vs 10.5 years; $P < 0.001$), had greater BMI (18.8 vs 18.2 kg/m^2; $P < 0.001$) and waist circumference (64.1 vs 62.1 cm; $P < 0.001$), lower WHtR (0.42 vs 0.44; $P < 0.001$) and waist-to-hip ratio (0.80 vs 0.82; $P < 0.001$), and were less likely to be obese (1.0% vs 1.8%; $P = 0.001$) or abdominally obese (4.8% vs 7.9%; $P = 0.001$).

3.2. Pregnancy hypertension

As shown in Table 2, after adjustment for age, area-level disadvantage in childhood, parity and occupation in adulthood, childhood overweight/obese and abdominal obesity measures were all associated with an increased risk of pregnancy hypertension (Model 1). To determine whether childhood abdominal obesity measures contributed to the risks of pregnancy hypertension were independent of childhood

Appendices

Table 1
Characteristics of participants in childhood (1985), CDAH-1 (2004–2006) and CDAH-2 (2009–2011), Childhood Determinants of Adult Health study.[a]

Characteristics[b]	Childhood (n = 985)	CDAH-1 (n = 806)	CDAH-2 (n = 641)
Age, years, Mean(SD)	12.1(2.0)	32.8(2.0)	37.5(2.0)
BMI, kg/m^2, Mean(SD)	18.8(2.8)	25.0(5.1)	25.2(5.5)
Waist circumference, cm, Mean(SD)	64.1(7.5)	79.3(10.9)	
Waist-to-height ratio, Mean(SD)	0.42(0.04)	0.48(0.07)	
Waist-to-hip ratio, Mean(SD)	0.80(0.06)	0.76(0.06)	
BMI category (%)			
Normal	91.2	60.7	59.9
Overweight	7.8	24.8	22.9
Obese	1.0	14.5	17.2
WHtR category (%)			
< 0.5	95.2	69.0	
≥0.5	4.8	31.0	
Area-level disadvantage (%)			
High	26.9	27.3	25.7
Medium-high	28.9	25.0	24.7
Medium-low	38.2	22.5	23.8
Low	6.0	25.2	25.8
Highest parental education (%)			
University education	23.3		
Vocational training	35.0		
High school	41.7		
Childhood smoking experimentation (%)			
None	56.1		
A few puffs	21.7		
< 10 cigarettes	8.5		
greater than10 cigarettes	13.8		
Parental smoking (%)			
None	57.8		
Either parent smoked	26.8		
Both parents smoked	15.4		
Childhood alcohol assumption (%)			
Never	67.6		
Less than once per week	26.3		
More than once per week	6.1		
Physical activity, mins/week, Mean(SD)[c]	406.7(365.7)	784.3(502.0)	819.4(507.0)
Systolic blood pressure, mmHg, Mean(SD)	108.9(12.0)		
Diastolic blood pressure, mmHg, Mean(SD)	66.6(11.0)		
Adulthood smoking status (%)			
Never smoker		49.7	56.1
Ex-smoker		28.0	30.4
Current smoker		22.4	13.5
Highest education attainment (%)			
University education		36.6	46.2
Vocational training		26.8	27.7
High school		36.6	26.1
Adulthood alcohol consumption (%)			
Non-drinkers		23.6	22.6
Light drinkers		56.8	57.8
Moderate drinkers		14.5	14.9
Heavy/very heavy drinkers		5.2	4.7
Occupation (%)			
Professional or manager		38.8	43.7
Nonmanual		28.3	27.6
Manual		5.5	6.1
Not in the labor force		27.4	22.6
Parity, Mean(SD)		1.6(1.0)	2.1(1.0)
Pregnancy hypertension (%)		13.8	10.6

Abbreviations: BMI, body mass index; CDAH, Childhood Determinants of Adult Health Study; SD, standard deviation; WHtR, waist-to-height ratio.

[a] Childhood overweight and obesity were defined according to the international cutoffs; the final sample (n = 985) included participants who participated in CDAH-1 (n = 806) or CDAH-2 (n = 641).

[b] Sample size in Childhood ranges from 415 to 985, CDAH-1 ranges from 549 to 806, CDAH-2 ranges from 596 to 641 due to missing data on some variables;

[c] Childhood physical activity was assessed by Australia Health and Fitness Survey, 1985; CDAH-1 and CDAH-2 physical activity was assessed by International Physical Activity Questionnaire;

Appendices

Table 2
Associations between adiposity measures in childhood with pregnancy hypertension, Childhood Determinants of Adult Health study.

