Systematic Review

Association of Body Mass Index with Circulating Leptin and Irisin in Infertile Men: A Systematic Review

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ABSTRACT

Background: Obesity is linked to male infertility, but how adiposity relates to the adipokine leptin and the myokine irisin in infertile men is unclear. This review synthesized the evidence on the association of body mass index (BMI) with serum leptin and irisin in infertile males.

Methods: PubMed/MEDLINE, Scopus, Web of Science and the Cochrane Library were searched between April and September 2026, supplemented by Google Scholar and citation searching. Observational studies of adult infertile men reporting BMI and circulating leptin or irisin were eligible. Two reviewers independently screened records, extracted data and assessed risk of bias with ROBINS-E. Narrative synthesis followed SWiM; certainty was rated with GRADE.

Results: Ten studies (2007–2022; 1,749 men, 1,398 infertile) were included: eight on leptin and two on irisin. All eight leptin studies found higher leptin with higher BMI, significant in seven. Within infertile men, correlations ranged from r = 0.31 to 0.72, and leptin rose stepwise across WHO BMI categories. Leptin–semen associations weakened after BMI adjustment. Both irisin studies suggested lower irisin at higher BMI, but one correlation was non-significant on recalculation and the other confounded obesity with subfertility. No study was at low risk of bias; four had some concerns, three were high and three very high. Certainty was low for leptin and very low for irisin.

Conclusion: Higher BMI may be associated with higher serum leptin in infertile men, largely reflecting adiposity rather than an independent fertility marker. Evidence for irisin is very uncertain. Within-infertile studies with body-composition measures and standardized assays are needed.

Keywords: *Body Mass Index; Fibronectins; Infertility; Leptin; Obesity*

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INTRODUCTION

Infertility, defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected intercourse, affects about one in six people of reproductive age worldwide[1]; a global meta-analysis estimated its lifetime prevalence at 17.5%[2]. A male factor contributes to approximately half of these cases[3], yet up to 40% of infertile men have no recognized cause after routine clinical and laboratory evaluation[4]. This idiopathic group has prompted a search for modifiable systemic factors that may impair spermatogenesis.

Obesity is one such factor. Its prevalence has risen sharply among men of reproductive age, in parallel with reported declines in semen quality[5]. Excess adiposity is associated with lower testosterone and sex hormone-binding globulin (SHBG), higher oestradiol through adipose aromatase activity, raised scrotal temperature, oxidative stress and low-grade inflammation[5,6]. An updated collaborative meta-analysis linked overweight and obesity to lower sperm count, concentration and motility and to lower testosterone[7], and a 2024 meta-analysis found lower total sperm number and motility in obese men[8]. The average differences, however, were small, about 2–6 percentage points for motility[8]. BMI alone therefore says little about how excess fat affects the testis, and attention has turned to the hormones released by fat and skeletal muscle.

Leptin is the most extensively studied of these hormones. It is a 167-amino-acid peptide

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encoded by the *ob* gene and secreted by white adipocytes in proportion to fat mass[9]. Leptin links energy stores to reproduction: it supports gonadotropin-releasing hormone secretion through hypothalamic kisspeptin neurones[10], and its receptors are expressed in Leydig cells[11]. At the high concentrations typical of obesity, however, leptin may suppress testicular steroidogenesis and, through central leptin resistance, the hypothalamic–pituitary–gonadal axis[5,12].

A meta-analysis reported higher leptin in infertile than in fertile men[13], whereas a clinical study found no independent link with sperm characteristics once BMI was taken into account[14].

Irisin approaches the same metabolic question from the side of skeletal muscle. It is a myokine cleaved from fibronectin type III domain-containing protein 5 (FNDC5) in response to exercise; it promotes browning of white adipose tissue and has been linked to insulin sensitivity[15,16].

In mice fed a high-fat diet, irisin supplementation reduced testicular oxidative stress and germ-cell apoptosis through AMP-activated protein kinase α (AMPKα) signaling, restoring sperm count, motility and testosterone[17]. If leptin rises and irisin falls as adiposity increases, measuring both could describe the metabolic state of an obese infertile man better than either marker alone.

Human data on these markers are scattered. Most studies compared infertile with fertile men rather than examining how BMI relates to each marker within infertile men, the population in whom any metabolic intervention would be applied. Some pooled fertile and infertile men when reporting BMI–leptin correlations. BMI was also handled inconsistently: as a continuous variable, against World Health Organization (WHO) categories, against Asian cut-offs[18] that define obesity at ≥ 25 kg/m², or by enrolling only obese men. Assay platforms, specimen types and sample sizes differ widely, and human data on irisin in infertile men remain scarce. Much of the leptin evidence comes from South Asia and the Middle East, including Pakistan, where cardiometabolic risk appears at lower BMI thresholds[18]. To our knowledge, no systematic review has jointly synthesized the evidence on BMI in relation to both serum leptin, an adipokine, and serum irisin, a myokine, in infertile males.

We therefore conducted this systematic review to synthesize the available observational evidence on the association of BMI with serum leptin and irisin levels in infertile males. Our question was: in infertile men, is higher BMI associated with serum leptin and irisin levels? We aimed to (i) describe the direction and strength of the BMI–leptin and BMI–irisin associations, (ii) compare how BMI was categorized and how each marker was measured across studies, and (iii) identify methodological gaps to guide future research. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement[19].

METHODOLOGY

Protocol and Reporting

The review was conducted and reported according to the PRISMA 2020 statement[19]. The review question, eligibility criteria, risk-of-bias approach and synthesis plan were agreed before the search began. The protocol was not registered in PROSPERO or any other registry. Ethical approval was not required because only published, de-identified data were used.

Review Question and Eligibility Criteria

The review question was framed with the PECOS (Population, Exposure, Comparator, Outcomes, Study design) framework recommended for questions about exposures rather than interventions[20]: *in infertile men, is higher BMI associated with serum leptin and irisin levels?* Eligibility criteria are summarized in (Table 1).

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Table 1. Eligibility criteria (PECOS)

Element	Inclusion	Exclusion
Population	Adult men (≥ 18 years) with infertility: male partners of couples unable to conceive after ≥ 12 months of regular unprotected intercourse[1], or men classified as infertile or sub-fertile on semen analysis by WHO criteria[21],[22], including idiopathic infertility. Studies that also enrolled fertile men were eligible if data for infertile men were reported or could be identified.	Studies limited to women, adolescents or animals; men with infertility secondary to a single specified cause unrelated to adiposity (e.g., post-chemotherapy, spinal cord injury) where no general infertile sample was reported.
Exposure	BMI (kg/m²) calculated from weight and height, analyzed as a continuous variable or in categories (WHO cut-offs[23], Asian cut-offs[18] or study-specific cut-offs).	Adiposity measured only by indices other than BMI (e.g., waist circumference or body fat alone) with no BMI data.
Comparator	Infertile men with lower or normal BMI (within-group comparison or correlation). Fertile men were accepted as a comparison group when BMI data were reported.	—
Outcomes	Primary: circulating (serum or plasma) leptin and/or irisin in relation to BMI (correlation coefficient, mean levels across BMI categories, or regression estimate). Secondary: relation of each marker to semen parameters and reproductive hormones (testosterone, LH, FSH, SHBG, inhibin B).	Leptin or irisin measured only in seminal plasma or tissue; no BMI–marker data reported.
Study design	Observational studies: cross-sectional, comparative cross-sectional, case-control and cohort studies; the human component of mixed human–animal studies.	Animal or in-vitro studies only; randomized trials of interventions; reviews, editorials, case reports, conference abstracts without full data, and theses not published in peer-reviewed journals.
Other	Full-text articles in English, published from database inception to the search date.	Duplicate publications of the same cohort (the most complete report was retained).

