Scoping Review

Exploring the physiological factors relating to energy balance in women with polycystic ovary syndrome: a scoping review

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Polycystic ovary syndrome (PCOS) occurs in 8%-13% of reproductive-aged women and is associated with reproductive, metabolic, and psychological dysfunction. Overweight and obesity are prevalent and exacerbate the features of PCOS. The aim of this review is to evaluate the extent of evidence examining the physiological factors affecting energy homeostasis, which may impact weight gain, weight loss, and weight maintenance in PCOS, and identify research gaps and recommendations for future research. Literature searches using MEDLINE, EMBASE, PsycInfo, AMED, CINAHL, and Cochrane Central Register of Controlled Trials were conducted up to June 22, 2022. Abstracts, non–English-language articles, and reviews were excluded. A total of n = 78 (n = 55 energy intake and n = 23 energy expenditure) primary research papers were included. Papers with multiple outcomes of interest were counted as separate studies. Energy-intake studies (n = 89) focussed on assessing food, nutrient, or supplements stimuli and were grouped into the outcomes of gastrointestinal appetite hormones (n = 43), adipokines (n = 34), subjective appetite (n = 9), functional brain imaging (n = 3), and neuropeptides (n = 0). Energy-expenditure studies (n = 29) were grouped into total energy expenditure (n = 1), resting energy expenditure (n = 15), meal-induced thermogenesis (n = 3), nutrient oxidation (n = 5), and metabolic flexibility (n = 5). Across both energy-intake and -expenditure papers, 60% of the studies compared outcome responses in women with PCOS with a control group. Results were inconsistent, with 57% reporting no differences and 43% reporting altered responses in PCOS compared with controls, including blunted appetite hormone responses, metabolic inflexibility, and reduced energy expenditure. The authors identified that there is inconsistent, yet preliminary, evidence of possible altered physiological factors, which may impact energy balance and weight management. Further work is needed to act on the identified clinical and research gaps to support women with PCOS and health professionals in informing and achieving realistic weight-management goals for women with PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine condition in women of reproductive age, with a prevalence of 8% to 13%.[1] PCOS is associated with reproductive (menstrual irregularity, hyperandrogenism, and infertility), metabolic (increased risk factors for and prevalence of type 2 diabetes and cardiovascular disease), and psychological (anxiety and depression) features.[2,3] The European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine or Rotterdam criteria are the most commonly accepted PCOS diagnostic criteria and recommended for use in the 2018 international evidence-based guidelines for the management of PCOS.[2] Diagnosis occurs when a woman has at least 2 of the following; oligo/anovulation, hyperandrogenism (either clinically or biochemically identified), or polycystic ovaries on ultrasound.[4] Intrinsic insulin resistance is a key pathophysiological feature of PCOS that occurs independently of excess weight.[5] This can lead to hyperinsulinemia, of which excess insulin can act on the ovaries and liver, contributing to hyperandrogenism. Weight gain and obesity are known to further worsen insulin resistance and the features of PCOS.[6] Women with PCOS have a higher prevalence of excess weight and obesity compared with a healthy population of women[7] and greater longitudinal weight gain.[8]

Weight management (prevention of excess weight gain, modest weight loss [∼5%], and maintenance of a reduced weight) through lifestyle (dietary, exercise, and behavioral) interventions is therefore a first-line management strategy according to the 2018 PCOS guidelines.[2] However, evidence of higher obesity rates,[7] longitudinal weight gain in community populations,[8] and high attrition rates in clinical dietary interventions[9] suggests that women with PCOS may experience challenges with lifestyle and weight management. Abnormalities in the physiological responses to energy intake and/or energy expenditure lead to a state of energy imbalance, whereby overall energy intake is greater than that expended,[10] thus perpetuating weight gain.

Women with PCOS exhibit abnormal pathophysiological mechanisms in energy homeostasis related to hormonal or metabolic abnormalities.[11] Appetite regulation is complex and controlled by processes, including gut hormones (eg, ghrelin) and neuropeptides (eg, neuropeptide Y [NPY]), which fluctuate throughout the short and long term related to factors including fat storage, blood glucose concentrations, and gastrointestinal tract sensation.[12,13]

To help understand the regulation of energy intake it is important to understand the intrinsic physiological response to actual nutrient or food stimuli. Postprandial studies have reported impaired appetite regulation in women with PCOS, showing increased postprandial hunger (visual analogue scale) and blunted gastrointestinal appetite hormone responses, including ghrelin and cholecystokinin (CCK).[14,15] In contrast, there are studies reporting no postprandial differences in ghrelin response between women with and without PCOS.[16,17] Women with PCOS also have an impaired relationship between ghrelin and NPY, which is partially influenced by insulin resistance,[18] and reduced postprandial CCK associated with hyperandrogenism.[15] Appetitive brain responses measured by functional magnetic resonance imaging (fMRI) to food pictures during a glucose challenge have been shown to be impaired in insulin-resistant women with PCOS, which may lead to increased non-homeostatic food consumption.[19] In addition, components of energy expenditure have been reported as being different in women with than in those without PCOS, including decreased meal-induced thermogenesis (MIT)[20] and resting metabolic rate[21]; however, the evidence is not always consistent, with some studies showing no differences.[22,23]

While there is evidence suggesting that impairments in mechanisms relating to energy homeostasis, including appetite regulation and energy expenditure, may contribute to difficulties with weight management in PCOS, the research to date is limited and inconsistent, with a lack of evidence synthesis. The aim of this scoping systematic review is to explore the current extent of evidence on the physiological factors affecting energy balance that may impact weight gain, weight loss, and weight maintenance in women with PCOS. This will help to identify physiological differences between women with and without PCOS and identify research gaps and highlight emerging areas that warrant further investigation and translation into clinical practice.

METHODS

This scoping review was conducted according to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews) and the methodological framework outlined by Arksey and O'Malley.[24]

Eligibility criteria

Studies on women with PCOS that reported on physiological outcomes that affect energy homeostasis were included. Both intervention and observational studies and those with and without a comparator/control group were included. Outcomes included gastrointestinal hormones, neuropeptides, subjective measures of hunger and satiety, fMRI, resting metabolic rate, and nutrient oxidation measured by the reference method of indirect

calorimetry and total energy expenditure (TEE) measured by the reference method of doubly labeled water. Briefly, doubly labeled water is a noninvasive technique based on the measurement of the dilution spaces and the elimination rates of the tracers (via spot urine collection) over a period of 7–14 days after the ingestion of water labeled with 2 nonradioactive stable isotopes, deuterium and oxygen-18. The difference in elimination rates is proportional to carbon dioxide production and used to calculate TEE.[25,26] The comprehensive list of study outcomes is detailed in the Medline search strategy in Table S1 (see the Supporting Information online).

We acknowledge that the analytes involved in energy homeostasis (eg, novel adipokines, peptide hormones) are constantly evolving and that this list is not exhaustive; therefore, relevant analytes identified that were not on the list were documented. Studies that only measured and reported behavioral change outcomes (eg, dietary behavior, physical activity) and did not report on any biological outcomes that can influence weight management were excluded. Non-primary research, such as review articles, grey literature, conference abstracts, and case studies, as well as non–English-language studies, were also excluded.

Literature search and study selection

The literature search was conducted to identify articles published up until June 22, 2022, on 6 electronic databases (MEDLINE, EMBASE, PsycInfo, AMED, CINAHL, and Cochrane Central Register of Controlled Trials). The MEDLINE (Ovid) search strategy is provided in Table S1 (see the Supporting Information online). All identified studies were exported in EndNote X9.2 (Clarivate, Philadelphia, PA) and duplicates were removed, with remaining studies imported into Covidence (www.covidence.org). Each of the studies identified in the database searches were assessed for inclusion first by abstract and title by 2 independent investigators (K.N., Z.D., S.P., A.L. D., L.J.M.), with discrepancies resolved by a third investigator (L.J.M.). Each of the studies that met or appeared to meet the inclusion criteria were retrieved as full text (K.N., M.M., M.C.) and were assessed for eligibility by 2 independent investigators (K.N., L.J.M., Z.D., M.M.), with discrepancies resolved by consensus (K.N., L.J.M., Z.D., M.M.).

Data charting and synthesis of results

Data were extracted using custom Microsoft Excel spreadsheets (Microsoft Corporation) that were developed and piloted by 2 investigators (K.N., L.J.M.) and that grouped the studies into the 2 broad categories of "energy homeostasis studies" and "non-energy homeostasis studies" and their outcomes of interest.