Body composition	n	Unadjusted model		Model 1		Model 2		Model 3	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI (kg/m^2)	985	**1.06**	**1.01–1.12**	**1.08**	**1.02–1.14**			1.04	0.97–1.11
BMI z score	985	**1.19**	**1.03–1.38**	**1.20**	**1.04–1.40**			1.09	0.92–1.30
BMI category									
Normal	898	Ref.	–	Ref.	–			Ref.	–
Overweight/obese	87	**1.64**	**1.05–2.49**	**1.66**	**1.07–2.57**			1.28	0.79–2.07
Waist circumference (cm)	985	**1.03**	**1.01–1.05**	**1.04**	**1.02–1.06**	**1.04**	**1.01–1.07**	**1.03**	**1.00–1.07**
Waist circumference z score	985	**1.28**	**1.11–1.41**	**1.29**	**1.12–1.49**	**1.28**	**1.01–1.61**	1.25	0.99–1.57
Waist circumference, per SD (7.51 cm)	985	**1.26**	**1.10–1.44**	**1.32**	**1.14–1.54**	**1.33**	**1.04–1.69**	**1.29**	**1.01–1.65**
Waist-to-hip ratio, per SD (0.06)	985	**1.22**	**1.05–1.42**	**1.25**	**1.07–1.47**	**1.22**	**1.04–1.43**	**1.20**	**1.03–1.41**
Waist-to-height ratio, per SD (0.04)	985	**1.33**	**1.17–1.51**	**1.33**	**1.15–1.53**	**1.35**	**1.09–1.67**	**1.24**	**1.06–1.43**
WHtR category									
< 0.5	938	Ref.	–	Ref.	–	Ref.	–	Ref.	–
≥ 0.5	47	**2.33**	**1.45–3.74**	**2.54**	**1.61–4.01**	**2.14**	**1.18–3.87**	**2.21**	**1.09–4.48**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Model 2: adjusted for age, area-level disadvantage and body mass index at childhood, parity and occupation at adulthood;
Model 3: adjusted for age, area-level disadvantage and body mass index at childhood (for abdominal obesity measures only), parity, occupation and body mass index at adulthood;
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

Table 3
Associations between abdominal measures in childhood with pregnancy hypertension in CDAH-1 clinic participants, Childhood Determinants of Adult Health study.

Body composition	n	Unadjusted model		Model 1		Model 2	
		RR	95% CI	RR	95% CI	RR	95% CI
Waist circumference (cm)	549	**1.03**	**1.00–1.06**	**1.04**	**1.01–1.07**	1.03	1.00–1.07
Waist circumference z score	549	**1.26**	**1.03–1.55**	**1.33**	**1.08–1.65**	1.22	0.96–1.56
Waist circumference, per SD (7.30 cm)	549	**1.22**	**1.01–1.48**	**1.36**	**1.09–1.69**	1.25	0.97–1.60
Waist-to-hip ratio, per SD (0.06)	549	1.15	0.93–1.42	1.21	0.96–1.52	1.20	0.94–1.52
Waist-to-height ratio, per SD (0.04)	549	**1.32**	**1.10–1.58**	**1.34**	**1.11–1.61**	**1.24**	**1.01–1.54**
WHtR category							
< 0.5	526	Ref.	–	Ref.	–	Ref.	–
≥ 0.5	23	**2.29**	**1.19–4.40**	**2.55**	**1.34–4.85**	**2.15**	**1.10–4.20**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Model 2: adjusted for age, area-level disadvantage at childhood, parity, occupation and corresponding abdominal measures at adulthood;
Abbreviations: CI, confidence interval; RR, risk ratio; SD, standard deviation; WHtR, waist-to-height ratio.

Table 4
Relative risk of pregnancy hypertension according to adiposity status from childhood to adulthood, Childhood Determinants of Adult Health Study.

Body composition from childhood to adulthood	n (%)[a]	Pregnancy hypertension			
		Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI
BMI category (N = 985)					
Persistently normal	860(59.4)	Ref.	–	Ref.	–
Normal to overweight/obese	469(32.4)	**1.49**	**1.11–2.01**	**1.49**	**1.10–2.02**
Overweight/obese to normal	13(0.9)	1.00	0.15–6.53	1.09	0.16–7.29
Persistently overweight/obese	105(7.3)	**2.05**	**1.27–3.29**	**2.06**	**1.29–3.29**
WHtR category [b] (N = 549)					
Persistently not abdominally obese	375(68.3)	Ref.	–	Ref.	–
Not abdominally obese to abdominally obese	151(27.5)	**1.56**	**1.00–2.43**	1.43	0.92–2.25
Abdominally obese to not abdominally obese	4(0.7)	2.18	0.39–12.18	2.13	0.40–11.43
Persistently abdominally obese	19(3.5)	**2.75**	**1.34–5.65**	**3.09**	**1.54–6.20**

Model 1: adjusted for age, area-level disadvantage at childhood, parity and occupation at adulthood;
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio; WHtR, waist-height ratio.
[a] n indicated the total number of observations in each BMI category from childhood to CDAH-1 and/or CDAH-2 and the number of participants in each WHtR category from childhood to CDAH-1;
[b] Subgroup analysis which only available in those who participated in 1985 Australian Schools Health and Fitness Survey and CDAH-1 clinics;

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BMI, we further adjusted for childhood BMI (Model 2), the associations between childhood abdominal obesity measures and pregnancy hypertension remained significant. Model 3 included additional adjustment for adult BMI to investigate whether associations with childhood overweight/obese and abdominal obesity measures were independent of adult BMI. Childhood overweight/obese was no longer associated with pregnancy hypertension after adjustment for adult BMI (Model 3). However, associations remained for childhood abdominal obesity measures. In the subsample of participants with measured waist circumference and height at the CDAH-1 clinics (Table 3), childhood abdominal obesity measures were associated with increased risk of pregnancy hypertension (Model 1). When further adjusted for corresponding abdominal measures in adulthood (Model 2), although there remained significant associations with childhood WHtR (RR = 1.24, 95% CI:1.01–1.54) and childhood abdominal obesity (WHtR ≥ 0.5) (RR = 2.15, 95% CI:1.10–4.20), these associations were attenuated with adjustment for adult WHtR.

