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Beyond PCOS: hormonal determinants of insulin resistance in normal-weight women of reproductive age - a scoping review

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Abstract

Background/Purpose: Insulin resistance (IR) in normal-weight women is poorly understood and traditionally associated almost exclusively with polycystic ovary syndrome (PCOS). We aimed to map the available literature on the hormonal determinants of IR in normal-weight women of reproductive age.

Methods: The review is compliant with the PRISMA-ScR (2020) guidelines and the Joanna Briggs Institute methodology. PubMed and the Cochrane Library (March 2026) were searched, intentionally omitting the term "PCOS" from the search strategy to capture evidence relevant to women without this condition. The review included 30 studies (approximately 6,500 participants from 17 countries) covering androgens, adipokines, and other factors. Study quality (Newcastle-Ottawa scale) averaged 7.4 out of 9.

Results: 29 of the 30 studies involved women with PCOS, indicating a narrowly defined research interest in this topic. Classic androgen markers - the free androgen index and sex hormone-binding globulin - lost their predictive value for IR in normal-weight women, unlike at higher body mass index (BMI), suggesting a different pathophysiological mechanism. Various adipokines and adipose tissue hormones maintained their association with IR regardless of BMI. The role of anti-Müllerian hormone remained ambiguous. In one study, thyroid-stimulating hormone emerged as an independent predictor of IR. IR was also observed in control groups without PCOS.

Conclusions: A methodologically robust literature on the determinants of IR in normal-weight women is needed, especially beyond the context of PCOS. Filling this gap could lead to improved diagnosis and treatment in this overlooked population. The current literature is heterogeneous and draws primarily correlational conclusions.

Keywords: Insulin Resistance; Polycystic Ovary Syndrome; Body Mass Index; Androgens; Adipokines

1. Introduction

Insulin resistance (IR) is a metabolic disorder characterised by reduced tissue sensitivity to insulin, despite normal or elevated blood insulin levels [1]. Although traditionally associated with a high body mass index (BMI), insulin resistance is not exclusive to overweight individuals [2]. An increasing number of publications are focusing on concepts such as 'metabolically obese normal weight' (MONW), describing normal-weight individuals who still show hyperinsulinemia, insulin resistance, and elevated cardiometabolic risk [3].

Many internal factors, not directly linked to increased body weight, can desensitise tissues to insulin. Excess androgens can impair insulin mechanism of action, reducing insulin receptor autophosphorylation, causing a reduction in expression or translocation of insulin-responsive glucose transporters and defects in downstream insulin signaling [4]. Thyroid dysfunction may also contribute to insulin resistance and disturbances in glucose homeostasis. Prospective clamp-based data demonstrated that high-normal free triiodothyronine (fT3) predicted lower future insulin sensitivity [5]. Other research shows that higher fT3 was associated with higher fasting glucose, higher fasting and postload insulin, higher Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and lower insulin sensitivity indices, especially in the younger population [6].

Adipose tissue is now regarded as an endocrine organ. The adipokines it produces may act as mediators of metabolic inflammation, which predisposes the body to insulin resistance [7]. People with a normal BMI may still have a high body fat percentage.

However, the existing literature on the determinants of insulin resistance has mainly focused on overweight populations. Despite the prevalence of normal-weight women with hormonal disorders, there is insufficient research on this topic. Most of the literature focuses on polycystic ovary syndrome (PCOS), which, though common, does not account for all cases of insulin resistance in lean women.

This scoping review aimed to map and summarise the available literature on the hormonal determinants of insulin resistance in normal-weight women of reproductive age.

2. Methods

2.1. Study design

Given the exploratory nature of the research question and the high heterogeneity of the data, the authors decided to conduct a scoping review. The research procedure was based on the classic five-step methodological framework developed by Arksey and O'Malley [8]. This process was updated with the latest methodological guidelines from the Joanna Briggs Institute (JBI) presented by Peters et al. [9]. The reporting of results and the structure of this article were prepared in accordance with the PRISMA-ScR (PRISMA Extension for Scoping Reviews) guidelines developed by Tricco et al. [10]. The selection of sources was carried out by the lead author, which constituted a modification of the standard JBI procedure [9]. To ensure consistency, this process was carried out in stages based on strict inclusion and exclusion

criteria (Population, Concept, Context [PCC]). Any ambiguities or borderline cases regarding the eligibility of articles were discussed and resolved by consensus with the research team. The protocol was not registered with PROSPERO, which constitutes a limitation.

2.2. Search strategy

In March 2026, two databases were searched: PubMed/MEDLINE and the Cochrane Library. The following search string was used when searching PubMed:

("Insulin Resistance"[Mesh] OR "insulin resistance"[tiab] OR HOMA-IR[tiab]) AND ("normal weight"[tiab] OR "normal BMI"[tiab] OR "lean"[tiab] OR "non-obese"[tiab]) AND ("Female"[Mesh] OR women[tiab] OR female[tiab]) AND ("premenopausal"[tiab] OR "reproductive age"[tiab] OR "hormonal"[tiab] OR "hormone"[tiab] OR "endocrine"[tiab]) NOT ("Pregnancy"[Mesh] OR "Adolescent"[Mesh] OR "Child"[Mesh])

In addition, the following automatic filters were applied: articles published in the last 10 years, in English, and studies in humans. The Cochrane Library was searched using the terms 'insulin resistance normal weight women hormones.' The Embase database was not searched due to a lack of institutional access, and this was noted as a limitation. The search was not restricted to specific hormonal factors or women with PCOS to identify the widest possible spectrum of hormonal determinants of IR.

2.3. Eligibility criteria

The inclusion criteria were established using the PCC framework and are presented in Table 1.

Table 1. Eligibility criteria defined according to the PCC framework

	Inclusion criteria	Exclusion criteria
Population	Premenopausal women aged between 18 and 49 with a BMI within the normal range (18.5–24.9 kg/m ²); studies with region-specific BMI thresholds (e.g., <23 kg/m ² for Asian populations) were also included	Pregnant or postmenopausal women; adolescents under 18 years of age; studies exclusively including overweight or obese participants without a normal-weight subgroup analysed separately
Concept	Assessment of at least one hormonal or endocrine determinant of insulin resistance; objective measurement of insulin resistance by an established method (HOMA-IR, hyperinsulinaemic-euglycaemic clamp, FSIVGTT, or QUICKI)	Studies in which hormonal determinants of insulin resistance were not reported; studies without an objective measure of insulin resistance
Context	No geographical restrictions; papers available in English; original studies	Reviews, editorials, case reports, conference abstracts, and animal studies; retracted articles; studies for which full text was unavailable

2.4. Study selection

The selection of studies for the review was carried out through a two-stage screening process. In the first stage, titles and abstracts were screened (n=248). Sixty studies were selected for the full-text review stage. At this stage, the reasons for exclusion were documented. A total of 30 studies were eventually included in the review. A single reviewer performed screening; however, any ambiguous cases were resolved by consensus with the research team. The flow of studies through the individual stages of selection is presented in the PRISMA-ScR 2020 diagram (Figure 1).