Energy homeostasis studies. Energy homeostasis studies were defined as studies focusing on energy intake or expenditure as per the criteria below.

Energy-intake studies were defined as studies that measured the study outcomes in response to food or nutrient intake or food cues (eg, postprandial studies, test meal studies, or dietary interventions). Outcomes were grouped into the categories below.

1. Gastrointestinal hormones and adipokines
2. Subjective appetite
3. fMRI
4. Neuropeptides

Energy-expenditure studies were defined as studies that measured energy-expenditure outcomes listed below using the reference methods of doubly labeled water and indirect calorimetry.

1. TEE
2. Resting energy expenditure (REE)
3. MIT
4. Nutrient oxidation
5. Metabolic flexibility

Study characteristics were extracted by 2 investigators (K.N., L.J.M.) and cross-checked by a third investigator (M.M.) and included author, year, relevant study aim in the context of this review, study design, sample size, age, body mass index (BMI), intervention, and outcomes. This information was further synthesized into another table to group the number of studies according to their broader category, outcome, intervening factor, and any comparisons with a control group (differences between groups were determined by what was reported within each paper by the authors) and cross-checked by a third investigator (M.M.). The intervening factors included oral-glucose-tolerance test (OGTT), acute meal tolerance test, diet/supplement intervention, visual food cues, and hyperinsulinemic euglycemic clamp. Papers measuring multiple outcomes were counted as independent studies. For example, a paper investigating ghrelin and peptide YY (PYY) in response to an acute meal tolerance test was counted as 1 study for ghrelin and 1 study for PYY.

Non–energy homeostasis studies. Studies that measured the study outcomes but not in the context of the defined energy homeostasis criteria above were grouped into non–energy homeostasis studies. For these studies, only higher-level study characteristics were extracted (S.P., M.M., M. C., M.H.) (author, year, study design, and relevant study outcomes) and 10% were cross-checked (M.M.). These studies were grouped into 6 broad categories according to their primary and any secondary focuses (if identified)

(cardiometabolic, fasting measures, receptors and gene expression, reproduction, medication and pharmaceuticals, and other).

RESULTS

Selection of sources of evidence

The database searches identified 8472 papers. Following removal of duplicates, 6756 papers underwent title and abstract screening and 681 underwent full-text screening. In total, 534 papers were retrieved for inclusion into the review comprising 78 energy homeostasis papers and 456 non–energy homeostasis papers (Fig. 1). Papers with multiple outcomes of interest were counted as separate studies.

Energy homeostasis papers

The number of papers in the energy-intake group was n = 55; the number of studies derived from these according to the intervening factor was n = 89, of which n = 56 (63%)

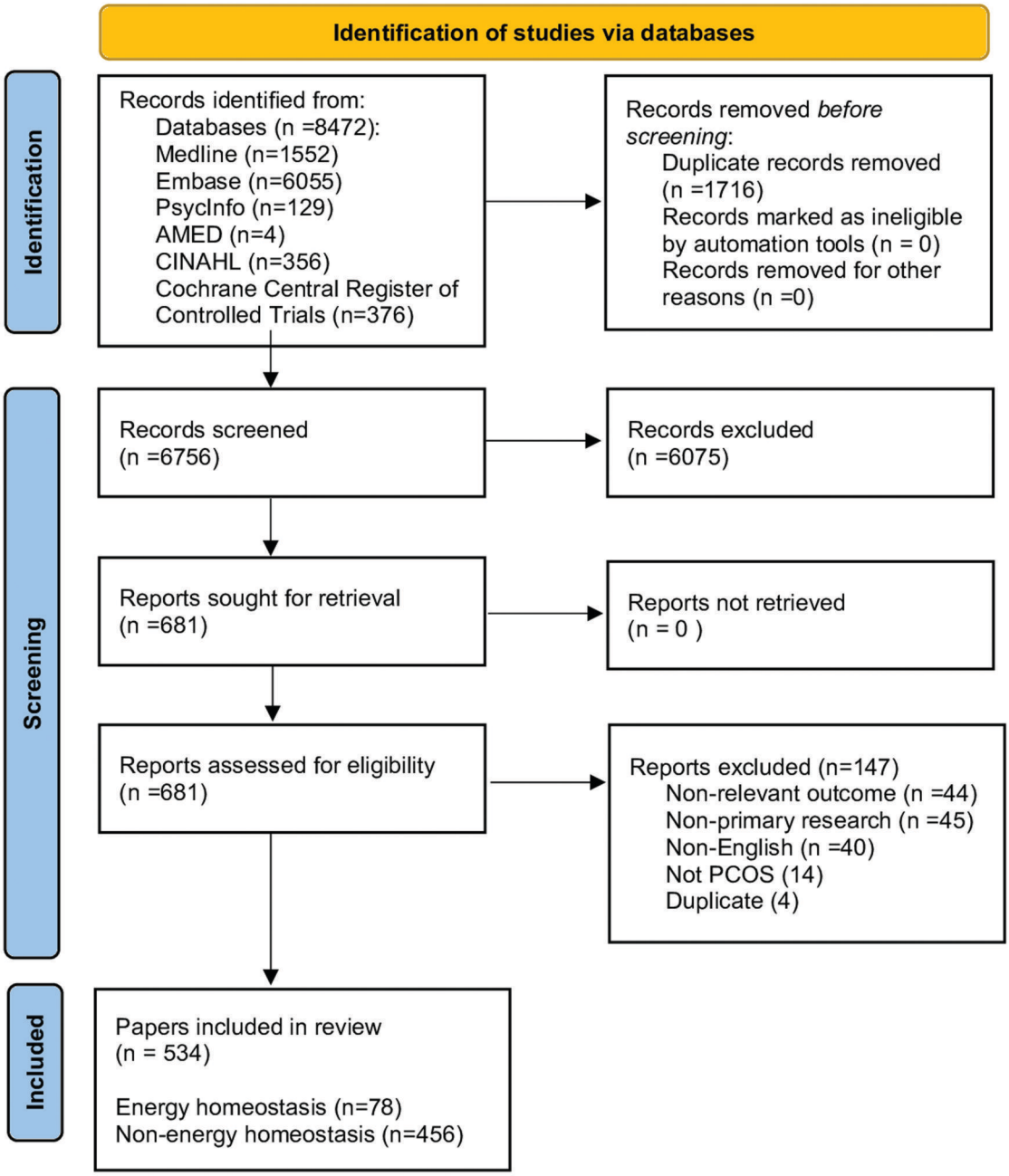

Figure 1 **Flow diagram of the literature search process.** *Abbreviations*: PICOS, polycystic ovary syndrome.

had a control group. The number of papers in the energy-expenditure group was n = 23; the number of studies derived from these according to the intervening factor was n = 29 of which n = 18 (60%) had a control group. Table 1[14–17,19,27–60,67,80,81,110–123] and Table 2[20–23,61–75,124–127] summarize the energy-intake and -expenditure papers, respectively, into their broad categories, outcomes, intervening factor, number of studies, and additionally any studies that compared the outcome in PCOS with a control group. Table S2 (see the Supporting Information online) provides characteristics of each paper, including sample size, age, BMI, intervention, and outcomes. The majority of these papers were from the United States (n = 15) and the United Kingdom (n = 10). Sample sizes of women with PCOS ranged from n = 5 to n = 156 (n = 20 papers with small [n = ≤10] sample sizes); mean age ranged from 13.6 to 37.1 years (n = 5 papers in adolescents), and mean BMI ranged from 18.6 kg/m^2 to 39.2 kg/m^2.

Energy intake. Gastrointestinal hormones. Gastrointestinal hormones were measured in 44 studies. The 2 most studied hormones were ghrelin (n = 15), with the majority (70%) measuring total ghrelin, and glucagon-like peptide-1 (GLP-1) (n = 11) followed by gastric inhibitory polypeptide (GIP) (n = 8) and PYY (n = 5). Very few studies examined the hormones CCK (n = 3) and amylin (n = 1). With regard to the type of intervening factor, from the total number of studies (n = 44), 17 examined gastrointestinal hormone response to an OGTT, 17 to an acute meal tolerance test, and 10 to a diet/supplement intervention. Thirty-five out of the 44 studies compared the response with a non-PCOS control group following either an OGTT, acute meal tolerance test, or diet/supplement intervention. Sixteen studies showed no difference between PCOS and control groups, 15 studies showed less response in the PCOS group compared with the control group (potentially indicative of an impairment in gastrointestinal hormonal appetite regulation in PCOS), and 4 studies showed greater response in the PCOS group compared with the control group.