3.3. Influence of adiposity change from childhood to adulthood

The relative risk of pregnancy hypertension by BMI and WHtR category change from childhood to adulthood is displayed in Table 4. Compared with participants who had persistently normal BMI in childhood and adulthood, those who became overweight/obese reported a higher risk of pregnancy hypertension with a RR of 1.49 (95% CI 1.10–2.02). The risk was highest for participants who were persistently overweight/obese from childhood into adulthood (RR = 2.06; 95% CI 1.29–3.29). In the subsample of participants who had WHtR data in both childhood and adulthood (N = 549), 19 (3.5%) were abdominally obese in both childhood and adulthood and 31.6% of them had pregnancy hypertension (Fig. 2). Compared with those who were not abdominally obese in childhood and adulthood (68.3% of the subset, 11.5% with pregnancy hypertension), those who were persistently abdominally obese had a significantly higher risk of pregnancy hypertension (RR = 3.09; 95% CI: 1.54–6.20) (Table 3). Subjects who were not abdominally obese in childhood but who developed abdominal obesity in adulthood (27.5%) also had a higher risk of pregnancy hypertension (RR = 1.56; 95% CI 1.00–2.43), but the significance of this association was attenuated after adjustment for confounders.

3.4. Sensitivity analysis

Similar results were observed after excluding women who reported they had pregnancy hypertension in CDAH-1 but not in CDAH-2 (n = 231). When restricting the sample to women with singleton pregnancies, the risk of pregnancy hypertension (RR = 2.55, 95% CI 1.28–5.09) remained significantly higher in those who were abdominally obese in childhood. A total of 415 girls aged 9, 12 and 15 years had blood pressure measured in childhood. The mean childhood SBP and DBP were similar in those with and without self-reported pregnancy hypertension in CDAH-1 (SBP: 110.4 ± 14.8 vs 109.0 ± 11.8, $P = 0.50$; DBP: 65.4 ± 12.2 vs 66.8 ± 10.8, $P = 0.43$) and CDAH-2 (SBP: 112.6 ± 12.7 vs 108.5 ± 11.8, $P = 0.06$; DBP: 67.8 ± 11.1 vs 66.1 ± 10.6, $P = 0.38$). Further adjustment for childhood SBP and DBP in these participants did not substantially change the main results: the changes in the magnitude of estimates were within 17.2% (Supplemental Table 1). In the subsample of women (n = 609) who had participated in the first follow-up (CDAH-1) clinics and had measured blood pressure, we found that compared with women who did not report pregnancy hypertension, those who reported ever having had pregnancy hypertension had significantly higher SBP (116.7 vs 110.0 mmHg, P < 0.001), and DBP (74.7 vs 68.7 mmHg, P < 0.001) and higher prevalence of hypertension (9.5% vs 1.1%, P < 0.001). Sensitivity analyses to address loss to follow-up by using combined multiple imputation and inverse probability weighting produced similar patterns of results as the unweighted analyses: changes in the magnitude of significant associations ranging from −23.5 to 58.0% (Supplemental Table 2).

When stratified by age, childhood BMI and BMI z score showed similar associations in 12 to 15 year-olds (RR = 1.07, 95% CI:1.00–1.15; RR = 1.21, 95% CI:1.00–1.45) to those younger than 12 years (RR = 1.09, 95% CI:0.99–1.19; RR = 1.20, 95% CI:0.94–1.53). However, the observed statistically significant association in the 12 to 15 year age group did not persist after further adjustment for adult BMI. In a subsample analysis, a stronger association with pregnancy hypertension was found with abdominal obesity before age 12 (RR = 5.38, 95% CI:2.67–10.82) than age 12–15 years (RR = 1.48, 95% CI:0.52–4.27). The significant associations with abdominal obesity before age 12 persisted after adjustment for adult WHtR (RR = 5.36, 95% CI:2.68–10.73).

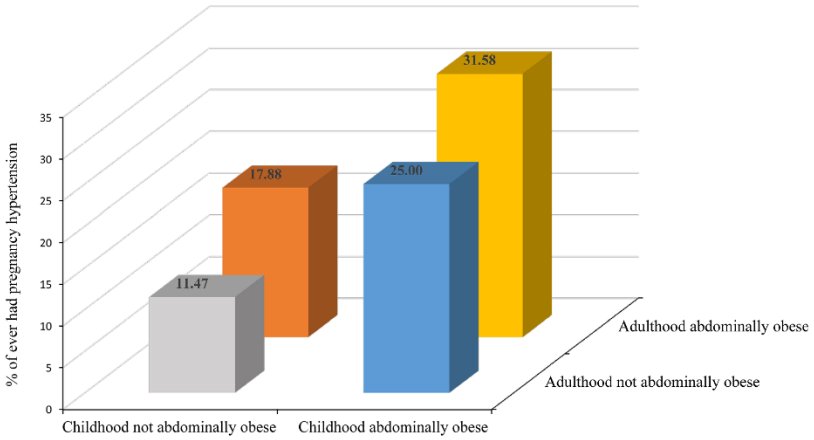

Fig. 2. Percentage of ever had pregnancy hypertension across abdominal obesity category from childhood to adulthood, Childhood Determinants of Adult Health Study.