2.5. Data extraction and quality assessment

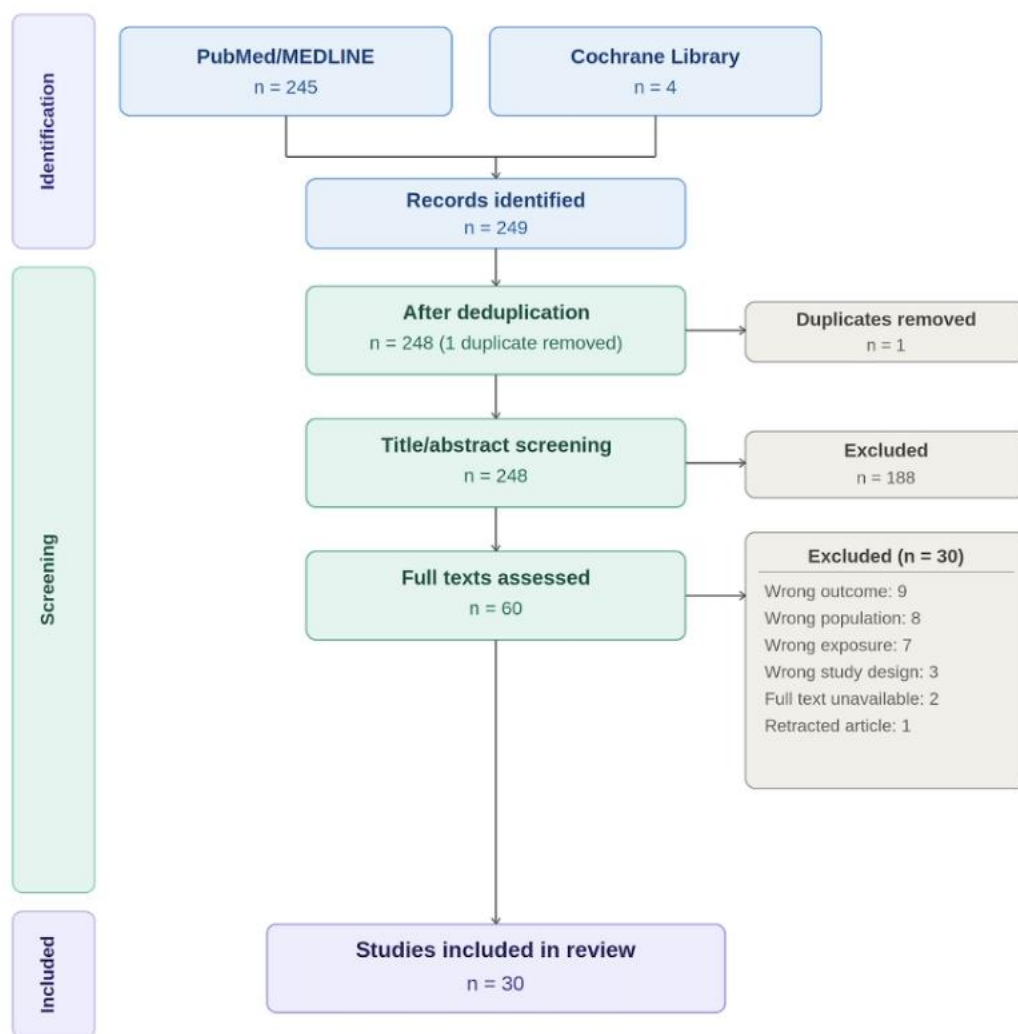
Data from the 30 selected studies were extracted into a structured form. The following information was entered into the table for each study: bibliographic details (author, year, country, journal), study design, diagnostic criteria for PCOS used (where applicable), the total sample size, the subgroup with normal body weight and the control group, the demographic characteristics of the participants (age, BMI), the definition of normal body weight adopted by the authors, the method of measuring insulin resistance along with the diagnostic threshold used, and the prevalence of IR in the study population. A key element was the extraction of hormonal factors (up to four per study) along with their findings regarding insulin resistance. The main conclusion of the study and its limitations were also noted.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS, 0–9 points): ≥ 7 = high, 4–6 = moderate, ≤ 3 = low.

3. Results

3.1. Study selection

A search of two databases (PubMed/MEDLINE and the Cochrane Library) identified 249 records (245 + 4). After removing 1 duplicate, 248 records underwent title and abstract screening. At this stage, 188 records were excluded, and 60 studies were selected for full-text assessment. Following a review of the full texts, 30 studies were excluded – the most common reasons were wrong outcome (n=9), wrong population (n=8), and wrong exposure (n=7), whilst the remaining reasons were wrong study design (n=3), unavailability of the full text (n=2), and one retracted article (n=1). Ultimately, 30 studies were included in the review. The full selection flow is shown in Figure 1 (PRISMA-ScR 2020 diagram).



Search conducted: March 2026 | Databases: PubMed/MEDLINE, Cochrane Library
Adapted from PRISMA-ScR 2020 (Tricco et al., Ann Intern Med 2018)

Figure 1. PRISMA-ScR 2020 flow diagram of study identification, screening, and inclusion. Of 249 records identified in PubMed/MEDLINE and the Cochrane Library (search conducted March 2026), 30 studies met the eligibility criteria and were included in the review.

3.2. Overview

The 30 studies included were published between 2016 and 2026, including seven in 2016 alone. The total number of study participants was 6,534, of whom 2,704 were of normal weight. The vast majority were cross-sectional studies with various designs; only two studies employed a prospective cohort design. Only one of the 30 included studies did not analyse women with PCOS. The predominant diagnostic criteria for PCOS were the 2003 Rotterdam criteria. Various BMI thresholds (e.g. one [\[11\]](#) using a threshold of BMI <27) and HOMA-IR cut-off points are used. Only one study used the euglycaemic clamp technique, which is considered the gold standard for assessing tissue sensitivity to insulin. The quality of the included studies was assessed using the Newcastle-Ottawa Scale. The average score across all 30 studies was 7.4. The quality of 25 studies was rated as high, and that of 5 as moderate.