INFORMATION SOURCES AND SEARCH STRATEGY

PubMed/MEDLINE, Scopus, Web of Science Core Collection and the Cochrane Library were searched between April and September 2026, covering all records from database inception to the final search in September 2026. Google Scholar (first 200 records ranked by relevance) was searched to identify records not indexed in the bibliographic databases. The reference lists of all included studies and of relevant reviews on obesity and male infertility were hand-searched, and forward citation searching of included studies was performed in Google Scholar.

The search combined three concept blocks (male infertility, BMI/obesity and the two markers) using Medical Subject Headings (MeSH) and free-text terms joined with OR within blocks and AND between blocks. The PubMed strategy is shown in (Table 2); it was translated for each database using the corresponding field tags (TITLE-ABS-KEY in Scopus; TS= in Web of Science). Irisin is indexed in MeSH under its precursor, FNDC5, so both names were searched.

Table 2. PubMed/MEDLINE search strategy

Block	Search terms
#1 Male infertility	"Infertility, Male"[MeSH] OR "male infertility"[tiab] OR "infertile men"[tiab] OR "infertile male*"[tiab] OR "male subfertility"[tiab] OR "sub-fertile men"[tiab] OR oligozoospermi*[tiab] OR azoospermi*[tiab] OR asthenozoospermi*[tiab] OR teratozoospermi*[tiab] OR "semen quality"[tiab]
#2 BMI / obesity	"Body Mass Index"[MeSH] OR "body mass index"[tiab] OR BMI[tiab] OR "Obesity"[MeSH] OR obes*[tiab] OR overweight[tiab] OR adiposity[tiab]
#3 Markers	"Leptin"[MeSH] OR leptin[tiab] OR "Fibronectins"[MeSH] OR irisin[tiab] OR FNDC5[tiab] OR "fibronectin type III domain-containing protein 5"[tiab] OR adipokine*[tiab] OR myokine*[tiab]
#4 Combined	#1 AND #2 AND #3; filter: Humans

Study Selection

Records from all sources were combined, and duplicates were identified and removed manually. Two reviewers (AM and AdM) then screened the titles and abstracts by hand, each working independently against the eligibility criteria, and read the full texts of records that appeared relevant. Reasons for excluding full-text articles were recorded. Disagreements at either stage were resolved by discussion and, when consensus could not be reached, by a third reviewer (HA). The selection process is presented in a PRISMA 2020 flow diagram (Figure 1)[19]. For studies with both human and animal components[17], only the human data were considered; for studies that enrolled both men and women[24], only data for men were used.

Data Extraction

Two reviewers extracted data independently using a standardized Microsoft Excel form, piloted on two included studies and refined before full use. Extracted data were cross-checked, and discrepancies were resolved by re-reading the full text and by discussion. The following items were extracted:

- **Study identifiers:** first author, year, journal, country and clinical setting, recruitment period and funding.
- **Design and population:** study design; number of infertile and, where present, fertile men; definition of infertility and semen classification; age; and key exclusion criteria (e.g., diabetes, hypertension, varicocele, medication use).
- **Exposure:** method of obtaining height and weight (measured or self-reported), how BMI was analyzed (continuous or categorical), cut-offs used (WHO, Asian or study-specific), mean BMI by group, and any additional adiposity measure (waist circumference, body fat % by bioelectrical impedance).
- **Outcome measurement:** specimen (serum or plasma), fasting status and time of sampling, storage conditions, assay type and manufacturer, and intra- and inter-assay coefficients of variation.
- **Results:** the BMI–leptin and/or BMI–irisin association (correlation coefficient with p-value and n, mean ± SD of the marker by BMI category, or adjusted regression estimate with 95% confidence interval), whether it was computed within infertile men or pooled across fertile and infertile men, covariates adjusted for, and associations of the marker with semen parameters and reproductive hormones.
- **Authors' conclusions** and limitations stated by the authors.

Values were transcribed as reported and harmonized afterwards. Leptin reported in µg/L was treated as equivalent to ng/mL. A standard error of the mean (SEM) was converted to a standard deviation (SD = SEM × √n)[25], and SDs implausibly small relative to the reported range were flagged as probable SEMs. Values presented only in figures were read from the figure and labelled as approximate. Correlations reported for fertile and infertile men combined were recorded as pooled estimates and kept separate from within-infertile estimates, because pooling groups that differ in both BMI and marker levels can create or inflate a correlation. Data not reported in the full text were recorded as "not reported".

Risk-of-Bias Assessment

Risk of bias was assessed for the result of interest in each study, the association of BMI or obesity category with serum leptin or irisin, using the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool, version 24 March 2024[26],[27]. Where a study also related the marker to semen quality or fertility status, that result was assessed as a secondary result. Two reviewers assessed each study independently and resolved disagreements by discussion.

ROBINS-E was developed for follow-up (cohort) studies. Because all included studies were cross-sectional or case-control, the tool was applied with adaptation. At the planning stage, the following confounders of the BMI–marker association were pre-specified: physical activity, muscle mass or body composition, diabetes or glycemic status, age, smoking, alcohol and diet, hypertension and relevant medication (e.g., metformin, statins, steroids), sampling conditions (fasting, time of day, recent exercise), abstinence period (for semen outcomes) and, where groups were pooled, fertility status. Physical activity and muscle mass were treated as critical for irisin, an exercise-induced myokine that BMI cannot distinguish from fat mass. Because leptin is secreted in proportion to fat mass, a large BMI–leptin association was judged less vulnerable to residual confounding.

For each study, the preliminary considerations and the evaluation of confounding factors were completed before the signaling questions for seven domains: (1) confounding, (2) measurement of the exposure, (3) selection of participants, (4) post-exposure interventions,

(5) missing data, (6) measurement of the outcome and (7) selection of the reported result. Each domain was judged as low risk, some concerns, high or very high risk of bias. In accordance with the ROBINS-E algorithm, a result for which question B2 (enough potential confounding to discard an unadjusted result) was answered "yes" or "probably yes" was judged at very high risk; the full domain judgments were nevertheless completed for transparency. The overall judgment corresponded to the most severe domain-level judgment.

Within domain 7, reviewers checked the internal consistency of reported statistics. Where a correlation coefficient and sample size were reported, the p-value was recalculated from $t = r\sqrt{(n-2)}/\sqrt{(1-r^2)}$ with $n-2$ degrees of freedom, and implausible SDs, values outside reported ranges and confidence intervals that did not contain their point estimate were recorded. Commercial irisin immunoassays have known validation problems[16], so assay platform and between-study differences in absolute irisin levels were considered in domain 6. Judgments were plotted as traffic-light and summary plots with the robvis tool (ROBINS-E template)[28].