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4. Discussion

To the best of our knowledge, this is the first study to report the long-term associations of childhood abdominal obesity and change in body composition from childhood to adulthood with pregnancy hypertension. We found that childhood abdominal obesity was associated with an increased risk of pregnancy hypertension. This association persisted after adjustment for adult abdominal obesity. Persistent overweight/obesity and abdominal obesity were associated with the highest risk of pregnancy hypertension.

Our finding that the association of childhood BMI with pregnancy hypertension was not independent of adult BMI was consistent with findings from the 1958 British birth cohort study [5] and that overweight/obesity that is proximal to pregnancy is especially important for pregnancy hypertension risk. A higher risk was found for women who were persistently overweight/obese in childhood and adulthood than those who became overweight/obese as adults, even though the difference did not reach statistical significance. This may be explained by the higher BMI in adulthood among those with persistently high adiposity status from childhood to adulthood than in those who had a normal BMI as children and were overweight/obese as adults (33.2 vs 29.5, $P < 0.001$).

Although childhood abdominal obesity has been observed in several cross-sectional studies to be associated with cardio-metabolic risk in childhood [12,18–20], the current understanding of the long-term effect of abdominal obesity on chronic conditions including pregnancy hypertension remains limited. Most studies from childhood have followed participants into adulthood and collected BMI due to ease of measurement. In our study, one SD of 0.04 unit increase in childhood WHtR was associated with 33% greater likelihood of reporting pregnancy hypertension and was largely unchanged after adjusting for childhood and adulthood BMI. Similar results were found in a subsample with adult abdominal obesity measures, the associations of childhood WHtR persisted with further adjustment for adult WHtR. These results indicated a detrimental impact of childhood abdominal obesity on the risk of pregnancy hypertension, which was not modified by BMI or adult abdominal obesity. It has been suggested that early onset obesity may have higher risks of adverse outcomes in later life [21]. Consistent with this we observed stronger associations with childhood abdominal obesity in girls younger than age 12 than in older girls. In the Bogalusa Heart Study, a stronger association of childhood BMI with pregnancy hypertension was reported between ages 12 to 17 than before age 12. In our study, similar associations of childhood BMI with pregnancy hypertension were found in these younger than age 12 and age 12 to 15 after accounting for adult BMI.

The exact mechanism by which childhood abdominal obesity influences risk of pregnancy hypertension remains unclear. Plausible mechanisms include the long-term adverse effects of excess childhood visceral fat on blood pressure, insulin resistance, inflammation upregulation, oxidative stress and endothelial dysfunction [22–25].

Some potential limitations of our study are acknowledged. The first is the measurement of pregnancy hypertension and that self-report may lead to misclassification [26,27]. However, the prevalence of pregnancy hypertension in our study is similar to global prevalence [1]. Beyond that, two validation studies to investigate the validity of self-reported pregnancy hypertension show good concordance of self-report with clinical records [26,28]. Second is the loss to follow-up. We applied inverse probability weighting to account for missingness but these did not appreciably change the results. Third is the potential over adjustment of adult BMI and abdominal obesity measures. Our findings were for ever-pregnant women, but we were unable to account for their BMI and abdominal measures immediately prior to pregnancy. Women's weight or waist circumference may increase after pregnancy, however, over adjustment of adult anthropometric measures tend to favor our study results. Fourth, we cannot classify the category of pregnancy hypertension exactly. Preeclampsia is a distinct cause of maternal morbidity and mortality and can lead to further systemic disorders [1]. Future studies that address pre-eclampsia specifically are needed. Finally, we did not have information on whether hypertension persisted beyond delivery. However, our finding of subsequent higher blood pressure and more prevalent hypertension in a subsample of women who reported a history of pregnancy hypertension is consistent with the literature [29,30], indicating that the risk of future chronic hypertension may be increased.

The strengths of our study include the following. Foremost, this is the first prospective study to investigate the long-term association between childhood abdominal obesity measures and pregnancy hypertension. Second, we conducted objective measurement of childhood anthropometrics including childhood BMI and abdominal obesity measures. Third, unlike previous two studies examining childhood BMI and pregnancy hypertension, a range of data on covariates has been collected in our study.

5. Conclusion

Childhood adiposity was associated with increased risk of pregnancy hypertension, with the association of childhood abdominal obesity independent of adult abdominal obesity. Women with persistently high adiposity from childhood to adulthood had the highest risk of pregnancy hypertension. Childhood abdominal obesity may be considered in addition to BMI, as an indicator of the risk of future cardiometabolic conditions including pregnancy hypertension.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.11.006.