Table 2. Characteristics of included studies (n = 30)

Study (ref)	Country	Design	N total / N NW	Age NW, mean $\pm$ SD (years)	Definition of "normal weight"	IR assessment method	NO S
Lazurova et al. (2021) (11)	Slovakia	Cross-sectional (preliminary)	64 / 34	27 $\pm$ 5	BMI <27 (non-standard)	HOMA-IR	5
Yildizhan et al. (2016) (12)	Turkey	Retrospective cross-sectional	100 / 100	24.2–24.9 (IR– / IR+)	BMI <25	HOMA-IR	6
Livadas et al. (2020) (13)	Greece/Serbia/Poland/Switzerland	Cross-sectional (multicentre)	1139 / 763	24.1 $\pm$ 4.9	BMI 20–25	HOMA-IR	8
Chen et al. (2021) (14)	China	Cross-sectional	161 / 49	28.6 $\pm$ 3.4	BMI <24 (Chinese)	HOMA-IR	8
Mansour et al. (2023) (15)	Iran	Cross-sectional (RCT baseline)	125 / 48	28 (22–32)*	BMI <25	HOMA-IR	7
Wang et al. (2016) (16)	Taiwan	Retrospective cross-sectional	229 / 229	26.9 $\pm$ 6.5	BMI <25	HOMA-IR	7
Reyes-Muñoz et al. (2016) (17)	Mexico	Retrospective cross-sectional	538 / 83	27.6 $\pm$ 4.2	BMI 18.5–24.9	HOMA-IR	7
Vitku et al. (2024) (18)	Czechia	Cross-sectional	51 / 10	28 (24–32)	Non-obese (median BMI 21.6)	HOMA-IR	8
Polak et al. (2020) (19)	Poland	Cross-sectional	73 / 39	23 (21–27)	BMI-matched (~22–24)	HOMA-IR	6
Peng et al. (2022) (20)	China	Cross-sectional	228 / NR	31–32 (median)	BMI <23 (Asian)	HOMA-IR; FSI	8
Foda & Foda (2019) (21)	Egypt	Case-control (pre-intervention)	180 / 50	NR	BMI <25	HOMA-IR	7

Pratama et al. (2024) (22)	Indonesia	Cross-sectional	110 / 110	25.7 ± 3.1	BMI 18.5–22.9 (Asia-Pacific)	HOMA-IR	5
Abdul-Maksoud et al. (2020) (23)	Egypt	Cross-sectional	210 / 70	34.2 ± 4.6	BMI <25	HOMA-IR	8
Sahin Ersoy et al. (2016) (24)	Turkey	Prospective cross-sectional	145 / 49	25.5 ± 5.1	BMI 18.5–24.9	HOMA-IR	8
Guvenc et al. (2016) (25)	Turkey	Cross-sectional	70 / 22	21.0 (16–38)	BMI 18.5–24.9 (WHO)	HOMA-IR	7
Lai et al. (2016) (26)	China	Cross-sectional (newly diagnosed)	199 / NR	26.0 ± 4.6	BMI <25	EHC (gold standard); HOMA-IR; OGTT	9
Li X-J et al. (2021) (27)	China	Prospective cohort	295 / 73	~27.5 ± 4.1	BMI 18.5–24.9	HOMA-IR	8
Yanachkova & Stankova (2025) (28)	Bulgaria	Retrospective cross-sectional	157 / 83	28.0 ± 5.2	BMI <25	HOMA-IR; OGTT	7
Li et al. (2024) (29)	China	Cross-sectional	319 / 145	24.2 ± 4.6	BMI 18.5–25 (Asia-Pacific)	HOMA-IR; OGTT	8
Dadachanji et al. (2021) (30)	India	Case-control	759 / 160	23.2 ± 4.4	BMI <23 (Asian/Indian)	HOMA-IR; QUICKI	8
Šimková et al. (2020) (31)	Czechia	Cross-sectional	39 / 9	28.9 ± 7.4	BMI 18.5–25	HOMA-IR	7
Feng et al. (2024) (32)	China	Cross-sectional	160 / 62	28.4 ± 4.3	BMI 18.5–25	HOMA-IR	7
Ganie et al. (2016) (33)	India	Cross-sectional	168 / 122	23.4 ± 5.4	BMI 18–25	HOMA-IR; QUICKI; OGTT	9

González et al. (2019) (34)	USA	Cross-sectional	39 / 10	28 ± 1	BMI 18–25	ISOGTT (Matsuda index)	8
Cundubey & Cam (2023) (35)	Turkey	Cross-sectional	80 / 30	25.7 ± 3.2	BMI 18.5–24.9	HOMA-IR	7
Fanelli et al. (2017) (36)	Italy	Cross-sectional (general population)	328 / 60	39.0 ± 8.6	BMI 18.5–24.9	HOMA-IR	9
Zhang H. et al. (2023) (37)	China	Cross-sectional	305 / 49	29.4 ± 5.8	BFP <35%; WHR <0.85	HOMA-IR; QUICKI; G/I	8
Zhang Y. et al. (2026) (38)	China	Cross-sectional	115 / 115	27.4 ± 4.0	BMI 18.5–24 (Chinese); BFP subgroups	HOMA-IR; OGTT	7
Dumesic et al. (2019) (39)	USA	Prospective cohort	28 / 10	26.0 ± 1.6	BMI 19–25	Adipose-IR; HOMA-IR; IVGTT	8
Anik İlhan et al. (2018) (40)	Turkey	Retrospective cross-sectional	120 / 120	24.4–25.4 (IR+ / IR–)	BMI <25	HOMA-IR; QUICKI; FGIR	5

NW — normal weight; IR — insulin resistance; NOS — Newcastle-Ottawa Scale (0–9); HOMA-IR — Homeostatic Model Assessment of Insulin Resistance; QUICKI — Quantitative Insulin Sensitivity Check Index; OGTT — oral glucose tolerance test; EHC — euglycemic-hyperinsulinemic clamp (gold standard); ISOGTT — insulin sensitivity index derived from OGTT; FSI — fasting serum insulin; FGIR — fasting glucose-to-insulin ratio; BFP — body fat percentage; WHR — waist-to-hip ratio; G/I — glucose-to-insulin ratio; IVGTT — intravenous glucose tolerance test; NR — not reported.

* Age reported for the whole cohort; not disaggregated for the normal-weight subgroup in the source study.