Adipokines. Leptin was measured in 16 studies. One study examined circulating leptin response to a glucose clamp,[27] 3 studies examined response to an OGTT,[28–30] 2 examined response to an acute meal tolerance test,[31,32] and 10 studies examined the response to a diet/supplement intervention.[14,33–41] Eight out of the 16 studies compared leptin response with a non-PCOS control group, with 6 showing no difference between PCOS and control,[14,28,29,31,38,39] 1 study showing a decreased response in PCOS compared with the control,[27] and 1 study showing a greater response in PCOS compared with the control.[30] Adiponectin was studied in 18 studies. Four examined adiponectin response to an OGTT,[28,42–44] 1 to an acute meal tolerance test,[31] and 13 to a diet/supplement intervention.[33–35,37,39,40,45–51] Six out of the 18 studies compared the response with a non-PCOS control group, with 4 showing no difference between PCOS and control,[31,39,42,51] 1 showing a decreased response in PCOS compared with the control,[28] and 1 showing greater response in PCOS compared with the control.[43] Differences in the response between PCOS and control groups may indicate that the regulatory role of circulating adiponectin and leptin in energy homeostasis may be altered in women with PCOS.

Subjective appetite. Subjective appetite was measured in 4 studies in response to an acute meal tolerance test,[15,52–54] with 2 studies showing no differences in satiety in PCOS compared with controls[52,53] and 2 studies showing a difference including an earlier return of hunger in women with PCOS after a meal.[15,54] Five studies assessed the impact of a diet/supplement intervention on subjective satiety[14,55–58]; 2 studies comprised a control group, which included the assessment of the impact of an energy-restricted diet on subjective satiety.[14,58] No differences in satiety between groups were seen after an 8-week intervention.[58] In contrast, after the 12-week intervention, women with PCOS were hungrier and less satiated than controls.[14]

Functional magnetic resonance imaging. Corticolimbic blood oxygen level–dependent (BOLD) responses to visual food cues were measured in 3 studies. None of these compared BOLD responses with a control group; rather, they sought to assess the BOLD response in women with PCOS with and without insulin resistance. All 3 studies reported compromised corticolimbic BOLD responses to visual food cues with insulin resistance.[19,59,60]

Neuropeptides. No papers were identified.

Energy expenditure. Total energy expenditure. Total energy expenditure measured using the reference method of doubly labeled water was conducted in only 1 study.[61] TEE was measured in a group of women with PCOS (no control) and reported that, to increase the precision of established equations for the estimation of energy requirements, accurate measures of physical activity are required.

Resting energy expenditure. Resting energy expenditure was measured in 15 studies. Twelve studies characterized REE, with 7 out of the 8 that compared REE in PCOS with controls showing no difference between groups[22,23,62–65] and 1 study showing reduced REE in

Table 1 **Energy-intake papers (n = 55) summarized respectively into their broad category, outcomes, intervening factor, number of studies, and any studies that compared the outcome in PCOS with a control group**

Category	Outcome	Intervening factor	No. of studies[a] (total) (n = 89)	Studies (n) comparing response between PCOS vs control group[b]	References
Gastrointestinal hormones	Ghrelin	OGTT[28,110–112]	4	PCOS < control (n = 2[28,112]); PCOS < control (OB not lean) (n = 1[111]); no control (n = 1[110])	Daghestani, 2011[16] Japur, 2014[17] Vejrazkova, 2017[28] Angeles Martinez-Garcia, 2021[31]
		Acute meal tolerance test[16,17,31,53,54,80]	6	PCOS = control (n = 4[16,17,31,54]); PCOS < control (n = 2[53,80])	Moran, 2004[14] Arusoglu, 2013[53] Japur, 2019[54] Hoover, 2021[57]
		Diet/supplement intervention[14,57,58,67,113]	5	PCOS = control (n = 1[113]); PCOS < control (n = 2[14,58]); No control (n = 2[57,67])	Moran, 2007a[58] Moran, 2006[67] Zwirska-Korczala, 2008[80] Kasim-Karakas, 2007[110] Ozgen, 2010[111] Barber, 2008[112] Rashad, 2019[113]
			(15)		
	PYY	OGTT	1	PCOS = control (n = 1[114])	Arusoglu, 2013[53] Hoover, 2021[57]
		Acute meal tolerance test[53,80]	2	PCOS = control (n = 1[53]); PCOS < control (n = 1[80])	Moran, 2007a[58] Zwirska-Korczala, 2008[80] Lin, 2015[114]
		Diet/supplement intervention[57,58]	2	PCOS = control (n = 1[58]); no control (n = 1[57])	
			(5)		
	CCK	OGTT	0	—	Arusoglu, 2013[53]
		Acute meal tolerance test[15,53]	2	PCOS = control (n = 1[53]); PCOS < control (n = 1[15])	Hirschberg, 2004[15] Moran, 2007a[58]
		Diet/supplement intervention[58]	1	PCOS = control (n = 1[58])	
			(3)		
	GIP	OGTT[28,115–118]	5	PCOS < control (n = 2[28,118]); PCOS > control (n = 2[115,116]); no control (n = 1[117])	Vejrazkova, 2017[28] Vrbikova, 2008[115] Gama, 1996[116] Ferjan, 2019[117]
		Acute meal tolerance test[119]	1	PCOS > control (n = 1[119])	Pontikis, 2011[118] Milewicz, 2016[119] Ferjan, 2018[120] Rao, 2021[121]
		Diet/supplement intervention[120,121]	2	PCOS = control (n = 1[121]); no control (n = 1[120]);	
			(8)		
	GLP-1	OGTT[28,114–118,122]	7	PCOS = control (n = 3[116,118,122]); PCOS < control (n = 2[28,115]);	Vejrazkova, 2017[28] Ozgen Saydam, 2017[52]

(continued)

Table 1 **Continued**

Category	Outcome	Intervening factor	No. of studies[a] (total) (n = 89)	Studies (n) comparing response between PCOS vs control group[b]	References
				PCOS > control (n = 1[114]); no control (n = 1[117])	Aydin, 2014[81] Lin, 2015[114] Gama, 1996[116]
		Acute meal tolerance test[52,81]	2	PCOS = control (n = 1[52]); PCOS < control (n = 1[81])	Vrbikova, 2008[115] Ferjan, 2019[117] Pontikis, 2011[118]
		Diet/supplement intervention[120,121]	2 (11)	PCOS = control (n = 2[120,121])	Ferjan, 2018[120] Rao, 2021[121] Glintborg, 2017[122]
	Amylin	OGTT[123]	1	PCOS > control (n = 1[123])	James, 2010[123]
		Acute meal tolerance test	0	—	
		Diet/supplement intervention	0 (1)	—	
Adipokines	Leptin	OGTT[28–30]	3	PCOS = control (n = 2[28,29]); PCOS > control (n = 1[30])	Ludwig, 2007[27] Vejrazkova, 2017[28] Sepilian, 2006[29]
		Glucose clamp[27]	1	PCOS < control (n = 1[27])	Vicennati, 1998[30] Angeles Martinez Garcia, 2021[31]
		Acute meal tolerance test[31,32]	2	PCOS = control (n = 1[31]); no control (n = 1[32])	Erturk, 2004[32] Saghafi-Asl, 2017[33] Vargas, 2011[34]
		Diet/supplement intervention[14,33–41]	10	PCOS = control (n = 3[14,38,39]); no control (n = 7[33–37,40,41])	Kalgaonkar, 2011[35] Stamets, 2004[36] Wang, 2022[37]
			(16)		Van Dam, 2002[38] Moran, 2004[14] Spanos, 2012[39] Haidari, 2020[40] Roelfsema, 2011[41]
	Adiponectin	OGTT[28,42–44]	4	PCOS = control (n = 1[42]); PCOS < control (n = 1[28]); PCOS > control (n = 1[43]); no control (n = 1[44])	Vejrazkova, 2017[28] Angeles Martinez Garcia, 2021[31] Naghafi-Asl, 2017[33] Vargas, 2011[34]
		Acute meal tolerance test[31]	1	PCOS = control (n = 1[31])	Kalgaonkar, 2011[35] Wang, 2022[37] Spanos, 2012[39] Haidari, 2020[40]
		Diet/supplement intervention[33–35,37,39,40,45–51]	13	PCOS = control (n = 2[39,51]); no control (n = 11[33–35,37,40,45–50])	Panidis, 2005[42] Güven, 2010[43] Lewandowski, 2005[44]
			(18)		Borzoei, 2018[45]