Data Synthesis

The studies differed substantially in how BMI was analyzed (continuous, WHO categories, Asian cut-offs, a cut-off of 24 or 28 kg/m², or restriction to BMI > 30 kg/m²), in whether estimates were computed within infertile men or across pooled samples, in specimen and assay platform, and in the effect measure reported. A meta-analysis was therefore not considered appropriate. For irisin, only two studies were available, and their absolute concentrations differed four- to five-fold, consistent with assay differences. A structured narrative synthesis was undertaken and reported according to the Synthesis Without Meta-analysis (SWiM) guideline[29].

Studies were grouped first by marker (leptin, irisin) and then by how BMI was handled: (i) correlation of continuous BMI with the marker and (ii) comparison of marker levels across BMI categories. Within each group, the direction of the association (positive, negative or no clear association) and its statistical significance were tabulated, and magnitude was described using the reported correlation coefficients or between-category differences. Effect direction rather than p-values was used as the standardized metric across studies. Estimates derived within infertile men were given priority over pooled fertile–infertile estimates, which were reported separately.

Heterogeneity was explored descriptively across pre-specified characteristics: BMI classification system (WHO, Asian, study-specific or restricted range), sample composition (infertile only versus pooled), region (South Asia and the Middle East versus other regions), assay platform and specimen type, and overall risk of bias. Robustness was examined by restricting the synthesis to studies with some concerns (excluding those at high or very high risk of bias).

Certainty of Evidence

The certainty of the evidence for each association (BMI–leptin and BMI–irisin) was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[30], adapted for non-randomized studies assessed with ROBINS tools[31]. Evidence was rated as high, moderate, low or very low after considering risk of bias, inconsistency, indirectness, imprecision and publication bias, and could be rated up for a large magnitude of association or a dose–response gradient. Formal assessment of publication bias (e.g., funnel plots) was not possible because fewer than ten studies contributed to each association.

RESULTS

Study Selection

The database searches identified 425 records, and 35 further records were identified through Google Scholar and citation searching. After removal of 60 duplicates, 400 titles and abstracts were screened, of which 350 were excluded. The full texts of 50 articles were assessed for eligibility, and 40 were excluded, most commonly because they did not report BMI–marker data, examined seminal-plasma leptin only, involved animal studies, or were review articles. Ten studies met the eligibility criteria and were included[14,17,24,32–38]; eight examined serum leptin and two examined circulating irisin. No study was suitable for meta-analysis (see Data synthesis). The selection process is shown in Figure 1.

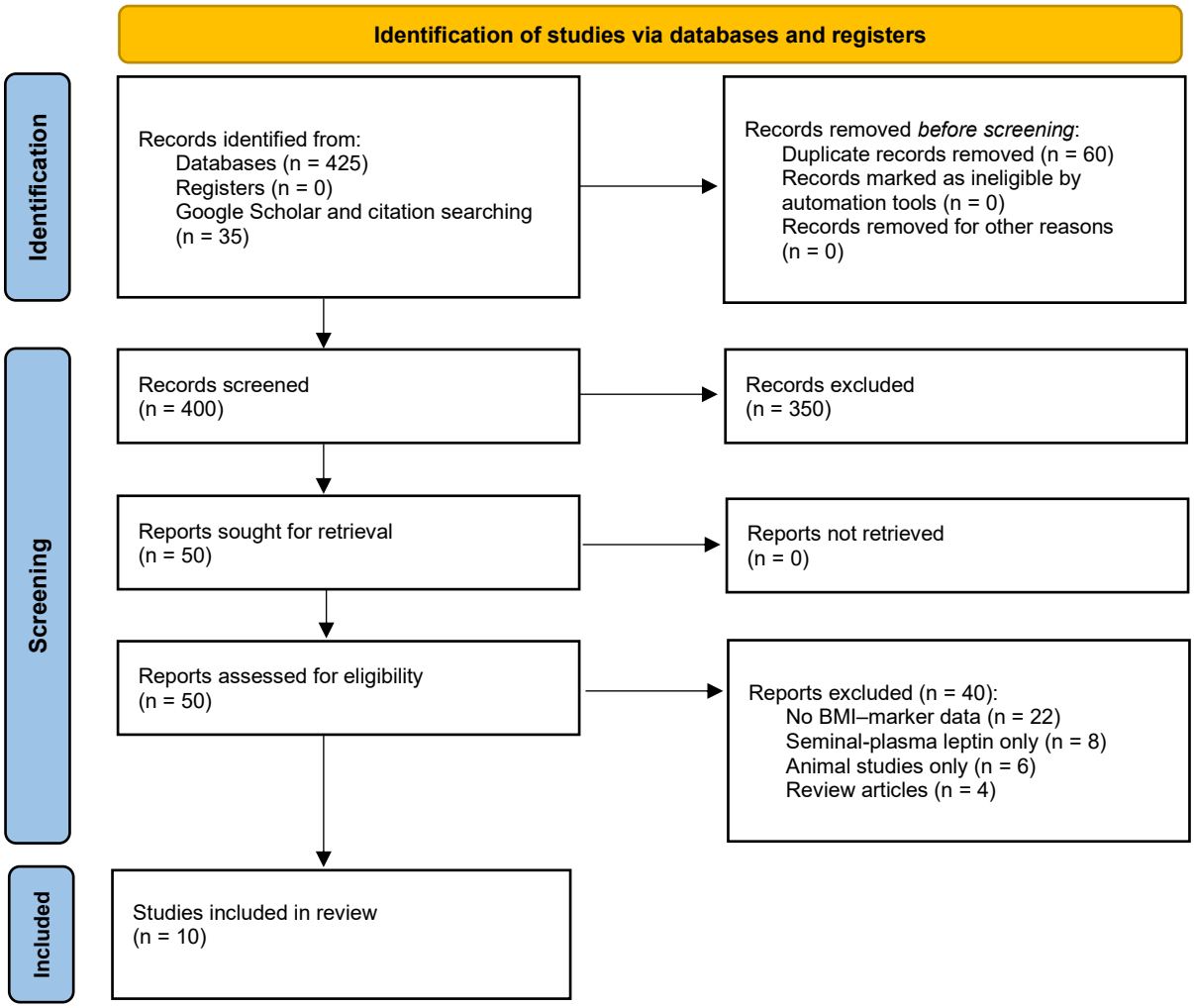


Figure 1. PRISMA 2020 flow diagram of study selection.

Characteristics of the Included Studies

The ten studies were published between 2007 and 2022 and together enrolled 1,749 men: 1,398 infertile or sub-fertile men and 351 fertile or healthy control men (Table 3). Sample sizes ranged from 19 to 526 (median 124). The eight leptin studies included 1,630 men and the two irisin studies 119 men.