3.3. Androgens, SHBG, and FAI as determinants of insulin resistance

The included studies assessed the relationship between androgens, sex hormone-binding globulin (SHBG)/free androgen index (FAI), and insulin resistance in normal-weight women in various ways, with the results regarding SHBG being particularly inconsistent.

Yildizhan et al. (2016) [12] compared women with PCOS of normal body weight, divided into two groups based on the presence or absence of insulin resistance. In the study, HOMA-IR values correlated positively with estradiol levels ($r = 0.218$, $p < 0.05$) and total testosterone levels ($r = 0.291$, $p < 0.01$). The presence of insulin resistance also correlated with metabolic factors such as waist-to-hip ratio (WHR; $r = 0.500$, $p < 0.01$), systolic blood pressure ($r = 0.265$, $p < 0.01$), and diastolic blood pressure ($r = 0.273$, $p < 0.01$).

Livadas et al. (2020) [13], in a multicentre study of 763 lean women with PCOS and 376 lean controls stratified by age (17–25, 26–35, 36–47 years), identified dehydroepiandrosterone sulfate (DHEAS) as an independent predictor of HOMA-IR in multiple regression ($\beta=0.382$, $SE=0.060$, $p<0.001$); in univariate analysis, however, age showed the strongest association ($\beta=-0.19$, $p=0.014$). HOMA-IR was higher in PCOS than in controls only in the youngest group (2.30 vs 1.88, $p<0.001$), with no difference at 26–35 or 36–47 years ($p=0.82$ and $p=0.54$), whereas androgens remained significantly elevated across all age groups ($p<0.001$ – 0.05). The authors argue this contradicts a simple model of hyperandrogenism driving insulin resistance in lean PCOS, proposing a bidirectional relationship. The cross-sectional design limits interpretation of age-related change.

A summary of the included studies reveals an ambiguous picture regarding SHBG. Chen et al. [14] demonstrated moderate discriminatory power of SHBG in identifying insulin resistance in women with PCOS and normal weight (area under the curve [AUC] = 0.774), but the predictive value of this index appears to decrease in more complex models incorporating other hormonal and metabolic variables. The authors propose SHBG as a potential screening marker for IR in normal-weight women with PCOS, though they acknowledge that its predictive value is greater in the overweight/obese subgroup (AUC=0.922 and 0.928, respectively). In the study by Mansour et al. [15], there was no significant correlation between SHBG and HOMA-IR in the subgroup of women with normal weight ($r = -0.120$, $p = 0.418$), in contrast to the overweight/obese subgroup, where the relationship was significant ($r = -0.372$, $p = 0.001$). In multivariate analysis by Wang et al. [16], SHBG was not an independent predictor of insulin resistance in the group of non-obese women, and thyroid-stimulating hormone (TSH) was the only significant predictor. This pattern suggests that the association between SHBG and insulin resistance may be less robust in normal-weight women than in those with excess adiposity.

In Reyes-Muñoz et al. (2016) [17], despite BMI stratification, conclusions on IR determinants were generalised to the whole cohort. The authors report correlations with HOMA-IR for androstenedione ($r=0.15$, $p=0.001$), FAI ($r=0.19$, $p=0.0001$), and SHBG ($r=-0.13$, $p=0.01$). These correlations, although significant, were weak ($r=0.13$ – 0.19) and, given the large sample ($n=538$), may not be clinically meaningful. The study also concerned exclusively infertile women.

Vitku et al. (2024) [18] found significant positive correlations with HOMA-IR for 11-ketotestosterone ($r=0.366$, $p=0.011$), androstenedione ($r=0.471$, $p=0.001$), and testosterone ($r=0.357$, $p=0.014$); the remaining 11-oxygenated androgens (11 β OHA4, 11OHT) were non-significant. These correlations derive from the combined analysis of all groups ($n=51$: lean PCOS $n=10$, obese PCOS $n=9$, idiopathic hirsutism $n=12$, controls $n=20$), precluding conclusions specific to the lean phenotype.

3.4. Adipokines and adipose tissue hormones

Several studies have examined the role of adipokines (leptin, ghrelin, irisin, visfatin, WNT1-inducible signaling pathway protein 1 [WISP1], betatrophin, chemerin, zinc- α 2-glycoprotein [ZAG]) as a potential link between hyperandrogenism and insulin resistance, regardless of BMI.

Polak et al. (2020) [19] highlight the importance of tissue-derived hormones in lean PCOS. In their study of non-obese BMI-matched women, leptin levels were significantly positively correlated with HOMA-IR in the PCOS group ($r=0.5$, $p<0.01$), whilst total ghrelin levels were significantly negatively correlated with HOMA-IR ($r=-0.4$, $p=0.03$). Leptin, ghrelin, and HOMA-IR did not differ significantly between PCOS patients and BMI-matched controls (all $p>0.05$). The authors emphasise that their findings are correlational and that causality cannot be established.

Peng et al. (2022) [20] demonstrated a moderate and significant correlation between leptin and HOMA-IR ($r = 0.415$), despite the lack of separate results for BMI subgroups. Analyzing the lean phenotype, leptin levels were higher in the hyperandrogenic than in the normoandrogenic PCOS subgroup, regardless of BMI, marking leptin as a potential bridge between hyperandrogenism and insulin resistance. Like Li X-J et al. (2021) [27], this study combined anti-Müllerian hormone (AMH) with leptin; the combination showed high predictive value for PCOS (AUC 92.3%, sensitivity 93.3%, specificity 78.3%).

Although Foda & Foda's (2019) [21] study was an interventional trial, we focused on the preliminary assessment before ovarian drilling. Irisin levels were significantly higher in PCOS patients, compared with matched controls, before drilling ($p<0.0001$ in both weight groups). In the normal-weight PCOS group (BMI < 25, $n = 50$), irisin correlated with HOMA-IR before drilling ($r = 0.77$; $p = 0.001$); in the overweight group, this correlation was also present but weaker ($r = 0.399$, $p = 0.048$). In the normal-weight PCOS group, no statistically significant association was found between irisin and BMI, in contrast to the overweight PCOS group ($r = 0.634$; $p = 0.002$). Unfortunately, the authors did not examine correlations for the control groups. The decrease in irisin following drilling was accompanied by a decrease in both androgens and HOMA-IR, which can be interpreted, as in the case of Pratama et al. (2024) [22] or Peng et al. (2022) [20], as supporting the theory that androgens influence insulin resistance via adipokines.