(continued)

Table 1 **Continued**

Category	Outcome	Intervening factor	No. of studies[a] (total) (n = 89)	Studies (n) comparing response between PCOS vs control group[b]	References
					Seyyed Abootorabi, 2018[46] Nasser, 2020[47] Nadjarzadeh, 2015[48] Mohammadi, 2012[49] Mejia-Montilla, 2018[50] Moran, 2007b[51]
Subjective appetite	Subjective appetite measures (eg, hunger, satiety)	OGTT	0	—	Moran, 2004[14] Ozgen Saydam, 2017[52]
		Acute meal tolerance test[15,52–54]	4	PCOS = control (n = 2[52,53]); PCOS > control (n = 2[15,54]) (craving, hunger)	Arusoglu, 2013[53] Japur, 2019[54] Hirschberg, 2004[15]
		Diet/supplement intervention[14,55–58]	5	PCOS = control (n = 1[58]) (hunger); PCOS > control (n = 1[14]) (hunger); no control (n = 3[55–57])	Herriot, 2008[55] Papakonstantinou, 2016[56] Hoover, 2021[57] Moran, 2007a[58]
			(9)		
Functional brain imaging (fMRI) studies	Corticolimbic BOLD responses	Visual food cues[19,59,60]	3	No control (n = 3[19,59,60])	Alsaadi, 2015[59] Van Vugt, 2014[19]
			(3)		Van Vugt, 2013[60]
Neuropeptides	—	Nil	NA	NA	—

Abbreviations: BOLD, blood oxygen level–dependent; CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon like peptide 1; NA, Not applicable; OGTT, oral-glucose-tolerance test; PCOS, polycystic ovary syndrome; PYY, peptide YY.

[a]Papers that measured multiple outcomes were counted independently as studies.

[b]PCOS = control (no difference between PCOS and control); PCOS < control (PCOS reduced outcome response than control); PCOS > control (PCOS greater outcome response than control).

Table 2 **Energy-expenditure (n = 23) papers summarized respectively into their broad category, outcomes, intervening factor, number of studies, and any studies that compared the outcome in PCOS with a control group**

Outcome	Intervening factor	No. of studies[a] (total) (n = 29)	Studies (n) comparing response between PCOS vs controls[b]	References
Total energy expenditure	No intervention[61]	1 (1)	No controls (n = 1[61])	Broskey, 2017[61]
Resting energy expenditure	No intervention[20–23,61–65,124–126]	12	PCOS = control (n = 7[20,22,23,62–65]); PCOS < control (n = 1[21]) no controls (n = 2[61,126])	Robinson, 1992[20] Georgopoulos, 2008[21] Cosar, 2008[22]
	Diet/supplement intervention[66–68]	3 (15)	PCOS vs control unclear (n = 2[124,125]) No control (n = 3[66–68])	Doh, 2016[23] Broskey, 2017[61] Larsson, 2016[62] Segal, 1990[63] Graff, 2013[64] Graff, 2017[65] Bruner, 2006[66] Moran, 2006[67] Pohlmeier, 2014[68] Kritikou, 2006[124] Koika, 2009[125] Rodrigues, 2018[126]
Meal-induced thermogenesis	Acute meal tolerance test[20,63]	2	PCOS = control (n = 1[63]); PCOS < control (n = 1[20])	Robinson, 1992[20] Segal, 1990[63] Pohlmeier, 2014[68]
	Diet/supplement intervention[68]	1 (3)	No controls (n = 1[68])	
Nutrient oxidation	No intervention[62]	1	PCOS > control (n = 1[62])	Larsson, 2016[62] Pohlmeier, 2014[68]
	Hyperinsulinemic euglycemic clamp[69–71]	3	PCOS = control (n = 2[69,70]); PCOS < control (n = 1[71])	Cree-Green, 2016[69] Kowalska, 2012[70] Michaliszyn, 2013[71]
	Acute meal tolerance test	0	—	
	Diet/supplement intervention[68]	1 (5)	No controls (n = 1[68])	
Metabolic flexibility	Hyperinsulinemic euglycemic clamp[72–75,127]	5 (5)	PCOS = control (n = 1[72]); PCOS < control (n = 3[73–75]); no control (n = 1[127])	Adamska, 2013[72] Kim, 2018[73] Broskey, 2018[74] Svendsen, 2008[75] Di Sarra, 2013[127]

Abbreviation: PCOS, polycystic ovary syndrome.
[a]Papers that measured the outcome from multiple intervening factors were counted independently as studies.
[b]PCOS = control (no difference between PCOS and control); PCOS < control (PCOS response less than control) PCOS > control (PCOS response greater than control).

women with PCOS.[21] Three studies assessed REE in response to a diet/supplement intervention, none compared with non-PCOS controls.[66–68]

Meal-induced thermogenesis. Meal-induced thermogenesis was measured in 3 studies. Two studies assessed MIT in response to an acute meal tolerance test.[20,63] From the 2 that compared women with PCOS with a control group,[63] one showed no difference and one showed reduced MIT in PCOS.[20] One study assessed MIT in response to a diet/supplement intervention, and did not compare with a non-PCOS control.[68]

Nutrient oxidation. Nutrient oxidation was measured in 5 studies. Three studies assessed nutrient oxidation in response to hyperinsulinemia euglycemic clamp.[69–71] From these 3 studies, 2 compared women with PCOS with a control group: 2 showed no difference[69,70] and 1 showed a reduced response in PCOS indicative of lower insulin-stimulated glucose oxidation.[71] One study characterized nutrient oxidation in PCOS, with the PCOS group showing a greater response than controls as evidenced by a greater respiratory exchange ratio, potentially reflecting greater carbohydrate intake,[62] and 1 study assessed nutrient oxidation in response to a diet/supplement intervention.[68]

Metabolic flexibility. Metabolic flexibility was measured in 5 studies using a hyperinsulinemic euglycemic clamp. From the 4 studies that compared women with PCOS with a control group, 1 showed no difference[72] and 3 showed a reduced response in PCOS indicating impaired metabolic flexibility.[73–75]

Non–energy homeostasis papers

For non–energy homeostasis papers, the numbers of papers (n = 456) categorized into the following primary and secondary focus categories, respectively, were cardiometabolic (n = 190, n = 26), receptors and gene expression (n = 85, n = 7), medication and pharmaceuticals (n = 89, n = 1), fasting measures (n = 59, n = 66), reproduction (n = 22, n = 23), and other (n = 11). From these, the numbers of papers with study outcomes from the primary and secondary focus categories, respectively, were adiponectin (n = 236, n = 56), leptin (n = 219, n = 56), ghrelin (n = 54, n = 13), nesfatin-1 (n = 9), and resistin (n = 7), and smaller numbers of papers for other outcomes (n = 21) (*see* Table S3 in the Supporting Information online).

Other analytes related to energy homeostasis

Analytes identified relating to energy homeostasis that were not in our list of outcomes were documented. These included adipsin, adropin, aprosin, kisspeptin, vaspin, spexin, chemerin, asprosin, ATF4, neudesin, obestatin, neuregulin 4, subfatin, secreted frizzled-related protein 4 (SFRP4), insulin-like peptide 5 (INSL5), and L-carnitine.

DISCUSSION

To our knowledge, this is the first scoping review to synthesize research exploring physiological factors affecting energy balance in PCOS. It identified 534 papers, of which 15% (n = 78) were categorized as energy homeostasis (energy intake and expenditure). The remainder were categorized as non–energy homeostasis as they examined outcomes outside the scope of energy homeostasis, highlighting their intricate physiological roles and interplay across other body systems, including fertility[76] and cardiometabolic health.[77]

Energy intake

The gastrointestinal tract plays a fundamental role in energy homeostasis. Peptides released in response to nutrients, including the appetite-stimulating hormone ghrelin and appetite-inhibitory hormones GLP-1, PYY, and CCK,[78] are important regulators of appetite.[79] We identified 53 studies across the response of appetite hormones and appetite to nutrient intake. Blunted postprandial appetite hormone responses, including ghrelin,[53,80] GLP-1,[81] and CCK,[15] were observed in some studies, but not all[16,17,31,54,52] studies, for women with PCOS compared with controls. These altered responses may potentially disrupt satiety cues contributing to greater food intake. A previous systematic review (n = 20 studies) by Gao et al[82] reported lower fasting ghrelin in women with PCOS compared with controls. As the magnitude of postprandial responses are related to fasting concentrations,[83,84] findings from Gao et al[82] further support the potential for altered appetite regulation in PCOS. Moreover, reduced fasting ghrelin concentrations have been strongly associated with the degree of insulin resistance,[85] highlighting that further research and evidence synthesis should focus on the pathophysiological mechanisms linking blunted ghrelin and other appetite hormone concentrations to altered energy homeostasis.

