VER
Vascular & Endovascular Review

Genetic and Secondary Causes of Obesity Among Adults in Saudi Arabia: A Systematic Review

Majed AlSaleh[1], Saeed AlAhmari[1], Abdullah Saeed[1], Mohammed Yahya Asiri[1], Meteb AlBraik[2], Mohammed Jahlan[2], Bander Alasmari[2], Khaled Abdullatef Alaseeri[2]

[1]Research department, Ministry of health, Saudi Arabia
[2]Family medicine department, ministry of health, Saudi Arabia

ABSTRACT

Background: Prevalence of obesity in Saudi Arabia is above 35% among the adult population, making it a major burden on public health. Lifestyle factors such as diet and physical activity are clearly involved, however secondary causes of obesity, such as endocrine disorders, drugs and genetic factors are still not well studied in this population. This systematic review was conducted to pool evidence for the rates and patterns of secondary causes of obesity in adults from the Saudi Arabian region.

Methods: Methods We performed a systematic review following the PRISMA 2020 statement. The search was conducted in PubMed and Cochrane databases to identify studies reporting secondary causes of obesity in adults in Saudi Arabia without date or language restrictions. Two reviewers independently screened articles, extracted data and assessed quality using relevant risk of bias tools. The primary results were the frequency of endocrine causes of (hypothyroidism, polycystic ovary syndrome [PCOS], Cushing's syndrome), drug-induced obesity and genetic aetiologias. Secondary results were the diagnostic criteria adopted, and distribution patterns according to demographic subgroups.

Results: Out of 1,247 records identified, 30 were assessed for full-text review and 7 studies were included (n=1,063 participants). Neither studies on Cushing's syndrome nor on drug-related obesity as secondary causes were identified. Five studies previously investigated genetic factors (n=750), mainly focusing on obesity-related polymorphisms in the FTO, MC4R, BDNF and ACE genes. In PCOS, FTO rs17817449 and rs1421085 were significantly associated with obesity ($p<0.05$). Strong associations with obesity were also observed for MC4R variants rs12970134 and rs17782313 (OR=1.348 and OR=1.364, p=0.002, respectively). The largest effect was detected for the BDNF variant rs10767664 (OR=1.923, p=0.00072). PCOS was studied in 4 (n=439) studies; these studies examined genetic and metabolic factors rather than prevalence. Only one study discussed hypothyroidism, evaluating remission after bariatric surgery but without records of baseline prevalence. Meta-analysis was not feasible due to major methodological heterogeneity and incomplete reporting. Quality assessment, Type of analysis. Most of the studies showed moderate to high risk of bias, with the majority of bias arising from small sample sizes, non population-based sampling and insufficient control for confounding.

Conclusions: This systematic review exposes a challenge of secondary causes of obesity in SA adults that the current evidence is insufficient to address and further high-quality research is needed. Although markers of genetic susceptibility show interesting associations, in particular for FTO, MC4R and BDNF variants, population-based studies on the prevalence of endocrine disorders and drug-related obesity virtually do not exist. The absence of screening data for hypothyroidism, Cushing's syndrome, and drug-induced obesity is a major void in clinical knowledge. Recommendations for future research Population-based studies using uniform diagnostic criteria should be given priority in order to serve as basis for screening recommendations and for clinical practice in Saudi Arabia.

KEYWORDS: Obesity; Saudi Arabia; secondary causes; hypothyroidism; polycystic ovary syndrome; genetic polymorphisms; medication-induced obesity; Systematic review.

How to Cite: Majed AlSaleh, Saeed AlAhmari, Abdullah Saeed, Mohammed Yahya Asiri, Meteb AlBraik, Mohammed Jahlan, Bander Alasmari, Khaled Abdullatef Alaseeri, (2026) Genetic and Secondary Causes of Obesity Among Adults in Saudi Arabia: A Systematic Review, Vascular and Endovascular Review, Vol.9, No.1, 165-182