In non-obese women with PCOS ($n=70$), Abdul-Maksoud et al. (2020) [23] found visfatin mRNA correlated with fasting insulin ($r=0.572$) and HOMA-IR ($r=0.543$), and sterol regulatory element-binding protein 1c (SREBP-1c) mRNA with insulin ($r=0.564$) and HOMA-IR ($r=0.679$; all $p<0.001$); these correlations were non-significant in obese PCOS. The authors propose visfatin as a compensatory response to insulin resistance, with both markers potentially contributing to PCOS pathogenesis independently of obesity.

Sahin Ersoy et al. (2016) [24] reported higher serum WISP1 and betatrophin in PCOS than in controls, with higher concentrations in the obese than the normal-weight PCOS subgroup. Both

correlated positively with HOMA-IR across the combined population (WISP1: $r=0.451$; betatrophin: $r=0.395$; both $p<0.001$), although not analysed separately in the normal-weight subgroup. In multivariate regression, HOMA-IR independently predicted both WISP1 ($\beta=0.149$, $p=0.002$) and betatrophin ($\beta=0.385$, $p=0.002$) after adjustment for BMI and other confounders, suggesting these associations are not entirely mediated by adiposity.

Guvenc et al. (2016) [25] reported a positive correlation between chemerin and HOMA-IR in normal-weight PCOS; however, no patient met the IR threshold (HOMA-IR ≥ 2.0), limiting clinical relevance.

Although Lai et al. (2016) [26] did not stratify their correlation analyses by body weight, their observation that ZAG remained lower in lean women with PCOS compared with lean controls (a descriptive comparison of mean values without p-values), combined with a significant negative correlation between ZAG and HOMA-IR ($r = -0.51$, $p < 0.001$) in the entire PCOS group, suggests, though doesn't directly prove, that the ZAG-IR relationship may not result solely from obesity.

3.5. AMH and the LH/FSH axis

The role of AMH in insulin resistance remains unclear – studies differ both in the direction of the relationship between AMH and IR and in whether AMH plays a causal or mediating role in the relationship with gonadotropic hormones.

Li X-J et al. (2021) [27] found that elevated AMH levels were associated with a higher risk of IR, specifically among obese women with PCOS, where high AMH levels corresponded to significantly higher HOMA-IR values. No such association was observed when comparing high and normal AMH levels among normal-weight PCOS women. Notably, in the normal-weight subgroup, high AMH was associated with significantly higher fasting insulin levels (20.14 vs. 10.71 $\mu\text{U/ml}$, $p<0.001$). The authors suggested that this may indicate a role for AMH in the early stages of insulin resistance pathogenesis, with the full-blown condition becoming apparent only in the presence of concomitant obesity. The study also incorporated in vitro experiments, which showed that the combination of high AMH and leptin increased insulin secretion from isolated rat islet cells and enhanced the expression of pro-apoptotic proteins (Bax, caspase-3, caspase-8) under hyperglycaemic conditions, suggesting a potential mechanism whereby chronically elevated AMH, in combination with leptin, may accelerate beta-cell dysfunction.

In contrast, the study by Pratama et al. (2024) [22] did not demonstrate a direct effect of AMH on insulin resistance - rather, it indicated the opposite relationship: insulin resistance (HOMA-IR) and hyperandrogenism (FAI) lead to elevated AMH levels, which in turn are directly associated with the luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. In the path analysis, AMH functioned as an intermediary variable in the HOMA-IR/FAI – AMH – LH/FSH ratio pathway, rather than as a factor influencing insulin resistance itself. This would be consistent with the findings of Yanachkov & Stankov (2025) [28], whose study revealed a positive correlation between AMH and LH levels ($r = 0.249$, $p = 0.002$).

Furthermore, the direction of the difference in AMH levels between the normal-weight and obese PCOS phenotypes varied across studies (Li et al. (2024) [29]: higher AMH in the obese group; Vitku et al.: higher AMH in the normal-weight group[18]), which may be due to population or methodological differences between the studies and makes it difficult to interpret the role of BMI in modulating AMH in PCOS unequivocally.

Dadachanji et al. (2021) [30] compared different phenotypes of insulin resistance. Among lean women, glycemic and core insulin-resistance markers (fasting/2h glucose, insulin, HOMA-IR, and the quantitative insulin sensitivity check index [QUICKI]) did not differ significantly between PCOS phenotypes, despite significant differences in LH:FSH ratio and androgen-related parameters. This suggests that, in lean women, phenotypic endocrine severity was not accompanied by measurable differences in insulin resistance.

Šimková et al. (2020) [31] found higher AMH, LH, LH/FSH ratio, total and free testosterone, androstenedione, and 7 β -OH-epiandrosterone in normal-weight PCOS than in controls, with no differences in metabolic parameters including HOMA-IR. The small normal-weight PCOS group (n = 9) limits the power to detect such differences.

3.6. Prolactin

Studies examining prolactin (PRL) as a potential factor account for a small proportion of those included in the review, but their findings are consistent. These studies suggest that higher prolactin levels are consistently associated with greater insulin resistance in women with PCOS, even when BMI is normal; however, they do not yet prove a direct causal effect, but rather indicate an association. Feng et al. (2024) [32] demonstrated that, in women with PCOS and normal body weight, HOMA-IR was positively associated with prolactin levels, and in a multivariate regression analysis, PRL remained a positive factor associated with HOMA-IR. In turn, Yanachkova and Stankova (2025) [28] showed that in women with PCOS, hyperprolactinaemia co-occurred with higher fasting glucose, insulin, and HOMA-IR levels, and was also associated with a more than threefold increased risk of insulin resistance (OR=3.33, 95% CI 1.54–7.19; p=0.002).

3.7. Vitamin D and thyroid function

About vitamin D, a study conducted by Ganie et al. (2016) [33] found no association between vitamin D deficiency and insulin resistance; there was no significant correlation between 25-hydroxyvitamin D (25OHD) and HOMA-IR (r=0.115; p=0.13) or QUICKI (r=-0.112; p=0.14). The authors noted that this is inconsistent with earlier studies on the effect of vitamin D deficiency on the metabolism of obese women with PCOS.

A different picture emerges from the analysis of thyroid function: Wang et al. [16], studying 229 non-obese women of reproductive age with TSH levels within the reference range, demonstrated significantly higher TSH concentrations in women with insulin resistance and a positive correlation between TSH and HOMA-IR after adjusting for age and BMI; in a multivariate analysis, TSH proved to be the sole independent predictor of insulin resistance, stronger than androgens or adipokines.