There is also some, albeit inconsistent, evidence of differences in subjective appetite between women with and without PCOS. For instance, in response to acute meal studies, 2 studies showed differences in satiety,[15,54]

while 2 studies showed no differences.[52,53] As food form (liquid vs solid) may affect postprandial appetite,[86] this discrepancy may be related to the meal, in that the former and latter studies were based on liquid and solid preloads, respectively. Insulin resistance may also impact appetite, with women with PCOS and insulin resistance having greater energy intake than those without insulin resistance.[54] Contrasting results were also seen in the 2 studies assessing the impact of an energy-restricted dietary intervention on satiety.[14,58] The discrepancy may relate to differences in the duration of the interventions (8 weeks vs 12 weeks). Future study designs should consider factors including standardization of preloads, intervention duration, and participant characteristics to reduce heterogeneity and increase the robustness of comparisons for appetite hormones and subjective appetite.

The brain releases neuropeptides such as the orexigenic NPY that play a crucial role in food-intake regulation by acting within the hypothalamus and other appetite-modulating centers in the brain.[87] Our review did not identify any studies examining neuropeptide response specifically to food or nutrient intake in women with PCOS. However, recent reviews on neuroendocrine regulation in PCOS, including in vitro and preclinical models, report possible impairments in PCOS.[18,88] Moreover, 1 small pilot study (n = 7) reported that women with PCOS have a blunted NPY response to ghrelin, with hyperinsulinemia potentially related to this impaired response.[89] Further studies are required to explore neuroendocrine mechanisms and their interactions with food intake and weight regulation in PCOS.

Leptin is a regulator of primarily long-term energy balance and functions to suppress food intake.[90] Adiponectin plays a role in the regulation of glucose concentrations, lipid metabolism, and insulin sensitivity.[91] Systematic reviews report elevated fasting leptin[92] and lower fasting adiponectin[93] in women with compared with those without PCOS. This occurred independently of adiposity[93] and in relation to insulin resistance[94] for adiponectin. These differences may have ramifications for altered appetite regulation. Our scoping review identified 16 and 18 studies for food- or nutrient-stimulated leptin and adiponectin, respectively, with the majority of these investigating dietary and/or supplement interventions. For studies with control groups, 3 studies[14,38,39] reported no effect of PCOS status on leptin and 2 studies[39,51] reported no effect of PCOS status on adiponectin following weight loss. Further research with these outcomes should include control groups to strengthen the study design.

The responses of neural activity to food cues, such as BOLD through fMRI,[95] are also important modulators of energy intake. A systematic review of 60 studies reported altered neural activity in overweight and obese individuals, which may potentiate the pathogenesis of overconsumption and weight gain.[96] We identified 3 fMRI studies measuring brain signals to food cues in women in PCOS.[19,59,60] While these studies reported compromised appetite brain responses to food pictures with women with insulin resistance in PCOS, they did not include a control group and findings should be interpreted with care. Future research should explore differences in response to food cues between women with and without PCOS and consider the additional impact of having overweight or obesity.

Energy expenditure

It has been hypothesized that decreased energy expenditure may play a role in energy imbalance in PCOS. Total energy expenditure can be divided into 3 main components: REE (~60%–70% of TEE), MIT (~10% of TEE[97]), and activity-induced energy expenditure (~30%–40% of TEE).[98] Only 1 study in our review assessing TEE in PCOS used doubly labeled water.[61] As a gold-standard reference method, further research needs to include this measure[25]; however, its cost (~1000 Australian dollars/person[99]) is a common barrier precluding its use.[100] Fifteen studies measured REE in women with PCOS, with 7 out of the 8 studies with a control group showing no differences in women with and without PCOS.[20,22,23,62–65] Future research should consider the contribution of body composition to energy expenditure, given that women with PCOS may have a greater percentage of fat mass[101] as a potential predisposing factor to weight gain given its lower contribution to REE (5%–7%) compared with fat-free mass (~60%–70%).[102] Brown adipose tissue contributes to energy balance through heat dissipation. This may be an additional mechanism contributing to energy homeostasis impairments in PCOS as it is lower in women with PCOS compared with controls.[103] Finally, of the limited studies assessing MIT in PCOS, 1 study,[20] but not the other,[63] showed reduced MIT compared with controls, particularly in those with insulin resistance. This, again, indicates that insulin resistance may be a possible contributing factor to impaired energy homeostasis in PCOS.

Metabolic inflexibility refers to the impaired metabolic capacity to switch from lipid oxidation in fasting conditions to lipid availability in nonfasting conditions. This can lead to lipid accumulation in ectopic tissues, such as skeletal and other peripheral tissues.[104] Three of the 4 papers in our review demonstrated metabolic inflexibility in women with PCOS compared with controls[73–75] and hyperandrogenemic women had lower glucose utilization and metabolic flexibility than non-hyperandrogenemic women.[74] A prior systematic review similarly reported greater metabolic inflexibility in women with PCOS compared with controls, associated with insulin resistance and

hyperandrogenemia, and similar to obesity and type 2 diabetes cohorts.[105] As metabolic flexibility improves with lifestyle changes in insulin-resistant individuals with overweight and obesity,[106,107] the effect of lifestyle management on metabolic flexibility in PCOS is thus an important area for future investigation.

Strengths and limitations

Strengths of this review include being conducted according to the PRISMA-ScR and methodological framework outlined by Arksey and O'Malley.[24] A further strength is that we only included papers with higher-quality measures of energy intake (response to nutrient/food stimulation) and energy expenditure (indirect calorimetry and doubly labeled water) to more accurately capture physiological regulation of energy homeostasis. Limitations include the lack of a risk-of-bias assessment, as we conducted a broad and comprehensive scoping review to map the extent of the existing literature. Limitations of the literature included small sample sizes, lack of control groups, and lack of clarity on which outcomes studies were powered on. As a result, the findings of individual studies should be interpreted with caution and not without further interrogation. Furthermore, only n = 5 (6%) studies were conducted with adolescents. Further work is warranted in this population as the higher weight gain observed in PCOS can occur across childhood and adolescence and early lifestyle management is crucial.[108] Finally, although psychological factors were beyond the scope of this review, they may also be contributors to weight-management challenges, given that depression is an independent predictor of attrition in weight-loss interventions and women with PCOS who are overweight or obese have higher levels of depressive symptoms.[109] The relative contribution of psychological and physiological factors to weight-management challenges in women with PCOS could be further explored.

Future research priorities

Several future research priorities have been identified, including the need for primary studies investigating the impact of energy intake on specific outcomes (eg, novel adipokines, gastrointestinal appetite hormones, fMRI, MIT, metabolic flexibility, and neuropeptides). These primary studies should comprise a control group, where possible, to help elucidate the direct effect of PCOS on outcomes. Future research is also needed to characterize TEE in women with PCOS, as well as to consider the influence of PCOS phenotype and pathophysiological features such as hyperandrogenism and hyperinsulinemia on energy homeostasis. Attention should also be given to the examination of PCOS in adolescent populations, where research is currently lacking.