INTRODUCTION

Worldwide, obesity is reaching an epidemic level, and in the Middle East region including the Kingdom of Saudi Arabia, prevalence rates are among the highest [1]. Recent data suggest that more than 35% of Saudi adult population is obese (body mass index [BMI] ≥30 kg/m [2]), and an additional 30–35% are considered overweight [2], [3]. This disquieting pattern has significant ramifications for the healthcare systems as obesity is a well-documented risk factor for a number of chronic diseases such as type 2 diabetes mellitus, cardiovascular disease, certain malignancies, and musculoskeletal illness [4]. The pathogenesis of obesity is multifactorial that depends on complex interplay of genetic susceptibility, environmental influences, behavioral factors and physiological mechanisms [5]. Although secondary obesity due to underlying diseases, drugs, or genetic syndromes constitutes a significant but frequently under-recognized portion of obese individuals, the bulk of patients with obesity are suffering from primary obesity—caused by energy imbalance, i.e., too much energy in taken relative to energy consumed [6]. The clinical importance for diagnosis and management of such secondary causes is that these disorders may lend to specific forms of therapy in addition to the customary weight management interventions [7]. Metabolic causes of obesity are treated separately: endocrine diseases, drugs, and genes [8]. Endocrine causes of obesity are hypothyroidism, Cushing's syndrome,

polycystic ovary syndrome (PCOS), growth hormone deficiency, and hypopituitarism [9]. Hypothyroidism, a disorder characterized by inadequate production of thyroid hormone, results in a low metabolic rate and weight gain and has been shown to have a prevalence of approximately 4-10% in the general population [10]. Cushing's syndrome, which is characterized by central obesity among other stigmata due to chronic glucocorticoid excess, is also a rare disease with an estimated incidence of 2-3 per million per year [11]. PCOS affects 5–15% of women of childbearing age worldwide and is often linked with obesity, insulin resistance, and metabolic abnormalities [12].

Drug-induced weight gain is another substantial cause of secondary obesity. Many such as antipsychotics (especially second generation), antidepressants, mood stabilizers, antiepileptic drugs, glucocorticoids, insulin and insulin secretagogues, and some antihypertensive drugs also cause weight gain [13]. The pathways are drug class specific and may involve increased appetite, changes in metabolism, fluid retention or energy expenditure [14]. Identification of medication-induced obesity is important for clinical management, as alternative therapeutic options may be considered (15).

Genetic components play a major role in predisposition to obesity with heritability estimates of 40%-70% [16]. Although rare monogenic forms of obesity (e. e.g., leptin deficiency, melanocortin-4 receptor [MC4R] mutations, proopiomelanocortin [POMC] deficiency) comprise less than 5% of severe early-onset obesity cases, common polygenic variants together influence the risk of obesity in the general population [17]. Over 900 genetic loci have been associated with BMI and obesity-related traits in genome-wide association studies (GWAS), with the fat mass and obesity associated (FTO) gene being the most robustly replicated locus [18]. However, the effect sizes of specific genetic variants may vary between populations because of differences in allele frequencies, gene-environment interactions, and population-specific factors [19].

In Saudi Arabia, the rapid epidemiological transition witnessed within the past few decades (urbanization, mechanization, greater affluence, and introduction of Western diets) has led to the establishment of an obesogenic environment [20]. Although the prevalence of obesity and its contributing lifestyle factors have been well documented among the Saudi population [21],[22],[23], there is a paucity of studies focusing specifically on secondary causes. This lack of knowledge is troubling for several reasons. First, untreated endocrine diseases can cause suboptimal weight management outcomes and progression of the primary cyst [24]. Second, unawareness of medication-induced obesity may cause to unnecessary polypharmacy or loss of opportunity of therapy substitution [25]. Third, population-based patterns of genetic susceptibility for disease may contribute to recommendations for personalized prevention and treatment [26]. Due to unique demographic and genetic profile of Saudi ethnic population, we need to study secondary causes of obesity in this population. Consanguinity is high in Saudi Arabia (approximately 50-60% of marriages) [27], a relatively young population may affect the prevalence of genetic diseases. The population also has a distinctive genetic ancestry profile, shaped by historical migrations and admixture [28]. "Environmental factors specific to the region such as intense heat that restricts outdoor physical exercise, traditional eating habits that influence dietary consumption, and widespread vitamin D insufficiency may interact with genetic and endocrine components to affect an individual's chance of becoming obese [29]."

Secondary causes of obesity are clinically and public health relevant, yet to our knowledge have never been systematically synthesized with respect to the Saudi Arabian population. Earlier reviews concentrated primarily on lifestyle and overall obesity rates [30], and did not systematically investigate endocrine, pharmacological, and genetic aspects. This lack of knowledge restricts health care practitioners' ability to develop suitable screening regimens and focused treatment.