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Appendix E 3 Publication of Chapter 5

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human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

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

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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 1516 participants (aged 26–41 years) from the Australian Childhood Determinants of Adult Health study (CDAH) and 1247 participants (aged 26–57 years) from the biracial USA Babies substudy 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.*, 2017; Harris *et al.*, 2018). 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; Wei *et al.*, 2009; Jacobsen *et al.*, 2012; Hahn *et al.*, 2013). 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 (Lake *et al.*, 1997; Laitinen *et al.*, 2003) 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 5770 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 2007 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 8498 school children (4191 girls) aged 7–15 years (Gall *et al.*, 2009) (Fig. 1). During 2004–2006, the first follow-up (CDAH-1) was conducted when participants were 26–36 years and 1598 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 2009–2011 when participants were aged 31–41 years and 1123 participants completed the same questions about menstrual cycles and PCOS. The current study included 1516 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 (World Health Organization, 2006). Waist circumference was taken at the level of the umbilicus to the nearest 0.1 cm. Waist/height ratio (WHtR), calculated

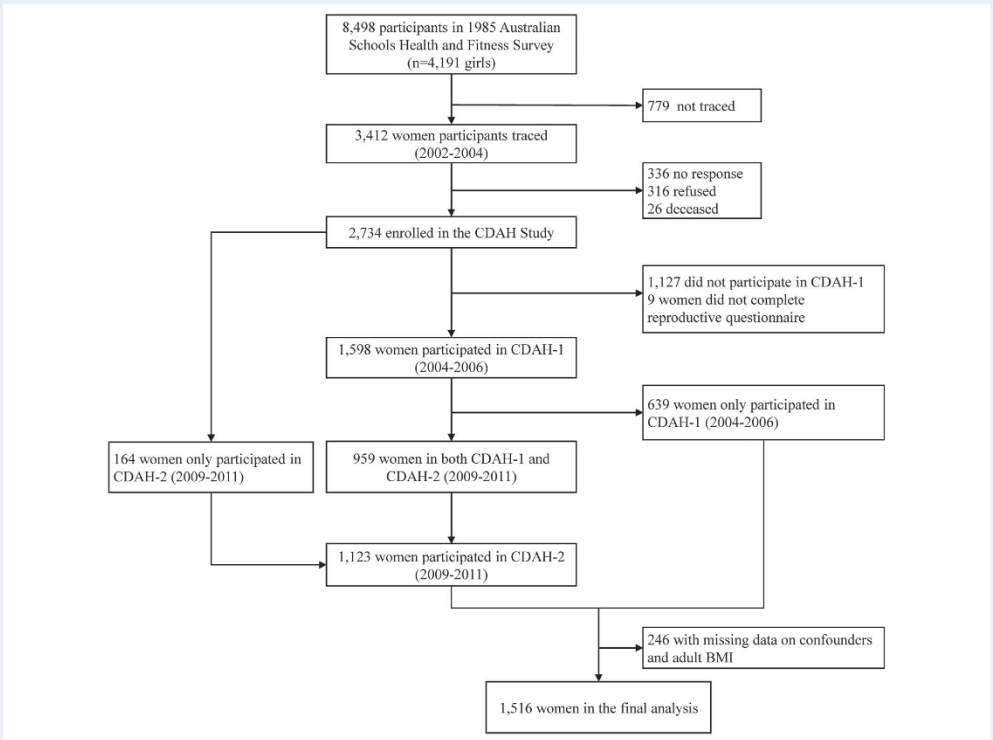

Figure 1 Flow chart of the study population for the Childhood Determinants of Adult Health Study in Australia, 1985–2011. CDAH: Childhood Determinants of Adult Health.

as waist circumference divided by height (cm), was the indicator of abdominal obesity when WHtR $\geq$ 0.5 (Brambilla *et al.*, 2013).

Adult anthropometric measurements

Participants who attended CDAH-1 clinics (n = 2329) had weight, height and waist circumference measured. Participants who did not visit clinics (n = 1556) 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 $\leq$ BMI $\leq$ 29.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) (World Health Organization, 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 $\geq$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 $\geq$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 $\geq$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),

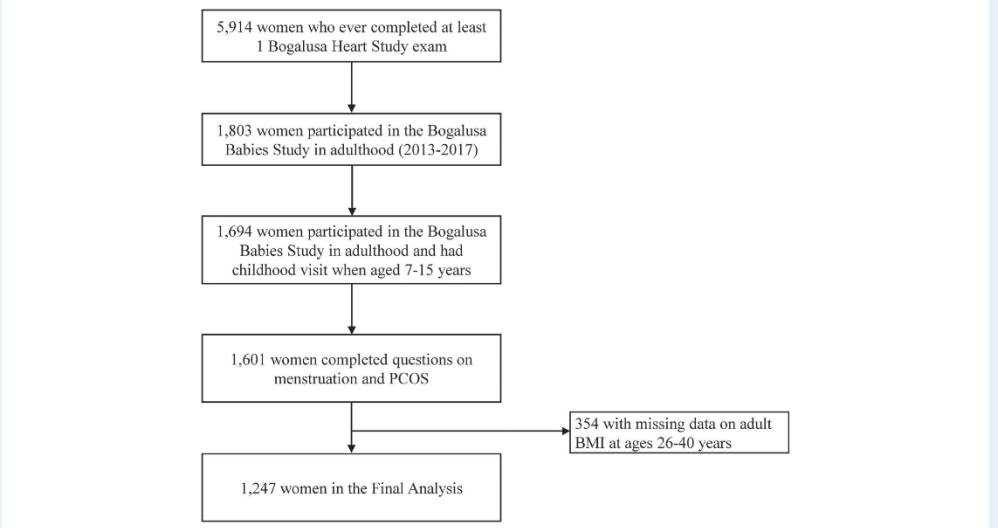

Figure 2 Flow chart of the study population for the Bogalusa Heart Study in the USA, 1973–2017. PCOS: polycystic ovary syndrome.