3.8. Oxidative stress and other hormonal and metabolic determinants

Although the study by González et al. (2019) [34] is a mechanistic study with very small sample sizes involving lean women with PCOS (n=10) and lean controls (n=10), it provides interesting insights into the impact of oxidative stress on insulin sensitivity. The authors reported significantly lower insulin sensitivity (the oral glucose tolerance test-derived insulin sensitivity index [ISOGTT], Matsuda index) in lean women with PCOS compared with lean controls (7.7 ± 1.1 vs. 14.1 ± 2.2 , $P < 0.007$), accompanied by significantly higher levels of LH, testosterone, and androstenedione, whilst DHEA-S did not differ. Across the combined study groups (without stratification by BMI), lipid-induced oxidative stress markers (leukocytic reactive oxygen species (ROS) generation, p47phox expression, plasma thiobarbituric acid reactive substances [TBARS]) were negatively correlated with ISOGTT and positively correlated with basal and human chorionic gonadotropin (hCG)-stimulated androgen secretion, suggesting that oxidative stress acts as a parallel mediator linking hyperandrogenism and insulin resistance in PCOS, rather than a direct hormone-to-insulin-resistance pathway.

Cundubey and Cam (2023) [35] reported that in normal-weight women with PCOS, insulin resistance (HOMA-IR) correlated positively with serum phoenixin-14 (PNX-14) levels ($r = 0.65$, $p = 0.03$). PNX-14 concentrations were significantly higher in lean women with PCOS than in lean controls (9.11 ± 2.09 vs. 2.04 ± 0.11 pg/mL, $p < 0.01$) and were positively correlated with HOMA-IR, LH, and testosterone. No such correlations were observed in the non-PCOS control group. The authors discuss two potential mechanisms by which PNX-14 may contribute to insulin resistance: (1) stimulation of glucose-mediated insulin secretion via the cAMP/Epac pathway in pancreatic β -cells, and (2) promotion of preadipocyte differentiation into mature adipocytes through GPR173, which may increase adipokine secretion and thereby contribute to insulin resistance. These mechanistic explanations remain hypothetical, and the findings should be interpreted cautiously, given the relatively small sample size and the lack of multivariable analyses.

The study by Lazurova I. et al. [11] compares two groups of women with PCOS – obese and non-obese – using a BMI of 27 as the cut-off point between the groups; as the authors state, this was due to the study sample being too small to be divided into three BMI categories. This unusual classification constitutes a limitation for the analysis in our review. However, as it was the only study to analyse insulin-like growth factor (IGF), it was included in the review. According to the data presented by the authors, in linear regression analysis, IGF-1 showed a negative association with insulin ($R^2 = 0.25$, $p = 0.022$) and HOMA-IR ($R^2 = 0.23$, $p = 0.033$), whilst showing no correlation with sex steroids. The authors conclude that lower IGF-1 levels may be a predictor of metabolic syndrome in PCOS.

According to Mansour et al. [15], the only biochemical factor –apart from fasting glucose and insulin – significantly correlated with HOMA-IR in lean women was alanine aminotransferase (ALT; $r=0.290$, $p=0.046$), a surrogate marker of non-alcoholic fatty liver disease. The authors suggest that insulin resistance in normal-weight PCOS may be linked to hepatic involvement independent of obesity.

Fanelli et al. (2017) [36] examined plasma concentrations of 2-arachidonoylglycerol (2AG), a mediator of the endocannabinoid system, in the context of metabolic characteristics in the general population of adult women and men, stratified by BMI and menopausal status. In premenopausal women of normal weight, no significant correlation was found between 2AG and HOMA-IR or fasting insulin. The authors suggest that the endocannabinoid system does not play a measurable role in insulin resistance in conditions of normal hormonal function, and its metabolic significance becomes apparent only after menopause, with a decline in sex hormones, although the mechanism of this relationship is uncertain. The uniqueness of this study in the context of our review should be emphasized, as it is the only study including normal-weight women without PCOS as a research group, not just a control group.

3.9. Body composition and insulin resistance

The strongest evidence for the superiority of body fat percentage (BFP) over traditional anthropometric measures comes from a study by Zhang H. et al. (2022) [37]. The study also indicates a stronger association between BFP and insulin resistance in the PCOS group than in the control group (linear regression analysis), which indirectly suggests that certain components of PCOS may exacerbate aspects of the pathogenic pathway underlying lipid-induced impairment of glucose metabolism. At the same time, LH and the LH/FSH ratio were significantly higher in the PCOS group than in the controls, regardless of WHR/BFP stratification –this suggests that gonadotropic abnormalities in PCOS are relatively independent of body composition (in contrast to insulin resistance, which is strongly dependent on BFP). This contrasts with the findings presented by Zhang Y. et al. (2026) [38]. That study did not show any significant difference in the prevalence of IR between the high-BFP group and the normal-BFP group (14.49% vs. 8.70%). However, other determinants of carbohydrate metabolism disorders, such as blood glucose and insulin levels 2 hours after sugar intake, were higher in the high-BFP group than in the normal-BFP group. It should be noted that the latter study compared subgroups within a PCOS population rather than against healthy controls, which may partly account for the discrepancy. Whilst the above studies indicate that body fat percentage differentiates the metabolic profile, the study by Dumesic et al. (2019) [39] shows that even with identical total body weight and body fat percentage, women with PCOS and a normal BMI had significantly higher adipose-specific insulin resistance (adipose-IR) than controls - suggesting that not only the amount but also the function of adipose tissue differs in PCOS.

Anik Ilhan et al. (2018) [40] enrolled one hundred and twenty lean women with PCOS, of whom 39 were insulin-resistant. The authors demonstrated that both lipid accumulation product (LAP) and visceral adiposity index (VAI) correlate positively with FAI (LAP: $r = 0.202$, $p < 0.05$; VAI: $r=0.318$, $p<0.01$) and were significantly higher in the group with hyperandrogenism as measured by FAI in the IR+ subgroup (3.45 vs 2.20, $p=0.034$). The authors even suggest that LAP and VAI could serve as markers of hyperandrogenism in lean women with PCOS. Both indices also correlated with HOMA-IR (LAP: $r=0.270$; VAI: $r=0.199$, both $p<0.05$) in a group of 120 lean women with PCOS. It should be noted, however, that the discriminatory ability of these indices for predicting insulin resistance was modest: the AUC for LAP was only 0.62 (95% CI 0.51–0.73), and VAI did not reach statistical significance as a predictor (AUC=0.59). Although LAP and VAI are metabolic indices, the rationale for their inclusion in this review stems from the association with androgens analysed in the study.