Seven studies were conducted in South Asia, the Middle East or North Africa: three in Pakistan[24,33,34], two in Egypt[32,37], and one each in Iran[36] and Yemen[38]. The remaining three were conducted in China[17,35] and Slovenia[14]. Eight studies were cross-sectional, including three comparative cross-sectional designs[32,33,38], and two were case-control studies[24,37]. Mu et al.[17] contributed a small human arm to a predominantly animal study. Three studies enrolled only infertile men[14,35,36]; the other seven compared infertile with fertile or healthy men, and two of these were restricted to idiopathic infertility[37,38].

BMI was analyzed as a continuous variable in six studies[14,24,32,34,37,38] and in categories in six. These used WHO cut-offs[36], an obesity threshold of ≥ 30 kg/m² (Mu et al.[17]), Asian cut-offs with obesity at ≥ 25 kg/m² (Amjad et al.[34]) or study-specific cut-offs (24 kg/m² in Jahan et al.[33], 25 kg/m² in Farooq et al.[24] and 28 kg/m² in Xin et al.[35]). Hofny et al.[32] enrolled only men with a BMI above 30 kg/m², which restricted the range of exposure. Height and weight were measured directly in four studies[14,34,36,38]; one study stated only that BMI was calculated from weight and height, without describing how they were obtained[37]; they were probably self-reported in one[17] and not described in the rest. Three studies also measured waist circumference[36,38] or body fat percentage by bioelectrical impedance[34].

All studies measured the marker by immunoassay (ELISA or EIA), using kits from at least six manufacturers. Serum was used in nine studies and plasma in one[17]. Fasting or early-morning sampling was reported in five

studies[32],[35–38]; samples were obtained at random times in one[24], and the remaining studies did not report sampling conditions.

Table 3. Characteristics of the included studies (n = 10; eight leptin studies, two irisin studies)

Study (year)	Marker	Country; setting	Design	Participants (n)	BMI measure	Sample; assay	Main BMI–marker finding	Authors' conclusion
Zorn et al. (2007)[14]	Leptin	Slovenia; Andrology Centre, University Medical Centre, Ljubljana	Cross-sectional	210 male partners of infertile couples: NOA 42, OA 15, OAT 68, NZ 85	Continuous; mean 26.1 kg/m²	Serum; immunoassay (DSL); log-transformed	Leptin–BMI r = 0.719, p < 0.001	Leptin tracks BMI and is linked to testicular function (inhibin B, testosterone, SHBG), not to sperm characteristics
Hofny et al. (2010)[32]	Leptin	Egypt; Andrology Department, Assiut University Hospital	Prospective comparative	122 obese men: 80 infertile oligozoospermic, 42 fertile normozoospermic	BMI > 30 kg/m² only (33.5 vs 31.2)	Serum; ELISA (DSL)	BMI–leptin r = 0.244, p < 0.01 (pooled); leptin 12.36 vs 7.93 ng/mL	Obese infertile men have higher leptin, which may inhibit testicular steroidogenesis
Jahan et al. (2011)[33]	Leptin	Pakistan; NIH Islamabad and a private infertility clinic, Islamabad	Analytical cross-sectional	154 men aged 20–48 y: 24 fertile, 130 infertile in 7 semen categories	BMI < 24 vs > 24 kg/m²	Serum; EIA (AssayMax)	Leptin higher at BMI > 24 in 6 of 7 infertile subgroups (e.g., OZ 9.62 vs 19.81; NOA 19.25 vs 26.1 ng/mL; mean ± SEM)	BMI influences leptin; leptin relates to testosterone and gonadotropins
Farooq et al. (2014)[24]	Leptin	Pakistan; Aziz Hospital, Karachi	Case-control	126 men: 66 obese infertile, 60 normal-BMI fertile	Normal 18.5–24.5 vs obese 25–40 kg/m²	Serum; ELISA (DSL-10-23100)	Leptin–BMI r = 0.54, p < 0.01 in infertile men; leptin 11.8 vs 7.0 ng/mL (25–35 y) and 10.0 vs 8.2 ng/mL (36–60 y)	Obesity and raised leptin are associated with infertility
Amjad et al. (2019)[34]	Leptin	Pakistan; infertility clinic, Islamabad; fertile men from the community	Cross-sectional	313 men aged 20–55 y: 178 infertile, 135 fertile	Asian cut-offs: normal 18–22.9, overweight 23–24.9, obese ≥ 25 kg/m²; body fat % by BIA	Serum; EIA (AssayMax)	Leptin 6.16 / 9.22 / 15.43 ng/mL across BMI groups, p < 0.001; leptin–BMI r = 0.572 (pooled)	Leptin rises with obesity but is not independently associated with infertility
Xin et al. (2019)[35]	Leptin	China; Shanghai Institute of Andrology, Renji Hospital	Cross-sectional	526 infertile men analysed (846 enrolled)	BMI ≤ 28 vs > 28 kg/m²	Serum; elevated leptin defined as > 6.02 ng/mL	BMI > 28 in 50% of men with elevated leptin vs 11.6% of controls, p < 0.001	High leptin, with chronic epididymitis, is linked to poorer sperm quality
Maghsoumi-Norouzabad et al. (2020)[36]	Leptin	Iran; Ahvaz Jundishapur University of Medical Sciences	Cross-sectional	119 infertile men: normal 30, overweight 56, obese 33	WHO groups 18.5–24.9 / 25–29.9 / ≥ 30 kg/m²; waist circumference	Serum; kit and units not reported	Leptin 18.20 ± 8.21 / 25.32 ± 5.98 / 33.93 ± 7.47 across BMI groups, p < 0.001	Overweight and obesity worsen the hormonal and semen profile of infertile men
Al-Nawd et al. (2022)[38]	Leptin	Yemen; andrology and infertility centre, Ibb	Comparative cross-sectional	60 men: 30 idiopathic infertile, 30 age-matched fertile	Continuous; groups BMI-matched; waist circumference	Serum; ELISA (DRG)	Leptin–BMI r = 0.309, p = 0.097 in infertile men (fertile r = 0.516, p = 0.004)	Leptin tracks central adiposity and correlates inversely with testosterone
Saleh et al. (2020)[37]	Irisin	Egypt; Benha University	Case-control	100 men: 50 idiopathic infertile, 50 fertile; age- and BMI-matched	Continuous (30.01 vs 28.59 kg/m²)	Serum; ELISA (SunRedBio)	Irisin–BMI r = −0.241, p = 0.042† in infertile men; irisin 3.02 vs 6.76 ng/mL	Low irisin marks insulin resistance in idiopathic infertility; BMI is an important contributor
Mu et al. (2021)[17]‡	Irisin	China; Renmin Hospital of Wuhan University	Cross-sectional human arm of a mouse study	19 men: 9 obese sub-fertile, 10 healthy lean controls	Obese ≥ 30 kg/m² (32.42 vs 20.92 kg/m²)	Plasma; ELISA	Irisin lower in obese sub-fertile men; negatively correlated with sperm count and progressive motility	Irisin protects against obesity-related spermatogenesis dysfunction via AMPKα

BIA, bioelectrical impedance analysis; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; NOA, non-obstructive azoospermia; NZ, normozoospermia; OA, obstructive azoospermia; OAT, oligoasthenoteratozoospermia; OZ, oligozoospermia; SEM, standard error of the mean. Values are mean ± SD unless marked SEM. † p-value as reported by the authors; recalculated from r = −0.241 and n = 50, p ≈ 0.09 (see Risk-of-bias assessment). ‡ Human component only; obesity and subfertility coincided completely in this sample, so the study was treated as supportive rather than independent evidence.