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 substudy (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 ($n = 5914$) were eligible to participate. We included 1247 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 0.1 cm or 0.1 kg 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 three to four 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, ~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 birth weight *z*-score and BMI *z*-score in childhood in a subsample of BBS ($n = 788$) with the relevant information on birth weight 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 (cFT) levels (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 1516 participants from the CDAH study and 1247 (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, sand 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 3-fold in those who were obese in childhood. Similarly, in the BBS, when further adjusted for race, childhood obesity was associated with nearly twice the risk of having menstrual irregularity.

Childhood adiposity and self-reported PCOS

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

Table 1 Participants' characteristics in the Childhood Determinants of Adult Health Study and the Babies substudy of the Bogalusa Heart Study[a].

Variable	CDAH ($n = 1516$)			BBS ($n = 1247$)	
	Childhood	Adulthood		Childhood	Adulthood
		CDAH-1	CDAH-2		BBS
Race, % (*n*)					
White				58.5(730)	
Black				41.5(517)	
Age, years, mean (SD)[b]	11.0 (2.5)	31.5 (2.6)	36.4 (2.6)	11.6(2.0)	44.1(7.9)
BMI, kg/m^2, mean (SD)[b]	18.2 (2.8)	24.9 (5.2)	25.4 (5.5)	19.5(4.0)	29.2(7.8)
BMI z-score, mean (SD)[b]	0.16 (0.90)			0.36(1.24)	
BMI category, % (*n*)[b]					
Normal	91.2 (1383)	62.4 (943)	58.7 (505)	74.9(934)	36.2(451)
Overweight	7.7 (116)	23.7 (358)	24.5 (211)	17.6(219)	24.9(310)
Obese	1.1 (17)	14.0 (211)	16.7 (144)	7.5(94)	39.0(486)
Waist/height ratio, mean (SD)[b]	0.43 (0.04)			0.46(0.07)	
WHtR category[b]					
< 0.5	94.7 (1436)			77.6(228)	
≥ 0.5	5.3 (80)			22.5(66)	
Highest parental education, % (*n*)					
University education	28.0 (425)			29.8(334)	
Vocational training	33.5 (508)			21.7(234)	
High school	38.5 (583)			48.5(543)	
Highest own-education, % (*n*)					
University education		46.6 (704)	54.0 (464)		28.1(350)
Vocational training		25.9 (392)	25.4 (218)		33.4(416)
High school		27.5 (416)	20.7 (178)		38.6(481)
Smoking, % (*n*)					
Never smoked	88.2 (1035)	54.7 (827)	59.2 (507)	76.8(763)	53.3(471)
Ever smoked	11.8 (1439)	45.3 (684)	40.8 (350)	23.2(230)	46.7(412)
Alcohol consumption, % (*n*)					
None, light, moderate drinker	99.1 (1166)	93.8 (1398)	95.8 (800)	98.5(400)	82.9(707)
Heavy and very heavy drinker	0.9 (11)	6.2 (93)	4.2 (35)	1.5(6)	17.1(146)
Age at menarche, years, mean (SD)	13.1 (1.3)			12.6(1.5)	
SHBG, nmol/l, mean (SD)[c]		52.1 (27.4)			
Testosterone, nmol/l, mean (SD)[c]		1.5 (0.6)			
Free testosterone, nmol/l, mean (SD)[c]		23.9 (14.0)			
Hirsutism, % (*n*)					
Yes		3.5 (52)	4.0 (34)		6.5(81)
No		96.5 (1439)	96.0 (820)		93.5(1160)
Menstrual irregularity, % (*n*)					
Yes		16.6 (139)	16.7 (87)		24.5(303)
No		83.4 (699)	83.3 (434)		75.5(935)
PCOS (menstrual irregularity+hirsutism), % (*n*)[d]					
Yes		1.5 (12)	1.4 (7)		2.2(27)
No		98.6 (817)	98.7 (513)		97.8(1211)
Self-reported doctor diagnosed PCOS, % (*n*)					
Yes		5.8 (88)	8.2 (70)		6.9(84)

Continued

Table I Continued.

Variable	CDAH ($n = 1516$)		BBS ($n = 1247$)	
	Childhood	Adulthood	Childhood	Adulthood
		CDAH-1	CDAH-2		BBS
No		94.2 (1423)	91.8 (785)		93.2(1142)
PCOS, % (*n*)					
Yes		6.2 (93)	8.6 (74)		8.0(100)
No		93.9 (1419)	91.4 (786)		92.0(1147)

[a]Sample size varied [range from 652–1512 for Childhood Determinants of Adult Health (CDAH) and range from 294–1241 for Babies substudy of the Bogalusa Heart Study (BBS)] because of the missing data
[b]The variables were calculated using the mean values in multiple childhood visits in BBS
[c]Available in a subsample of 622 participants who attended the first follow-up clinic in CDAH
[d]Defined as reporting menstrual cycle ≥ 35 days/totally variable and presenting hirsutism
PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; WHtR, waist/height ratio

Table II Associations of adiposity in childhood with menstrual irregularity in adulthood in CDAH and BBS.