CONCLUSION

This scoping review has systematically synthesized and mapped the literature on physiological factors relating to energy balance in women with PCOS. Over half of the existing studies compared responses between women with and without PCOS with varying degrees of heterogeneity in responses within each energy homeostasis category. Although detailed synthesis of the individual study results is beyond the scope of this review, we provide preliminary, but inconsistent, evidence of possible altered intrinsic physiological factors that may impact weight management in PCOS. Several priorities for future research have been identified, which will provide a clearer understanding on the potential physiological factors that may impact energy homeostasis. Addressing these gaps in women with PCOS will contribute significantly to understanding the etiology of weight gain and obesity and assist with informing future research and interventions consistent with international evidence-based guidelines for PCOS. Clinically, it should be acknowledged that women with PCOS likely face altered physiological factors, which may impact energy balance, although the specific mechanisms require further investigation.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Medline search strategy**

Table S2 **Characteristics of the energy intake and energy-expenditure papers**

Table S3 **Non–energy homeostasis papers**

REFERENCES

1. Lim SS, Hutchison SK, Van Ryswyk E, et al. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database Syst Rev*. 2019;3:CD007506.
2. Teede HJ, Misso ML, Boyle JA, et al. Translation and implementation of the Australian-led PCOS guideline: clinical summary and translation resources from the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Med J Aust*. 2018;209:S3–S8.
3. Damone AL, Joham AE, Loxton D, et al. Depression, anxiety and perceived stress in women with and without PCOS: a community-based study. *Psychol Med*. 2019;49:1510–1520.
4. ESHRE R. ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod (Oxf Engl)*. 19(1):41-7.
5. Stepto NK, Cassar S, Joham AE, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. *Hum Reprod*. 2013;28:777–784.
6. Lim S, Norman RJ, Davies M, et al. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev*. 2013;14:95–109.
7. Lim SS, Davies MJ, Norman RJ, et al. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18:618–637.
8. Teede HJ, Joham AE, Paul E, et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring)*. 2013;21:1526–1532.
9. Lim S, Smith CA, Costello MF, et al. Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: a qualitative study. *BMC Endocr Disord*. 2019;19:106.
10. Barber TM, Hanson P, Weickert MO, et al. Obesity and polycystic ovary syndrome: implications for pathogenesis and novel management strategies. *Clin Med Insights Reprod Health*. 2019;13:1179558119874042.
11. Joham AE, Norman RJ, Stener-Victorin E, et al. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol*. 2022;10:668–680.
12. Camilleri M. Peripheral mechanisms in appetite regulation. *Gastroenterology*. 2015;148:1219–1233.
13. Hopkins M, Blundell JE. Energy balance, body composition, sedentariness and appetite regulation: pathways to obesity. *Clin Sci (Lond)*. 2016;130:1615–1628.
14. Moran LJ, Noakes M, Clifton PM, et al. Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. *J Clin Endocrinol Metab*. 2004;89:3337–3344.
15. Hirschberg AL, Naessén S, Stridsberg M, et al. Impaired cholecystokinin secretion and disturbed appetite regulation in women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2004;19:79–87.
16. Daghestani MH, Daghestani MH, El-Mazny A. Circulating ghrelin levels and the polycystic ovary syndrome: correlation with the clinical, hormonal and metabolic features. *Eur J Obstet Gynecol Reprod Biol*. 2011;155:65–68.
17. Japur CC, Diez-Garcia RW, De Oliveira Penaforte FR, et al. Imbalance between postprandial ghrelin and insulin responses to an Ad libitum meal in obese women with polycystic ovary syndrome. *Reprod Sci*. 2014;21:1020–1026.
18. Romualdi D, Immediata V, De Cicco S, et al. Neuroendocrine regulation of food intake in polycystic ovary syndrome. *Reprod Sci*. 2018;25:644–653.
19. Van Vugt DA, Krzemien A, Alsaadi H, et al. Glucose-induced inhibition of the appetitive brain response to visual food cues in polycystic ovary syndrome patients. *Brain Res*. 2014;1558:44–56.
20. Robinson S, Chan SP, Spacey S, et al. Postprandial thermogenesis is reduced in polycystic ovary syndrome and is associated with increased insulin resistance. *Clin Endocrinol (Oxf)*. 1992;36:537–543.
21. Georgopoulos NA, Saltamavros AD, Vervita V, et al. Basal metabolic rate is decreased in women with polycystic ovary syndrome and biochemical hyperandrogenemia and is associated with insulin resistance. *Fertil Steril*. 2009;92:250–255.
22. Cosar E, Koken G, Sahin FK, et al. Resting metabolic rate and exercise capacity in women with polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2008;101:31–34.
23. Doh E, Mbanya A, Kemfang-Ngowa JD, et al. The relationship between adiposity and insulin sensitivity in African women living with the polycystic ovarian syndrome: a clamp study. *Int J Endocrinol*. 2016;2016:9201701.
24. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8:19–32.
25. Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. *J Appl Physiol Respir Environ Exerc Physiol*. 1982;53:955–959.
26. INTERNATIONAL ATOMIC ENERGY AGENCY. *Assessment of Body Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques*, IAEA Human Health Series No. 3. Vienna, Austria: IAEA; 2009.
27. Ludwig AK, Weiss JM, Tauchert S, et al. Influence of hypo- and hyperglycaemia on plasma leptin concentrations in healthy women and in women with polycystic ovary syndrome. *Hum Reprod*. 2007;22:1555–1561.
28. Vejrazkova D, Lischkova O, Vankova M, et al. Distinct response of fat and gastrointestinal tissue to glucose in gestational diabetes mellitus and polycystic ovary syndrome. *Physiol Res*. 2017;66:283–292.
29. Sepilian VP, Crochet JR, Nagamani M. Serum soluble leptin receptor levels and free leptin index in women with polycystic ovary syndrome: relationship to insulin resistance and androgens. *Fertil Steril*. 2006;85:1441–1447.
30. Vicennati V, Gambineri A, Calzoni F, et al. Serum leptin in obese women with polycystic ovary syndrome is correlated with body weight and fat distribution but not with androgen and insulin levels. *Metabolism*. 1998;47:988–992.
31. Angeles Martinez-Garcia M, Moncayo S, Insenser M, et al. Postprandial responses of circulating energy homeostasis mediators to single macronutrient challenges: influence of obesity and sex hormones. *Food Funct*. 2021;12:1051–1062.
32. Erturk E, Kuru N, Savci V, et al. Serum leptin levels correlate with obesity parameters but not with hyperinsulinism in women with polycystic ovary syndrome. *Fertil Steril*. 2004;82:1364–1368.
33. Saghafi-Asl M, Ebrahimi-Mameghani M. The effects of raw red onion consumption on serum levels of adiponectin, leptin, and hs-CRP in overweight/obese females with polycystic ovarian syndrome: a randomized controlled-clinical trial. *Iran Red Crescent Med J*. 2017;19:e58674.
34. Vargas ML, Almario RU, Buchan W, et al. Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. *Metabolism*. 2011;60:1711–1718.
35. Kalgaonkar S, Almario RU, Gurusinghe D, et al. Differential effects of walnuts vs almonds on improving metabolic and endocrine parameters in PCOS. *Eur J Clin Nutr*. 2011;65:386–393.
36. Stamets K, Taylor DS, Kunselman A, et al. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril*. 2004;81:630–637.
37. Wang X, Xu T, Liu R, et al. High-fiber diet or combined with acarbose alleviates heterogeneous phenotypes of polycystic ovary syndrome by regulating gut microbiota. *Front Endocrinol (Lausanne)*. 2021;12:806331.
38. Van Dam EW, Roelfsema F, Veldhuis JD, et al. Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS. *Am J Physiol Endocrinol Metab*. 2002;282:E865–E872.
39. Spanos N, Tziomalos K, Macut D, et al. Adipokines, insulin resistance and hyperandrogenemia in obese patients with polycystic ovary syndrome: cross-sectional correlations and the effects of weight loss. *Obes Facts*. 2012;5:495–504.
40. Haidari F, Banaei-Jahromi N, Zakerkish M, et al. The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial. *Nutr J*. 2020;19:8.
41. Roelfsema F, Kok P, Veldhuis JD, et al. Altered multihormone synchrony in obese patients with polycystic ovary syndrome. *Metabolism*. 2011;60:1227–1233.
42. Panidis D, Farmakiotis D, Rousso D, et al. Decrease in adiponectin levels in women with polycystic ovary syndrome after an oral glucose tolerance test. *Fertil Steril*. 2005;83:232–234.
43. Güven A, Ozgen T, Aliyazicioğlu Y. Adiponectin and resistin concentrations after glucose load in adolescents with polycystic ovary syndrome. *Gynecol Endocrinol*. 2010;26:30–38.
44. Lewandowski KC, Szosland K, O'Callaghan C, et al. Adiponectin and resistin serum levels in women with polycystic ovary syndrome during oral glucose tolerance test: a significant reciprocal correlation between adiponectin and resistin independent of insulin resistance indices. *Mol Genet Metab*. 2005;85:61–69.
45. Borzoei A, Rafraf M, Asghari-Jafarabadi M. Cinnamon improves metabolic factors without detectable effects on adiponectin in women with polycystic ovary syndrome. *Asia Pac J Clin Nutr*. 2018;27:556–563.
46. Seyyed Abootorabi M, Ayremlou P, Behroozi-Lak T, et al. The effect of vitamin D supplementation on insulin resistance, visceral fat and adiponectin in vitamin D deficient women with polycystic ovary syndrome: a randomized placebo-controlled trial. *Gynecol Endocrinol*. 2018;34:489–494.
47. Nasser FA. Evaluating the role of high molecular weight adiponectin in women with polycystic ovary syndrome treated with omega-3 fatty acids. *Indian J Forensic Med Toxicol*. 2020;14:1932–1939.
48. Nadjarzadeh A, Dehghani-Firouzabadi R, Daneshbodi H, et al. Effect of omega-3 supplementation on visfatin, adiponectin, and anthropometric indices in women with polycystic ovarian syndrome. *J Reprod Infertil*. 2015;16:212–220.
49. Mohammadi E, Rafraf M, Farzadi L, et al. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. *Asia Pac J Clin Nutr*. 2012;21:511–518.
50. Mejia-Montilla J, Reyna-Villasmil E, Dominguez-Brito L, et al. Supplementation with omega-3 fatty acids and plasma adiponectin in women with polycystic ovary syndrome. *Endocrinol Diabetes Nutr*. 2018;65:192–199.
51. Moran LJ, Noakes M, Clifton PM, et al. C-reactive protein before and after weight loss in overweight women with and without polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2007;92:2944–2951.
52. Ozgen Saydam B, Has AC, Bozdag G, et al. Structural imaging of the brain reveals decreased total brain and total gray matter volumes in obese but not in lean women with polycystic ovary syndrome compared to body mass index-matched counterparts. *Gynecol Endocrinol*. 2017;33:519–523.
53. Arusoglu G, Koksal G, Cinar N, et al. Basal and meal-stimulated ghrelin, PYY, CCK levels and satiety in lean women with polycystic ovary syndrome: effect of low-dose oral contraceptive. *J Clin Endocrinol Metab*. 2013;98:4475–4482.