Risk of Bias in the Included Studies

No study was at low overall risk of bias (Figure 2). Four studies were judged at some concerns[14,34,36,38], three at high risk[32,33,35] and three at very high risk[17,24,37]. Both irisin studies were at very high risk. Confounding (D1), selection of participants (D3) and selection of the reported result (D7) most often drove the overall judgment.

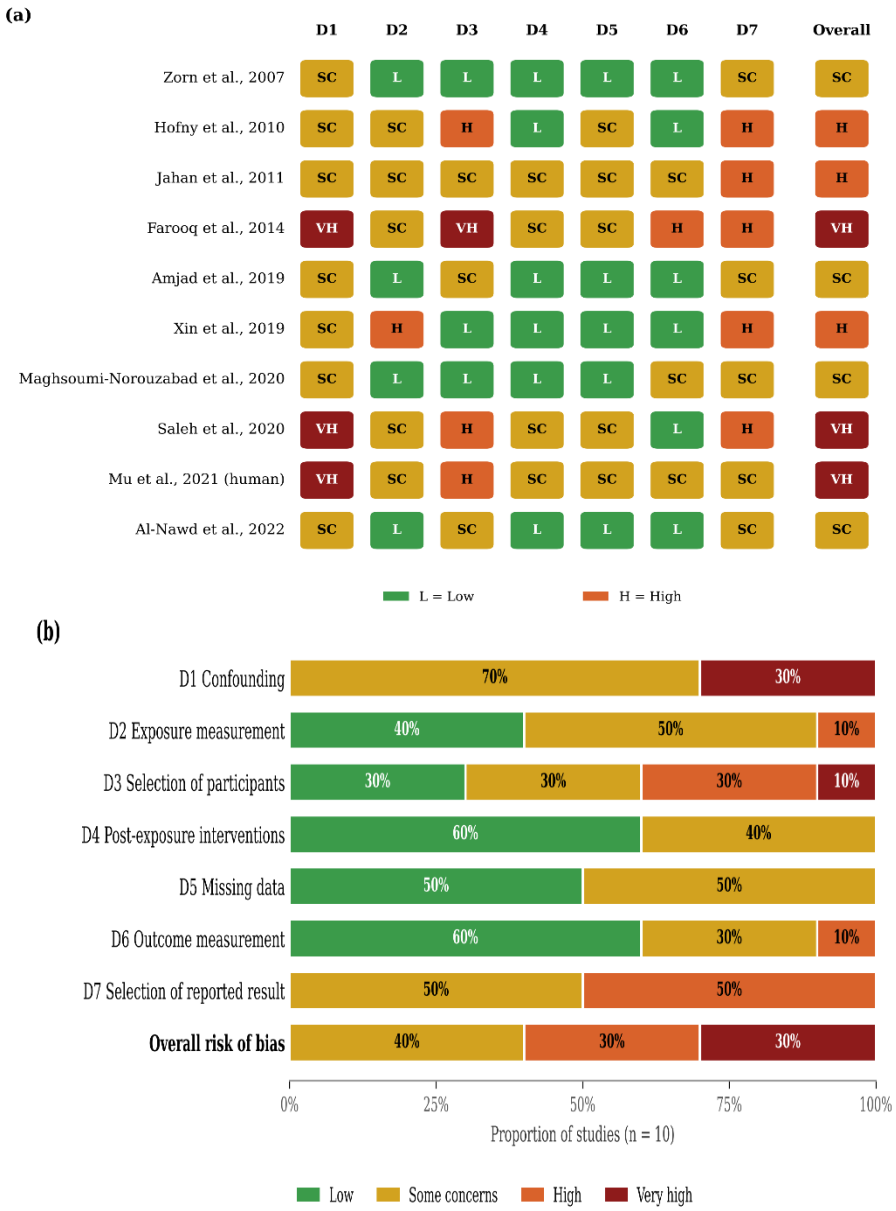


Figure 2. Risk of bias

Figure 2. Risk of bias of the included studies assessed with ROBINS-E. (a) Traffic-light plot of domain-level and overall judgments for each study. (b) Summary plot showing the proportion of studies in each risk-of-bias category, by domain. D1, confounding; D2, measurement of the exposure; D3, selection of participants; D4, post-exposure interventions; D5, missing data; D6, measurement of the outcome; D7, selection of the reported result. The overall judgment corresponds to the most severe domain judgment; Farooq, Saleh and Mu met the ROBINS-E B2 criterion for very high risk (an unadjusted result with enough potential confounding to discard it).

Confounding (D1). No study controlled for all important confounders; seven were judged at some concerns and three at very high risk. Most relied on restriction (excluding men with diabetes, hypertension or relevant medication) rather than statistical adjustment. Only Xin et al.[35] used multivariable adjustment (for age, BMI, smoking and type of infertility), and only Zorn et al.[14] adjusted leptin–semen and leptin–hormone correlations for BMI. Maghsoumi-Norouzabad et al.[36] showed that their BMI groups were balanced for age, physical activity, abstinence period and smoking. No study measured muscle mass, and physical activity was not reported in either irisin study. In the three studies at very high risk, BMI or obesity was fully or largely entangled with fertility status: in Farooq et al.[24] every fertile man had a normal BMI and every infertile man was obese; in Mu et al.[17] every obese man was sub-fertile and every lean man healthy; and Saleh et al.[37] reported only unadjusted correlations in a sample that included men with diabetes.

Measurement of the Exposure (D2). BMI was judged at low risk in four studies that measured height and weight directly[14,34,36,38] and at some concerns in five where the method was not described, height and weight were probably self-reported, or BMI was dichotomized at an unjustified cut-off. Xin et al.[35] was at high risk because the adiposity marker was dichotomized at a cut-off derived from the same sample's semen outcomes, and BMI was reported only as above or below 28 kg/m².

Selection of Participants (D3). Three studies that recruited a single clinical population of infertile men were at low risk[14,35,36]. Selection by fertility status, which is itself influenced by obesity, led to high or very high risk in four studies[17,24,32,37]. In Amjad et al.[34], infertile men came from a clinic and fertile men from the community, and the stated definition of fertility did not match the semen data reported for the fertile group.

Post-exposure Interventions (D4) and Missing Data (D5). These domains were at low risk or some concerns in all studies. Concerns arose mainly because medication use was not reported, the number of men contributing to each analysis was unclear[32,37], or hormone data were missing for about half of each group[33].

Measurement of the Outcome (D6). Six studies were at low risk. Concerns related to serum stored refrigerated rather than frozen[33], unreported leptin units[36] and the use of leftover clinical samples[17]. Farooq et al.[24] was at high risk because samples were taken at random times, although leptin is diurnal and sensitive to fasting. The two irisin studies reported concentrations that differed four- to five-fold (about 3–7 ng/mL[37] versus 15–28 ng/mL[17]), consistent with known differences between commercial irisin assays[16].