Childhood adiposity	CDAH				BBS			
	Unadjusted model ($n = 1010$)		Model 1 ($n = 1010$)		Unadjusted model ($n = 1238$)		Model 1[a] ($n = 1238$)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.11	0.94–1.31	1.13	0.96–1.34	**1.09**	**1.00–1.18**	1.09	1.00–1.19
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	1.50	0.99–2.28	**1.62**	**1.06–2.48**	1.07	0.88–1.29	1.07	0.88–1.30
Obese	**2.72**	**1.60–4.64**	**2.84**	**1.63–4.96**	**1.43**	**1.08–1.89**	**1.44**	**1.08–1.92**
WHtR, per 0.01 unit[b]	1.03	1.00–1.06	1.03	0.99–1.06	1.03	1.00–1.06	1.03	0.99–1.06
WHtR category[b]								
< 0.5	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥ 0.5	1.44	0.87–2.39	1.47	0.89–2.45	**1.62**	**1.06–2.46**	1.56	1.00–2.45

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education
[a]Model 1 further adjust for race in the BBS
[b]$n = 293$ in BBS
RR, relative risk

with CDAH: childhood obesity was associated with a higher risk of self-reported PCOS and every 0.01 unit increase in WHtR was associated with 8% greater likelihood of PCOS (Table III).

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

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

Influence of weight status from childhood into adulthood

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

Table III Associations of adiposity in childhood with PCOS in adulthood in CDAH and BBS.

Childhood adiposity	CDAH				BBS			
	Unadjusted model ($n = 1516$)		Model 1 ($n = 1516$)		Unadjusted model ($n = 1247$)		Model 1[a] ($n = 1247$)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI z-score	1.25	0.98–1.58	1.26	0.98–1.62	**1.31**	**1.10–1.56**	**1.42**	**1.19–1.69**
BMI category								
Normal	Ref.	—	Ref.	—	Ref.	—	Ref.	—
Overweight	**2.33**	**1.30–4.15**	**2.28**	**1.25–4.16**	**1.73**	**1.21–2.46**	**1.96**	**1.35–2.83**
Obese	3.08	0.85–11.21	**4.05**	**1.10–14.83**	1.68	1.00–2.83	**1.95**	**1.19–3.29**
WHtR, per 0.01 unit[b]	**1.06**	**1.01–1.10**	**1.06**	**1.01–1.11**	1.05	0.98–1.11	**1.06**	**1.01–1.11**
WHtR category[b]								
<0.5	Ref.	—	Ref.	—	Ref.	—	Ref.	—
≥0.5	**2.22**	**1.11–4.42**	**2.26**	**1.16–4.42**	0.99	0.34–2.91	1.09	0.39–3.07

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education
[a]Model 1 further adjust for race in BBS
[b]$n = 294$ in BBS

Table IV Associations of adiposity in childhood with PCOS in adulthood in BBS, by race.

Race and childhood adiposity	n	PCOS			
		Unadjusted model		Model 1	
		RR	95% CI	RR	95% CI
White	730				
BMI z-score		**1.50**	**1.25–1.79**	**1.54**	**1.28–1.87**
BMI category					
Normal		Ref.	—	Ref.	—
Overweight		**2.07**	**1.38–3.11**	**2.19**	**1.42–3.35**
Obese		**2.82**	**1.63–4.86**	**2.93**	**1.65–5.22**
WHtR, per 0.01 unit[a]		**1.08**	**1.04–1.11**	**1.11**	**1.05–1.17**
WHtR category[a]					
<0.5		Ref.	—	Ref.	—
≥0.5		2.00	0.66–6.07	2.00	0.64–6.27
Black	517				
BMI z-score		1.00	0.70–1.43	1.03	0.72–1.47
BMI category					
Normal		Ref.	—	Ref.	—
Overweight		1.36	0.59–3.13	1.43	0.64–8.26
Obese		0.29	0.04–2.35	0.19	0.03–2.78
WHtR, per 0.01 unit[a]		0.89	0.76–1.04	0.88	0.76–1.02
WHtR category[a]					
<0.5		Ref.	—	Ref.	—
≥0.5		N/A		N/A	

Model 1: adjust for childhood age, age at menarche, highest parental education and own-education
[a]$n = 109$ in white race and $n = 185$ in black race in BBS

Table V Associations of weight status change from childhood to adulthood with menstrual irregularity in CDAH and the BBS.

Weight status from childhood to adulthood	CDAH						BBS					
	n	Cases (%)[a]	Unadjusted model		Model I		*n*	Cases (%)[a]	Unadjusted model		Model I[a]	
			RR	95% CI	RR	95% CI			RR	95% CI	RR	95% CI
	1010						1238					
Persistently normal		786 (57.9)	Ref.	—	Ref.	—		850 (36.4)	Ref.	—	Ref.	—
Normal to overweight/obese		447 (32.9)	0.97	0.93–1.30	1.04	0.77–1.39		889 (38.0)	**1.26**	**1.01–1.57**	**1.29**	**1.03–1.61**
Overweight/obese to normal		16 (1.2)	1.57	0.65–3.81	1.65	0.70–3.89		44 (1.9)	1.47	0.89–2.43	1.47	0.88–2.46
Persistently overweight/obese		108 (8.0)	**1.63**	**1.09–2.45**	**1.76**	**1.15–2.71**		554 (23.7)	**1.36**	**1.01–1.83**	**1.39**	**1.01–1.90**