54. Japur CC, Diez-Garcia RW, de Oliveira Penaforte FR, et al. Insulin, ghrelin and early return of hunger in women with obesity and polycystic ovary syndrome. *Physiol Behav*. 2019;206:252–258.
55. Herriot AM, Whitcroft S, Jeanes Y. An retrospective audit of patients with polycystic ovary syndrome: the effects of a reduced glycaemic load diet. *J Hum Nutr Diet*. 2008;21:337–345.
56. Papakonstantinou E, Kechribari I, Mitrou P, et al. Effect of meal frequency on glucose and insulin levels in women with polycystic ovary syndrome: a randomised trial. *Eur J Clin Nutr*. 2016;70:588–594.
57. Hoover SE, Gower BA, Cedillo YE, et al. Changes in ghrelin and glucagon following a low glycemic load diet in women with PCOS. *J Clin Endocrinol Metab*. 2021;106:e2151–e2161.
58. Moran LJ, Noakes M, Clifton PM, et al. Postprandial ghrelin, cholecystokinin, peptide YY, and appetite before and after weight loss in overweight women with and without polycystic ovary syndrome. *Am J Clin Nutr*. 2007;86:1603–1610.
59. Alsaadi HM, Van Vugt DA. Insulin sensitivity affects corticolimbic brain responses to visual food cues in polycystic ovary syndrome patients. *Horm Mol Biol Clin Investig*. 2015;24:101–115.
60. Van Vugt DA, Krzemien A, Alsaadi H, et al. Effect of insulin sensitivity on corticolimbic responses to food picture in women with polycystic ovary syndrome. *Obesity (Silver Spring)*. 2013;21:1215–1222.
61. Broskey NT, Klempel MC, Gilmore LA, et al. Assessing energy requirements in women with polycystic ovary syndrome: a comparison against doubly labeled water. *J Clin Endocrinol Metab*. 2017;102:1951–1959.
62. Larsson I, Hulthén L, Landén M, et al. Dietary intake, resting energy expenditure, and eating behavior in women with and without polycystic ovary syndrome. *Clin Nutr*. 2016;35:213–218.
63. Segal KR, Dunaif A. Resting metabolic rate and postprandial thermogenesis in polycystic ovarian syndrome. *Int J Obes*. 1990;14:559–567.
64. Graff SK, Mario FM, Alves BC, et al. Dietary glycemic index is associated with less favorable anthropometric and metabolic profiles in polycystic ovary syndrome women with different phenotypes. *Fertil Steril*. 2013;100:1081–1088.
65. Graff SK, Mario FM, Magalhaes JA, et al. Saturated fat intake is related to heart rate variability in women with polycystic ovary syndrome. *Ann Nutr Metab*. 2017;71:224–233.
66. Bruner B, Chad K, Chizen D. Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. *Appl Physiol Nutr Metab*. 2006;31:384–391.
67. Moran LJ, Noakes M, Clifton PM, et al. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. *Am J Clin Nutr*. 2006;84:77–87.
68. Pohlmeier AM, Phy JL, Watkins P, et al. Effect of a low-starch/low-dairy diet on fat oxidation in overweight and obese women with polycystic ovary syndrome. *Appl Physiol Nutr Metab*. 2014;39:1237–1244.
69. Cree-Green M, Bergman BC, Coe GV, et al. Hepatic steatosis is common in adolescents with obesity and PCOS and relates to de novo lipogenesis but not insulin resistance. *Obesity (Silver Spring)*. 2016;24:2399–2406.
70. Kowalska I, Adamska A, Malecki MT, et al. Impact of the FTO gene variation on fat oxidation and its potential influence on body weight in women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2012;77:120–125.
71. Michaliszyn SF, Lee S, Tfayli H, et al. Polycystic ovary syndrome and nonalcoholic fatty liver in obese adolescents: association with metabolic risk profile. *Fertil Steril*. 2013;100:1745–1751.
72. Adamska A, Karczewska-Kupczewska M, Nikolajuk A, et al. Normal metabolic flexibility despite insulin resistance women with polycystic ovary syndrome. *Endocr J*. 2013;60:1107–1113.
73. Kim JY, Tfayli H, Michaliszyn SF, et al. Impaired lipolysis, diminished fat oxidation, and metabolic inflexibility in obese girls with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2018;103:546–554.
74. Broskey NT, Tam CS, Sutton EF, et al. Metabolic inflexibility in women with PCOS is similar to women with type 2 diabetes. *Nutr Metab (Lond)*. 2018;15:75.
75. Svendsen PF, Nilas L, Norgaard K, et al. Obesity, body composition and metabolic disturbances in polycystic ovary syndrome. *Hum Reprod*. 2008;23:2113–2121.
76. Estienne A, Bongrani A, Reverchon M, et al. Involvement of novel adipokines, chemerin, visfatin, resistin and apelin in reproductive functions in normal and pathological conditions in humans and animal models. *Int J Mol Sci*. 2019;20:4431.
77. Baldani DP, Skrgatic L, Ougouag R. Polycystic ovary syndrome: important underrecognised cardiometabolic risk factor in reproductive-age women. *Int J Endocrinol*. 2015;2015:786362.
78. Suzuki K, Jayasena CN, Bloom SR. The gut hormones in appetite regulation. *J Obes*. 2011;2011:528401.
79. Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. *Philos Trans R Soc Lond B Biol Sci*. 2006;361:1187–1209.
80. Zwirska-Korczala K, Sodowski K, Konturek SJ, et al. Postprandial response of ghrelin and PYY and indices of low-grade chronic inflammation in lean young women with polycystic ovary syndrome. *J Physiol Pharmacol*. 2008;59(suppl 2):161–178.
81. Aydin K, Arusoglu G, Koksal G, et al. Fasting and post-prandial glucagon like peptide 1 and oral contraception in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2014;81:588–592.
82. Gao T, Wu L, Chang F, et al. Low circulating ghrelin levels in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Endocr J*. 2016;63:93–100.
83. Nguo K, Walker KZ, Bonham MP, et al. Systematic review and meta-analysis of the effect of meal intake on postprandial appetite-related gastrointestinal hormones in obese children. *Int J Obes (Lond)*. 2016;40:555–563.
84. Carlson JJ, Turpin AA, Wiebke G, et al. Pre- and post-prandial appetite hormone levels in normal weight and severely obese women. *Nutr Metab (Lond)*. 2009;6:32.
85. Schofl C, Horn R, Schill T, et al. Circulating ghrelin levels in patients with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2002;87:4607–4610.
86. Leidy HJ, Apolzan JW, Mattes RD, et al. Food form and portion size affect postprandial appetite sensations and hormonal responses in healthy, nonobese, older adults. *Obesity (Silver Spring)*. 2010;18:293–299.
87. Parker JA, Bloom SR. Hypothalamic neuropeptides and the regulation of appetite. *Neuropharmacology*. 2012;63:18–30.
88. Ruddenklau A, Campbell RE. Neuroendocrine impairments of polycystic ovary syndrome. *Endocrinology*. 2019;160:2230–2242.
89. Romualdi D, De Marinis L, Campagna G, et al. Alteration of ghrelin-neuropeptide Y network in obese patients with polycystic ovary syndrome: role of hyperinsulinism. *Clin Endocrinol (Oxf)*. 2008;69:562–567.
90. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obes Rev*. 2007;8:21–34.
91. Nguyen TMD. Adiponectin: role in physiology and pathophysiology. *Int J Prev Med*. 2020;11:136.
92. Zheng SH, Du DF, Li XL. Leptin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Reprod Sci*. 2017;24:656–670.
93. Lin K, Sun X, Wang X, et al. Circulating adipokine levels in nonobese women with polycystic ovary syndrome and in nonobese control women: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2020;11:537809.
94. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab*. 2001;86:1930–1935.
95. Macdonald IA, Francis ST, Gowland PA, et al. Brain activation in relation to specific dietary components: what does fMRI measure and how should one interpret cravings for certain foods? *Am J Clin Nutr*. 2013;98:633–634.
96. Pursey KM, Stanwell P, Callister RJ, et al. Neural responses to visual food cues according to weight status: a systematic review of functional magnetic resonance imaging studies. *Front Nutr*. 2014;1:7.
97. Levine JA. Measurement of energy expenditure. *Public Health Nutr*. 2005;8:1123–1132.
98. Westerterp KR. Control of energy expenditure in humans. *Eur J Clin Nutr*. 2017;71:340–344.
99. Porter J, Nguo K, Collins J, et al. Total energy expenditure measured using doubly labeled water compared with estimated energy requirements in older adults ($\geq$65 y): analysis of primary data. *Am J Clin Nutr*. 2019;110:1353–1361.
100. Tatucu-Babet OA, Nguo K, Lambell KJ, et al. Doubly labelled water for determining total energy expenditure in adult critically ill and acute care hospitalized inpatients: a scoping review. *Clin Nutr*. 2022;41:424–432.
101. Sanchez-Ferrer ML, De La Cruz-Sanchez E, Arense-Gonzalo JJ, et al. Body composition and characterization of skinfold thicknesses from polycystic ovary syndrome phenotypes. A preliminary case-control study. *Int J Environ Res Public Health*. 2021;18:2977.
102. Blundell JE, Caudwell P, Gibbons C, et al. Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation. *Dis Model Mech*. 2012;5:608–613.
103. Shorakae S, Jona E, de Courten B, et al. Brown adipose tissue thermogenesis in polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2019;90:425–432.
104. Galgani JE, Moro C, Ravussin E. Metabolic flexibility and insulin resistance. *Am J Physiol Endocrinol Metab*. 2008;295:E1009–E1017.
105. Rimmer M, Tan BK, Teede H, et al. Metabolic inflexibility in women with polycystic ovary syndrome: a systematic review. *Gynecol Endocrinol*. 2020;36:501–507.
106. Huffman KM, Redman LM, Landerman LR, et al. Caloric restriction alters the metabolic response to a mixed-meal: results from a randomized, controlled trial. *PLoS One*. 2012;7:e28190.
107. Malin SK, Haus JM, Solomon TP, et al. Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes. *Am J Physiol Endocrinol Metab*. 2013;305:E1292–E1298.
108. Tay CT, Hart RJ, Hickey M, et al. Updated adolescent diagnostic criteria for polycystic ovary syndrome: impact on prevalence and longitudinal body mass index trajectories from birth to adulthood. *BMC Med*. 2020;18:389.
109. Moran LJ, Noakes M, Clifton P, et al. Predictors of lifestyle intervention attrition or weight loss success in women with polycystic ovary syndrome who are overweight or obese. *Nutrients*. 2019;11:492.