4. Discussion

4.1. Summary of key findings

We conducted this scoping review to map the literature on hormonal determinants of insulin resistance in normal-weight, reproductive-age women. Of the 30 included studies, 29 focused on women with PCOS, the only exception being Fanelli et al. (2017) [36], which was conducted in the general population. The search strategy intentionally omitted the term "PCOS", aiming to obtain hormonal determinants of insulin resistance, regardless of whether the disorder was isolated or part of a syndrome. Nevertheless, almost all identified publications focused on PCOS, a significant finding reflecting the narrowing of research focus to this condition.

Two pairs of publications with likely cohort overlap were identified: Šimková et al. (2020) [31] and Vitku et al. (2024) [18], from the same centre in Prague, and Yildizhan et al. (2016) [12] and Anik Ilhan et al. (2018) [40], from the same research team (Marmara University). In both cases, the lack of sufficient information about the recruitment stage prevents us from confirming or ruling out partial participant overlap. This further limits the effective number of independent sources.

The heterogeneity in the definitions used across the included studies is a notable limitation of this field, evident in the BMI thresholds used to classify normal body weight, the methods used to assess insulin resistance, and the HOMA-IR cut-off points used to diagnose it.

The evidence was predominantly correlational, rather than causal. Almost all of the included studies were cross-sectional; only Dumesic et al. [39] and Li X-J et al. [27] used a prospective cohort design, which makes it impossible to determine whether insulin resistance results from or is a cause of the hormonal disturbances studied. Finally, insulin resistance is not a phenomenon limited to PCOS; in several studies (e.g. Zhang H. et al. [37], and in the only non-PCOS study, Fanelli et al. [36]), insulin resistance or its correlates were also present in control groups, suggesting that insulin resistance in normal-weight women extends beyond PCOS, even if the available literature rarely goes beyond this context.

Across the included studies, a recurring pattern was the weakening of classic androgenic markers (FAI, SHBG) as predictors of IR in normal-weight women: these associations were reported as non-significant in lean subgroups while remaining significant in overweight or obese women [15]. Several studies instead examined adipokines (leptin, irisin, visfatin, WISP1, betatrophin) as potential mediators between hyperandrogenism and IR. Evidence on AMH was inconsistent, both in the direction of differences between lean and obese PCOS phenotypes and in its proposed position in the causal chain; Pratama et al. [22] modelled AMH as an intermediate rather than a determinant of IR.

4.2. Comparison with existing literature

Despite the limited evidence base - only one included study used a euglycemic clamp and most data came from cross-sectional PCOS cohorts - the overall pattern was that lean women can still show clinically relevant insulin resistance. This is consistent with a clamp-based meta-

analysis reporting a 27% reduction in insulin sensitivity in PCOS versus controls independent of BMI, with higher BMI further worsening the defect [41].

In our review, SHBG and FAI often lost significance in lean subgroups, whereas their associations were clearer in overweight or obese women. This partly contrasts with the wider PCOS literature, where low SHBG has been linked to lower insulin sensitivity independent of BMI in clamp-based meta-analysis and has shown predictive value for metabolic abnormalities in mixed-BMI cohorts, while BMI itself still outperforms hormonal markers as the strongest overall predictor of metabolic risk [41, 42].

Our review's emphasis on adipose dysfunction is in agreement with existing literature. Mechanistic and clinical studies increasingly describe adipose tissue as an endocrine organ whose secreted adipokines influence insulin sensitivity and reproductive function [43]. This framework fits this review's findings on leptin, ghrelin, visfatin, chemerin, irisin, WISP1, betatrophin, and adipose-IR, and is reinforced by prospective evidence that normal-weight women with PCOS can have increased adipose-specific insulin resistance even when body weight and body fat percentage are similar to controls [39].

The most evident inconsistency concerns AMH. This review presents results regarding AMH as inconsistent: some studies linked higher AMH to higher fasting insulin or HOMA-IR, whereas others suggested AMH is better viewed as an intermediate within the HOMA-IR/FAI-AMH-LH/FSH pathway rather than a direct determinant of insulin resistance. This inconsistency mirrors the wider literature, where older and newer cohort studies reported positive AMH-HOMA-IR correlations [44,45], but a 2024 meta-analysis found the pooled association weak and statistically non-significant [46], indicating substantial heterogeneity between studies.

Of particular interest is the finding by Wang et al.[16], which identified TSH within the normal range as the only independent predictor of insulin resistance in a multivariate analysis conducted in a mixed population of women with normal body weight, not just PCOS. The relationship between thyroid function and insulin resistance has also been described in the general population: in a cross-sectional cohort study of healthy euthyroid men, thyroid function remained intrinsically linked to insulin sensitivity and was more pronounced in the lean group [47]. In contrast, in another cross-sectional study of a large obese cohort, TSH was not associated with insulin resistance after adjustment for confounders [48].

One of the central findings of our review is the presence of insulin resistance in lean women also outside the context of PCOS, including in control groups and in the only included study without PCOS [36]. This observation fits with the concept of "metabolically obese, normal weight" (MONW) women described previously in the literature, meaning individuals with a normal BMI who nevertheless experience hyperinsulinemia, insulin resistance, and increased cardiometabolic risk [3]. Contemporary studies confirm that the MONW phenotype remains a current, yet still poorly understood clinical problem [49]. This suggests that insulin resistance in lean women is not a phenomenon limited to hyperandrogenism or PCOS, but rather a component of a broader metabolic phenotype, directly justifying the research gap we identified regarding lean women with hormonal disorders other than PCOS.

However, in the broader literature, the relationship between age, hormonal profile, and metabolism in PCOS remains ambiguous. Huddleston et al.'s longitudinal study even demonstrated an increase in cardiovascular risk markers (triglycerides [TG], HOMA-IR) over time despite decreasing hyperandrogenemia [50]. It should be noted, however, that the follow-up period in this study was short (average 3.5–4 years) and the study cohort was relatively young, precluding the assessment of long-term cardiovascular risk trajectories, including perimenopause. The discrepancy between Livadas et al.'s observation and Huddleston et al.'s results emphasizes that hormonal and metabolic trajectories in PCOS may decouple with age, and the Livadas et al. result [13] is inconclusive and requires confirmation in prospective studies with a longer follow-up period.