Selection of the Reported Result (D7). Five studies were at high risk and five at some concerns; none had a pre-registered analysis plan. Checks of internal consistency found errors in five studies (Table 4).

Table 4. Internal reporting inconsistencies identified during risk-of-bias assessment

Study	Inconsistency	Implication for this review
Saleh et al., 2020[37]	BMI–irisin r = −0.241 (n = 50) reported with p = 0.042; recalculated p ≈ 0.09. BMI–HOMA-IR r = 0.033 and irisin–HOMA-IR r = −0.071 reported with p = 0.023 (recalculated p = 0.82 and 0.62). Patient irisin SD of 0.077 is incompatible with the range of 1.88–4.22 ng/mL.	The main BMI–irisin association is not statistically significant at the reported sample size.

Hofny et al., 2010[32]	Leptin SDs of 0.05 and 0.17 ng/mL are implausibly small and probably SEMs; BMI–abnormal forms r = 0.049 reported with p < 0.01 (≈ 0.6 for n ≈ 122); signs missing from correlation table.	Group comparisons may appear more precise than they are; the BMI–leptin correlation (r = 0.244, p ≈ 0.007) is consistent.
Farooq et al., 2014[24]	Paired t-test used for independent groups; r = 0.86 reported both as leptin–age and as leptin–BMI correlation; age ranges differ between Methods and tables; infertility not defined by semen analysis.	Estimates are unreliable and not comparable with other studies.
Xin et al., 2019[35]	All adjusted odds ratios for elevated leptin are below 1 (e.g., OR 0.172, 95% CI 0.047–0.63), contradicting the authors' conclusion; one OR (0.043) lies outside its own 95% CI (0.078–0.584).	Probable coding or reporting error; leptin–semen estimates cannot be interpreted.
Jahan et al., 2011[33]	Abstract and Results contradict each other on testosterone by BMI group; height reported as 1.73 ± 1.15 m; subgroups of 5–16 men.	Hormone findings uncertain; subgroup estimates imprecise.

Recalculated p-values were derived from the reported r and n using $t = r\sqrt{(n-2)}/\sqrt{(1-r^2)}$ with n − 2 degrees of freedom (two-sided). CI, confidence interval; OR, odds ratio; SEM, standard error of the mean.

Association of BMI with Serum Leptin

All eight leptin studies reported higher serum leptin in men with higher BMI, and the association was statistically significant in seven (Table 5). Estimates are presented separately for infertile men alone and for samples that pooled fertile and infertile men.

Correlation with Continuous BMI. Within infertile men, correlation coefficients were 0.719 in Zorn et al. (n = 210, p < 0.001)[14], 0.54 in Farooq et al. (n = 66, p < 0.01)[24] and 0.309 in Al-Nawd et al. (n = 30, p = 0.097)[38]. The non-significant result of Al-Nawd et al. reflects its small sample; in the same study the correlation in fertile men was 0.516 (p = 0.004). In studies that pooled fertile and infertile men, the correlation was 0.572 in Amjad et al. (n = 313, p < 0.001)[34] and 0.244 in Hofny et al. (p < 0.01)[32]. The weaker correlation in Hofny et al. is explained at least partly by range restriction, since only men with a BMI above 30 kg/m² were enrolled.

Comparison across BMI categories. Maghsoumi-Norouzabad et al.[36], the only study to compare all three WHO BMI categories within infertile men alone, found a graded increase in leptin from normal weight (18.20 ± 8.21) to overweight (25.32 ± 5.98) and obesity (33.93 ± 7.47; p < 0.001); leptin was also higher with a waist circumference of ≥ 102 cm (31.93 vs 22.25). Using Asian cut-offs in a pooled sample, Amjad et al.[34] reported a similar gradient (6.16, 9.22 and 15.43 ng/mL; p < 0.001). Jahan et al.[33] found higher leptin at a BMI above 24 kg/m² in six of seven infertile subgroups and in fertile men (14.03 vs 5.16 ng/mL; p < 0.001), although subgroups contained only 5–16 men. In Xin et al.[35], 50% of men with elevated leptin had a BMI above 28 kg/m², compared with 11.6% of men with normal leptin (p < 0.001). Farooq et al.[24] reported higher leptin in obese infertile than normal-weight fertile men, but because BMI and fertility status coincided completely, this difference cannot be attributed to BMI.

Sensitivity and heterogeneity. When the synthesis was restricted to the four leptin studies at some concerns[14],[34],[36],[38] (702 men), all four showed a positive association, statistically significant in three, so the conclusion was unchanged. The direction of the association was consistent across WHO, Asian and study-specific BMI definitions, across regions (including all three Pakistani studies) and across assay platforms. Absolute leptin concentrations varied widely, from a mean of 6.16 ng/mL in normal-weight men in Amjad et al.[34] to 18.20 in Maghsoumi-Norouzabad et al.[36], whose units were not reported, which precludes comparison of absolute levels across studies.

Table 5. Direction and size of the BMI–marker association in each study

Study	Marker	Sample analyzed	BMI analysis	Estimate	Direction	Significant	Overall RoB
Zorn et al., 2007[14]	Leptin	Infertile only (n = 210)	Continuous	r = 0.719, p < 0.001	▲ Positive	Yes	Some concerns
Hofny et al., 2010[32]	Leptin	Pooled (n ≈ 122)	Continuous; BMI > 30 only	r = 0.244, p < 0.01	▲ Positive	Yes	High
Jahan et al., 2011[33]	Leptin	Infertile subgroups and fertile	< 24 vs > 24 kg/m²	Higher at BMI > 24 in 6 of 7 infertile subgroups (e.g., NOA 19.25 vs 26.1 ng/mL)	▲ Positive	Yes (most subgroups)	High
Farooq et al., 2014[24]	Leptin	Infertile only (n = 66)	Continuous	r = 0.54, p < 0.01	▲ Positive	Yes	Very high
Amjad et al., 2019[34]	Leptin	Pooled (n = 313)	Continuous; Asian categories	r = 0.572; 6.16 / 9.22 / 15.43 ng/mL, p < 0.001	▲ Positive	Yes	Some concerns
Xin et al., 2019[35]	Leptin	Infertile only (n = 526)	≤ 28 vs > 28 kg/m²	BMI > 28 in 50% (elevated leptin) vs 11.6%, p < 0.001	▲ Positive	Yes	High
Maghsoumi-Norouzabad et al., 2020[36]	Leptin	Infertile only (n = 119)	WHO categories	18.20 / 25.32 / 33.93, p < 0.001	▲ Positive (graded)	Yes	Some concerns
Al-Nawd et al., 2022[38]	Leptin	Infertile only (n = 30)	Continuous	r = 0.309, p = 0.097	▲ Positive	No	Some concerns
Saleh et al., 2020[37]	Irisin	Infertile only (n = 50)	Continuous	r = −0.241; reported p = 0.042, recalculated p ≈ 0.09	▼ Inverse	No (on recalculation)	Very high
Mu et al., 2021[17]	Irisin	Obese sub-fertile (n = 9) vs lean fertile (n = 10)	≥ 30 kg/m² vs lean	About 15 vs 28 ng/mL (read from figure), p < 0.05	▼ Inverse	Yes (confounded)	Very high

▲, marker higher with higher BMI; ▼, marker lower with higher BMI. Pooled, fertile and infertile men analysed together. NOA, non-obstructive azoospermia; RoB, risk of bias.