110. Kasim-Karakas SE, Cunningham WM, Tsodikov A. Relation of nutrients and hormones in polycystic ovary syndrome. *Am J Clin Nutr*. 2007;85:688–694.
111. Ozgen IT, Aydin M, Guven A, et al. Characteristics of polycystic ovarian syndrome and relationship with ghrelin in adolescents. *J Pediatr Adolesc Gynecol*. 2010;23:285–289.
112. Barber TM, Casanueva FF, Karpe F, et al. Ghrelin levels are suppressed and show a blunted response to oral glucose in women with polycystic ovary syndrome. *Eur J Endocrinol*. 2008;158:511–516.
113. Rashad NM, Saraya YS, Afifi SA, et al. Impact of weight loss on plasma ghrelin level, clinical, and metabolic features of obese women with or without polycystic ovary syndrome. *Middle East Fertil Soc J*. 2019;24:12.
114. Lin T, Li S, Xu H, et al. Gastrointestinal hormone secretion in women with polycystic ovary syndrome: an observational study. *Hum Reprod*. 2015;30:2639–2644.
115. Vrbikova J, Hill M, Bendlova B, et al. Incretin levels in polycystic ovary syndrome. *Eur J Endocrinol*. 2008;159:121–127.
116. Gama R, Norris F, Wright J, et al. The entero-insular axis in polycystic ovarian syndrome. *Ann Clin Biochem*. 1996;33(Pt 3):190–195.
117. Ferjan S, Jensterle M, Oblak T, et al. An impaired glucagon-like peptide-1 response is associated with prediabetes in polycystic ovary syndrome with obesity. *J Int Med Res*. 2019;47:4691–4700.
118. Pontikis C, Yavropoulou MP, Toulis KA, et al. The incretin effect and secretion in obese and lean women with polycystic ovary syndrome: a pilot study. *J Womens Health (Larchmt)*. 2011;20:971–976.
119. Milewicz T, Migacz K, Kiałka M, et al. Basic and meal stimulated plasma GIP levels are higher in lean PCOS women with FAI over 5. *Exp Clin Endocrinol Diabetes*. 2016;124:77–81.
120. Ferjan S, Janez A, Jensterle M. Dpp4 inhibitor sitagliptin as a potential treatment option in metformin-intolerant obese women with polycystic ovary syndrome: a pilot randomized study. *Endocr Pract*. 2018;24:69–77.
121. Rao M, Zumbro EL, Broughton KS, et al. Whey protein preload enhances the active GLP-1 response and reduces circulating glucose in women with polycystic ovarian syndrome. *Nutr Res*. 2021;92:84–98.
122. Glintborg D, Mumm H, Holst JJ, et al. Effect of oral contraceptives and/or metformin on GLP-1 secretion and reactive hypoglycaemia in polycystic ovary syndrome. *Endocr Connect*. 2017;6:267–277.
123. James S, Moralez J, Nagamani M. Increased secretion of amylin in women with polycystic ovary syndrome. *Fertil Steril*. 2010;94:211–215.
124. Kritikou S, Saltamavros AD, Adonakis G, et al. The $alpha_{2B}$ and $beta_3$ adrenergic receptor genes polymorphisms in women with polycystic ovarian syndrome (PCOS) and their association with insulin resistance and basal metabolic rate (BMR). *Rev Clin Pharmacol Pharmacokinet Int Ed*. 2006;20:238–240.
125. Koika V, Marioli DJ, Saltamavros AD, et al. Association of the Pro12Ala polymorphism in peroxisome proliferator-activated receptor gamma2 with decreased basic metabolic rate in women with polycystic ovary syndrome. *Eur J Endocrinol*. 2009;161:317–322.
126. Rodrigues A, Costa ABP, Campos DL, et al. Low validity of predictive equations for calculating resting energy expenditure in overweight and obese women with polycystic ovary syndrome. *J Hum Nutr Diet*. 2018;31:266–275.
127. Di Sarra D, Tosi F, Bonin C, et al. Metabolic inflexibility is a feature of women with polycystic ovary syndrome and is associated with both insulin resistance and hyperandrogenism. *J Clin Endocrinol Metab*. 2013;98:2581–2588.

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