4.3. Strengths and limitations

Our review follows PRISMA-ScR guidelines with a clear flow diagram, defined PCC, and systematic data extraction, facilitating the analysis of a heterogeneous field. We applied formal quality assessment (Newcastle-Ottawa Scale) for all 30 studies (mean 7.4/9; 25/30 high quality), which isn't common in scoping reviews. We also openly flag possible overlapping of cohorts, small sample sizes, and the correlational nature of the results. Above all, the intentional omission of "PCOS" from the search strategy revealed a significant literature gap: an overlooked group of lean women with hormonal disorders other than PCOS.

Our database is dominated by cross-sectional designs – only 2/30 studies (Dumesic [39], Li X-J [27]) were prospective. Some studies had very small sample sizes (Šimková n=9 [31], González n=10 [34], Cundubey & Cam n=30 [35]), limiting statistical power. A common design compared PCOS groups without a healthy control group, preventing conclusions on whether findings are specific to PCOS. We question the inclusion of Guvenc et al., which showed no IR in the NW PCOS group (HOMA-IR median 1.51). A single author performed selection and extraction, increasing the risk of bias. The review was not registered in PROSPERO, Embase was omitted due to a lack of institutional access, and no formal certainty-of-evidence assessment (e.g. the Grading of Recommendations, Assessment, Development and Evaluations [GRADE] approach) was applied.

4.4. Implications for future research and clinical practice

Further work on this topic would require an attempt to standardize the definition of "normal weight". Uniform BMI thresholds are needed to facilitate comparative analysis and exclude the influence of excess body weight on results. This would require the authors to abandon non-standard thresholds such as Lazurova's <27 kg/m² [11] and to strive for consensus on international differences in thresholds. The HOMA-IR thresholds for diagnosing IR would also require standardization to clearly define this disorder.

To establish the direction of hormonal dependencies and metabolic disorders, prospective studies are essential. Given the identified gap, we suggest that the authors conduct further studies in a normal-weight population, excluding women with PCOS, to determine whether the hormonal mechanisms described in this review are specific to PCOS or generalizable. This would facilitate clinicians' management of lean women, who, despite being at a healthy weight, struggle with insulin resistance but do not meet other diagnostic criteria for PCOS.

Standardization of the IR measurement method is also necessary. The gold standard (euglycemic clamp) was used in only one study [26]. There is a clear need for broader use of more precise methods than HOMA-IR in future studies.

Regarding the clinical implications of the specific results we extracted, further attention should be paid to the limited utility of classically cited determinants of insulin resistance in women with normal body mass. Since studies indicate that FAI and SHBG lose their predictive value in the normal-weight population, clinical assessment of IR risk in lean women with PCOS should not be based solely on these markers. Further research is needed on the potential role of adipokines and other biomarkers, such as TSH, as complementary screening tools for IR risk assessment.

The Livadas et al. finding (disappearance of the HOMA-IR difference after age 25) highlights the need to treat age as an outcome-related variable. Future studies should analyze IR in PCOS, taking into account age/time of onset of the disorder, rather than looking at populations cross-sectionally at a single time point. Future reviews should include a broader range of databases and register protocols in PROSPERO.

5. Conclusions

This scoping review mapped the available literature on hormonal determinants of insulin resistance in normal-weight, reproductive-age women. Analysis of 30 studies revealed significant heterogeneity in the evidence base and a clear research gap. This field is almost entirely dominated by studies focusing on women with polycystic ovary syndrome. The literature lacks studies specifically addressing lean women with insulin resistance unrelated to this syndrome.

The results of the analysis indicate that classic markers of hyperandrogenism, such as free androgen index and SHBG, lose their predictive value for insulin resistance in the normal-weight population, suggesting a different pathophysiological mechanism than in women with high BMI. Adipokines and adipose tissue hormones, however, appear to retain predictive value regardless of body weight, as do isolated, yet promising, findings regarding the role of TSH. The role of AMH remains ambiguous and requires further research to clarify its place in the causal chain.

Due to the significant methodological heterogeneity of the included studies, the predominance of cross-sectional designs, the correlational nature of most studies, and the limitations of the review itself, including the limited scope of the databases searched and the involvement of a single reviewer at the selection and data extraction stages, the ability to draw clear conclusions is limited.

Future research should strive to standardize the definition of normal body weight and insulin resistance thresholds, and, above all, include lean women with insulin resistance independent of PCOS – this will allow us to determine whether the hormonal mechanisms described are generalized or specific to this syndrome.

List of abbreviations

2-AG - 2-arachidonoylglycerol
25OHD - 25-hydroxyvitamin D
ALT - alanine aminotransferase
AMH - anti-Müllerian hormone
AUC - area under the curve
BFP - body fat percentage
BMI - body mass index
DHEAS - dehydroepiandrosterone sulfate
FAI - free androgen index
FSH - follicle-stimulating hormone
fT3 - free triiodothyronine
GRADE - Grading of Recommendations, Assessment, Development and Evaluations
hCG - human chorionic gonadotropin
HOMA-IR - homeostatic model assessment of insulin resistance
IGF - insulin-like growth factor
IR - insulin resistance
ISOGTT - insulin sensitivity index derived from the oral glucose tolerance test
JBI - Joanna Briggs Institute
LAP - lipid accumulation product
LH - luteinizing hormone
MONW - metabolically obese, normal-weight
NOS - Newcastle-Ottawa Scale
PCC - Population, Concept, Context
PCOS - polycystic ovary syndrome
PNX-14 — phoenixin-14
PRISMA-ScR - Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PRL - prolactin
QUICKI - quantitative insulin sensitivity check index
ROS - reactive oxygen species
SHBG - sex hormone-binding globulin
SREBP-1c - sterol regulatory element-binding protein 1c
TBARS - thiobarbituric acid reactive substances
TG - triglycerides
TSH - thyroid-stimulating hormone
VAI - visceral adiposity index
WHR - waist-to-hip ratio
WISP1 - WNT1-inducible signaling pathway protein 1
ZAG - zinc- α 2-glycoprotein

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Declaration of generative AI and AI-assisted technologies in the writing process.

During the preparation of this work, the authors used a generative AI assistant (a large language model) for the following purposes: language correction and improvement of the English text (as English is not the authors' first language); formatting and consistency checking of the reference list; formatting adjustments of the manuscript; partial preparation of tables and figures, organisation of the extracted data and structuring of work-flow. After using this tool, the authors reviewed and edited the content as needed and take responsibility for the content of the publication. The AI tool was not used to generate scientific interpretations, conclusions, or original data, and is not listed as an author.

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