Association of BMI with Serum Irisin

Two studies with 119 men (59 infertile or sub-fertile) examined irisin, and both suggested an inverse association with BMI (Table 5). In Saleh et al.[37], irisin correlated inversely with BMI among 50 men with idiopathic infertility (r = −0.241). The reported p-value was 0.042, but the recalculated value for this r and sample size is about 0.09, so the association was not statistically significant. Irisin was markedly lower in infertile than fertile men (3.02 vs 6.76 ng/mL), although mean BMI was similar in the two groups (30.0 vs 28.6 kg/m²; p = 0.070). In Mu et al.[17], plasma irisin was lower in 9 obese sub-fertile men than in 10 lean healthy men (about 15 vs 28 ng/mL, read from a figure; p < 0.05). Because every obese man was sub-fertile and every lean man fertile, the lower irisin could reflect obesity, subfertility or both.

Both irisin studies were at very high risk of bias, neither measured physical activity or muscle mass (the main determinants of circulating irisin), and their absolute concentrations differed four- to five-fold. The direction of the evidence is consistent with lower irisin at higher BMI, but no reliable estimate of the BMI–irisin association within infertile men can be drawn from these data.

Secondary Outcomes: Semen Quality and Reproductive Hormones

Leptin and Fertility Status. Leptin was higher in infertile than fertile men in three studies: Hofny et al. (12.36 vs 7.93 ng/mL, all men obese)[32], Jahan et al. (oligozoospermic, oligoasthenoteratozoospermic and azoospermic men)[33] and Al-Nawd et al. (7.07 vs

3.14 ng/mL, p = 0.020, despite similar BMI of 23.9 vs 22.2 kg/m²)[38]. In contrast, the largest comparative study, Amjad et al.[34], found no difference (12.62 vs 12.00 ng/mL, p = 0.36), and leptin was not associated with infertility after adjustment for age, BMI and body fat (prevalence ratio 0.993). The difference reported by Farooq et al.[24] cannot be separated from BMI.

Leptin and Semen Parameters.

In Zorn et al.[14], leptin correlated inversely with sperm count (r = −0.202), but the correlation weakened and lost significance after adjustment for BMI (r = −0.125, p = 0.089), suggesting that BMI confounds unadjusted leptin–semen associations. Xin et al.[35] concluded that elevated leptin was linked to poorer semen quality, but all of their adjusted odds ratios were below 1 (Table 4), so these results could not be interpreted.

Leptin and Reproductive Hormones.

Zorn et al.[14] found that leptin correlated with inhibin B, testosterone and SHBG independently of BMI. Leptin correlated inversely with testosterone in Al-Nawd et al.[38], and testosterone was lower in obese than overweight infertile men in Maghsoumi-Norouzabad et al.[36] Jahan et al.[33] gave contradictory accounts of testosterone by BMI group in the abstract and results.

Irisin.

Mu et al.[17] reported strong associations between irisin and sperm count (R^2 = 0.79) and progressive motility (R^2 = 0.88), but these were computed across two well-separated groups (obese sub-fertile and lean fertile) and mainly reflect the difference between groups rather than a within-group relationship. Saleh et al.[37] reported an inverse correlation between irisin and insulin resistance (HOMA-IR; r = −0.071), which was not statistically significant on recalculation (p ≈ 0.62).

Certainty of Evidence

The GRADE assessment is summarized in Table 6. Following the approach recommended for non-randomized studies assessed with ROBINS tools[31], the evidence started at high certainty and was rated down. The certainty that BMI is positively associated with serum leptin in infertile men was low, downgraded for risk of bias and for indirectness, because half of the estimates pooled fertile and infertile men or compared groups defined by fertility status. Consistency of direction across all eight studies and the graded increase across BMI categories in two studies support the direction of this association. The certainty for an inverse association between BMI and irisin was very low, as was the certainty for an association between leptin and semen quality.

Table 6. GRADE summary of the certainty of evidence

Association	Studies (men)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty	Summary of findings
BMI and serum leptin in infertile men	8 (1,630)	Serious (−1): 4 of 8 at high or very high risk	Not serious: all 8 positive	Serious (−1): half of estimates pooled fertile and infertile men; varied BMI definitions	Not serious	Dose–response gradient in 2 studies; publication bias not assessable	⨁⨁◯◯ Low	Higher BMI may be associated with higher serum leptin in infertile men (r ≈ 0.3–0.7 within infertile men)
BMI and serum irisin in infertile men	2 (119)	Very serious (−2): both at very high risk	Not serious: both inverse	Serious (−1): BMI does not capture muscle mass; obesity confounded with subfertility in one study	Serious (−1): 59 infertile men; main correlation not significant on recalculation	Large assay differences	⨁◯◯◯ Very low	The evidence is very uncertain; irisin may be lower at higher BMI
Leptin and semen quality	3 (890)	Very serious (−2): BMI confounding; reporting errors	Serious (−1): association absent after BMI adjustment in one study	Not serious	Not serious	—	⨁◯◯◯ Very low	The evidence is very uncertain; associations appear largely explained by BMI

Certainty started at high, as recommended for non-randomized studies assessed with ROBINS tools[31], and was rated down for each serious concern. Studies contributing to leptin and semen quality: Zorn et al.[14], Jahan et al.[33] and Xin et al.[35]. ⨁⨁◯◯, low; ⨁◯◯◯, very low.

DISCUSSION

Summary of Main Findings

This review found that higher BMI was consistently associated with higher serum leptin in infertile men. All eight leptin studies reported a positive association, seven reached statistical significance, and within infertile men the correlation was moderate to strong (r = 0.31–0.72)[14,24,38]. A graded rise across BMI categories in two studies supported a dose–response relationship[34,36]. The two irisin studies pointed towards lower irisin at higher BMI, but neither provided a reliable within-infertile estimate[17,37]. Certainty was low for the BMI–leptin association and very low for BMI–irisin and for leptin–semen quality.

BMI and Serum Leptin

The direction and size of the BMI–leptin association agree with the physiology of leptin. Leptin is secreted by white adipocytes in proportion to fat mass[9], so a strong positive correlation with BMI is expected in any male population. That this held across WHO, Asian and study-specific BMI definitions, across regions and across assay platforms strengthens the finding. The weaker correlation in Hofny et al.[32] fits the expected effect of range restriction, since only men with a BMI above 30 kg/m² were enrolled, and the non-significant result in Al-Nawd et al.[38] reflects a sample of only 30 infertile men.