Model I: adjust for age at menarche, highest parental education and own education
[a]The total number of observations in each weight status category from childhood to adulthood

Sensitivity analyses

Similar estimates were found in sensitivity analyses, in which the US CDC standards were used to calculate childhood BMI *z*-score and classify childhood obesity according to BMI (Supplementary Table SI, Tables SII and 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 birth weight 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 ($\beta = 2.82$ pmol/l, 95% CI: 1.67–3.98) and childhood WHtR ($\beta = 0.59$ 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

Table VI Associations of weight status change from childhood to adulthood with PCOS in CDAH and BBS.

Weight status from childhood to adulthood	CDAH						BBS				
			Unadjusted model		Model I				Unadjusted model		Model I [b]	
	n	Cases (%)[a]	RR	95% CI	RR	95% CI	*n*	Cases (%)[a]	RR	95% CI	RR	95% CI
Overall	1516						1247					
Persistently normal		1414 (59.7)	Ref.	—	Ref.	—		855 (36.2)	Ref.	—	Ref.	—
Normal to overweight/obese		455 (31.9)	1.19	0.81–1.73	1.34	0.93–1.94		900 (38.1)	0.80	0.52–1.22	1.00	0.65–1.53
Overweight/obese to normal		31 (1.3)	0.92	0.13–6.40	1.02	0.15–6.93		46 (2.0)	1.99	0.78–5.05	**2.69**	**1.10–6.62**
Persistently overweight/obese		169 (7.1)	**2.93**	**1.65–5.18**	**3.66**	**2.05–6.56**		560 (23.7)	**2.55**	**1.47–4.43**	**3.72**	**2.12–6.54**
White							730					
Persistently normal								651 (44.9)	Ref.	—	Ref.	—
Normal to overweight/obese								489 (33.7)	1.03	0.67–1.60	1.06	0.69–1.63
Overweight/obese to normal								25 (1.7)	**4.00**	**1.66–9.62**	**4.70**	**1.93–11.43**
Persistently overweight/obese								286 (19.7)	**4.66**	**2.62–8.28**	**5.41**	**2.98–9.83**
Black							517					
Persistently normal								204 (22.4)	Ref.	—	Ref.	—
Normal to overweight/obese								411 (45.2)	0.43	0.13–1.42	0.46	0.15–1.43
Overweight/obese to normal								21 (2.3)	N/A		N/A	
Persistently overweight/obese								274 (30.1)	0.75	0.21–2.65	0.88	0.28–2.80

Model 1: adjust for age at menarche, highest parental education and own-education
[a]The total number of observations in each BMI category from childhood to adulthood
[b]Model 1 further adjust for race in the overall BBS

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 (Marcovecchio and Chiarelli, 2013; Elizondo-Montemayor *et al.*, 2017). 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 (Legro, 2012; de Zegher *et al.*, 2018). 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 (Knochenhauer *et al.*, 1998; Azziz *et al.*, 2004; 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 (Hillman *et al.*, 2014; Chan *et al.*, 2017), 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 significantly higher risk of PCOS, suggesting independent effects of childhood adiposity that need to be confirmed in larger studies.

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

A second potential limitation of this study was the exclusion of women using hormonal contraception (28.4%) in the analysis of menstrual irregularity in CDAH. Since hormonal contraception is commonly prescribed for menstrual irregularity (Bulletins—Gynecology, 2013), we may have under-estimated the prevalence of menstrual irregularity. Third, we have limited information on the age at which PCOS was diagnosed in the two cohorts. Only in the second follow-up in CDAH were participants asked to report the age when their PCOS was diagnosed (ages ranged from 14–36 years with only four participants reporting the diagnosis of PCOS before age 18 years). It has been suggested that adolescents with characteristics of PCOS should be reassessed at or before full reproductive maturity, at 8 years post menarche (Teede *et al.*, 2018) to confirm a diagnosis. In this study, participants reporting a diagnosis of PCOS during adolescence may have been misclassified. Fourth, the diagnostic criteria for PCOS have recently changed (Teede *et al.*, 2018) and there may have been differences in how PCOS was diagnosed in Australia compared to the USA. Despite all of these limitations, we showed that the prevalence of menstrual irregularity and PCOS in the two cohorts was consistent with the literature (Weller and Weller, 1998; March *et al.*, 2010).

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

Strengths of our study include that this is the first prospective study to investigate the long-term associations between childhood abdominal obesity measures and menstrual irregularity and PCOS. Second, we

used two independent cohorts from two countries and reported consistent findings. Third, we were able to consider associations by race in BBS.

In conclusion, greater childhood BMI was associated with an increased risk of menstrual irregularity in adulthood in both CDAH and BBS. Greater childhood BMI and WHtR were associated with an increased risk of PCOS in adulthood in CDAH, and in BBS white participants. These risks were significantly higher in women with persistent overweight/obesity since childhood. No significant association of adiposity with PCOS was found in BBS black participants, suggesting there are racial differences in childhood adiposity associating with the development of PCOS, and other environmental or genetic 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.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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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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