Two of the Pakistani studies are worth noting. They used cut-offs lower than the WHO standard (24 kg/m² and Asian obesity at ≥ 25 kg/m²)[33,34], and both still found leptin rising with BMI. This is consistent with evidence that South Asian men carry more body fat, and more cardiometabolic risk, at a given BMI than European men[18]. It suggests that Asian cut-offs are the more appropriate exposure definition for studies in this region, and that applying WHO cut-offs may misclassify metabolically obese men as normal weight.

A separate question is whether leptin only marks adiposity or acts as an independent route to impaired fertility. Experimental work supports a direct testicular effect, and leptin is increasingly recognized as a regulator of male reproductive function[39]. Leptin receptors are expressed in Leydig cells, where high leptin reduces steroidogenic acute regulatory protein expression and testosterone synthesis[11], and elevated leptin reduces Leydig cell responsiveness to pituitary gonadotrophins[6]. In infertile men, higher serum leptin has been linked to metabolic syndrome and to poorer progressive motility and morphology[40], and central leptin resistance may further suppress the hypothalamic–pituitary–gonadal axis[5,12]. These mechanisms are biologically plausible, but the clinical studies in this review provide limited support for an effect of leptin beyond that of adiposity itself.

Leptin, Semen Quality and Reproductive Hormones

In the secondary outcomes, leptin was hard to separate from BMI. In the only study that adjusted leptin–semen correlations for BMI, the inverse correlation between leptin and sperm count weakened and lost significance after adjustment[14]. In the largest comparative study, leptin did not differ between infertile and fertile men and was not associated with infertility after adjustment for age, BMI and body fat[34]. Studies that did report higher leptin in infertile men either compared groups with different adiposity or did not adjust for it[24,32,33]. The exception was Al-Nawd et al.[38], who found higher leptin in idiopathic infertile men despite similar BMI, although with only 30 men per group.

Hormonal findings were more consistent with a testicular role. Leptin correlated with inhibin B, testosterone and SHBG independently of BMI in Zorn et al.[14], and inversely with testosterone in Al-Nawd et al.[38], which agrees with experimental and clinical evidence of leptin-mediated suppression of steroidogenesis[6,11]. Overall, the evidence suggests that leptin in infertile men largely tracks adiposity, and that any independent effect is more likely to act on Leydig cell function than directly on semen parameters. This may also explain why meta-analyses of BMI and semen quality have found only modest average differences in semen quality[7,8]. BMI is an imperfect proxy for the hormonal milieu that adiposity creates[6]. Consistent with this, a recent study of 218 infertile men found that BMI and waist circumference were associated with poorer sperm morphology after adjustment for confounders[41].

BMI and serum irisin

The irisin evidence is too weak to draw a conclusion. Irisin is a myokine released mainly from skeletal muscle in response to exercise[15], and circulating levels are thought to vary with muscle mass, physical activity and metabolic status[16]. BMI cannot separate fat mass from lean mass, so it is a poor exposure for studying irisin, and neither included study measured muscle mass or physical activity. The main correlation in Saleh et al. was not statistically significant on recalculation[37], and in Mu et al.

obesity and subfertility coincided completely, so the lower irisin in obese sub-fertile men cannot be attributed to either[17].

Measurement adds a further difficulty. Absolute irisin concentrations differed four- to five-fold between the two studies. Commercial irisin immunoassays have been criticized for poor validation in biological samples, and published ELISA-based irisin levels are considered methodologically compromised, with human values reported across about six orders of magnitude[16]. Until mass-spectrometry-validated assays are used, differences in reported irisin levels across studies cannot be interpreted with confidence.

There is still a biological reason to study irisin in male infertility. In animal models, irisin reduces testicular oxidative stress, protects Leydig cells and improves testosterone and sperm parameters, effects linked to AMPKα signalling[42], and in obese mice irisin supplementation restored spermatogenesis[17]. These findings justify well-designed human studies, but they do not yet show that irisin is lower in obese infertile men or that it mediates the effect of obesity on fertility.

Implications for Practice and Research

For clinicians, the findings support measuring BMI, and ideally waist circumference or body fat, as part of the routine assessment of infertile men, particularly in South Asian populations where Asian cut-offs are more appropriate[18]. Serum leptin adds little beyond adiposity as a marker of infertility and is not ready for routine clinical use. Serum irisin should not be used as a clinical marker in male infertility on the current evidence.

Future studies should examine BMI–marker associations within infertile men rather than pooling them with fertile controls, recruit enough men to estimate a correlation precisely, and report correlation coefficients with exact p-values and sample sizes. Body composition (fat and lean mass), physical activity, glycemic status and sampling conditions should be measured and adjusted for, and leptin–semen associations should be reported both before and after adjustment for adiposity. Irisin studies need validated assays and measures of muscle mass. Prospective cohorts and weight-loss or exercise trials in infertile men would help establish whether changes in leptin or irisin follow, and mediate, changes in adiposity and semen quality. Pre-registration of analysis plans would reduce the reporting errors identified in this review.

Strengths and Limitations

As far as we know, this is the first review to synthesize the evidence on BMI in relation to both an adipokine and a myokine in infertile men. The methods were set before the search and reported according to PRISMA 2020[19]. The question was framed with the PECOS approach for exposure studies[20], and four major databases were searched, with supplementary citation searching. Risk of bias was assessed with ROBINS-E, a tool designed for exposure studies[26], and certainty was graded with GRADE, including its guidance for non-randomized evidence[30],[31]. Within-infertile estimates were separated from pooled estimates, and reported statistics were checked for internal consistency, which identified errors that would otherwise have been carried into the synthesis.

There are limitations. The protocol was not prospectively registered, so post hoc changes to the methods cannot be fully excluded. Only ten studies met the inclusion criteria, and only two examined irisin. Heterogeneity in BMI definitions, effect measures, sample composition and assays precluded meta-analysis, so the synthesis relied on effect direction, which does not weight studies by size or precision[29]. All included studies were cross-sectional or case-control, so causal inference is not possible, and ROBINS-E had to be adapted for these designs. No study was at low risk of bias, and most did not adjust for key confounders. The restriction to English-language publications may have excluded relevant studies, and publication bias could not be assessed formally because fewer than ten studies contributed to each association. Finally, six of the eight leptin studies came from South Asia, the Middle East and North Africa, which may limit generalizability to other populations, although the direction of the association was the same in studies from China and Slovenia.

CONCLUSION

In infertile men, higher BMI may be associated with higher serum leptin, with a consistent direction across studies, BMI definitions and regions, and a dose–response gradient across BMI categories. The certainty of this evidence is low, and leptin appears largely to reflect adiposity rather than act as an independent marker of impaired semen quality, although it may influence testicular steroidogenesis. Evidence that irisin is lower at higher BMI in infertile men is very uncertain, limited by small samples, confounding and assay problems. Well-designed studies within infertile men that measure body composition, physical activity

and validated markers are needed before leptin or irisin can inform the clinical management of obesity-related male infertility.

Author Contributions
AM: Study conception, design, study selection, and manuscript drafting
HA: Data collection, analysis, and interpretation
MF: Data collection, analysis, and interpretation
MA: Critical revision and final approval
AdM: Study selection, critical revision, and final approval

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