STUDY OBJECTIVES

The objective of this systematic review was to summarize all the available evidence on secondary causes of obesity in the adult population in Saudi Arabia, with the following specific aims:

Prevalence of endocrine (hypothyroidism, PCOS, Cushing's syndrome) amongst obese Saudi adults

1. To describe the prevalence, type of medication and the degree of obesity in this population associated with medicine induced obesity.
2. To investigate the genetic predictors and polymorphisms related with obesity susceptibility in Saudi Arabians.
3. To report the diagnostic criteria and measures as employed in different studies.
4. To investigate the pattern of distribution of secondary causes by demographic subgroups (age, sex, and geographic region).
5. To identify gaps in the evidence to guide future research priorities

By fulfilling these objectives, the review will have the potential to provide clinicians, policy makers, and researchers with a solid evidence base on which to base clinical practice, screening recommendations, and future research priorities for causes of secondary obesity in Saudi Arabia.

METHODS

2.1 Protocol and Registration

This SR has been conducted following the PRISMA 2020 statement [31]. The review protocol was prospectively registered with PROSPERO (International Prospective Register of Systematic Reviews PROSPERO 2025 CRD420251168769) before the start of the study. The protocol defined the research question, the inclusion and exclusion criteria, the search strategy, the data to be extracted and the analyses to be performed.

2.2 Eligibility Criteria

The studies included were based on the following criteria using the PECOS (population, exposure, comparator, outcome, and study design) framework:

Population: Adults (≥18 years) with obesity (BMI ≥30 kg/m2) living in the KSA. Studies involving obese and non-obese subjects were eligible if data on obese adults were reported separately or could be obtained.

Exposures/Conditions of Interest: -Endocrine disorders (eg, hypothyroidism, ESS, adrenal insufficiency, Cushing syndrome), PCOS, hypothalamic disorders, certain pharmacologic agents that cause weight gain, and genetic factors (eg, monogenic obesity, genetic variants that predispose to obesity). Agents: any agent known or suspected to cause or contribute to weight gain or obesity. Genetic components: genetic polymorphisms linked to obesity, such as polymorphisms in the fat mass and obesity-associated gene FTO; monogenic obesity syndromes; family-related cases of obesity.

Comparators: There were no prespecified comparators. Studies with or without control groups could be included.

Outcomes: Primary - Prevalence of secondary causes of obesity (endocrine disorders, medication-induced obesity, genetic factors) Secondary - Diagnostic criteria used Patterns of distribution by age, sex, and geographic region Associations strength between genetic variants and obesity

Types of studies: The following study types were eligible: observational (cross-sectional, case-control and cohort) and interventional (RCTs, non-randomized trials). Editorials, commentaries, narrative reviews, abstracts from conferences or studies not published were excluded.

Other Criteria: -- No language restrictions were applied - No date restrictions were applied── Studies to be conducted in Saudi Arabia or including a clearly identifiable Saudi Arabian subgroup with data that could be extracted.

2.3 Information Sources and Search Strategy

A total of two electronic databases were searched comprehensively: 1. PubMed (MEDLINE) 2. Cochrane Central Register of Controlled Trials (CENTRAL)

The search strategy was developed with the help of a medical librarian and included terms for: (1) obesity, (2) Saudi Arabia, and (3) secondary causes (endocrine disorders, medications, genetic factors). Both Medical Subject Headings (MeSH) and keywords in text were used. The search date was 1 November 2025 and no date limits were used.

Sample PubMed Search Strategy:

("obesity"[MeSH Terms] OR "obesity"[Title/Abstract] OR "obese"[Title/Abstract])
AND
("Saudi Arabia"[MeSH Terms] OR "Saudi Arabia"[Title/Abstract] OR "Saudi Arabian"[Title/Abstract] OR "Saudi"[Title/Abstract])
AND
("hypothyroidism"[MeSH Terms] OR "thyroid diseases"[MeSH Terms] OR "Cushing syndrome"[MeSH Terms] OR "polycystic ovary syndrome"[MeSH Terms] OR "genetic"[Title/Abstract] OR "polymorphism"[Title/Abstract] OR "gene"[Title/Abstract] OR "medication"[Title/Abstract] OR "drug-induced"[Title/Abstract] OR "endocrine"[Title/Abstract] OR "secondary cause"[Title/Abstract])

Reference lists of included studies and relevant review articles were manually searched to identify additional eligible studies. No grey literature sources were systematically searched.

2.4 Selection Process

Results All records identified via the database searching were imported into a reference management software and duplicates were removed. Two reviewers independently screened titles and abstracts for eligibility. Studies considered potentially relevant by either reviewer were taken forward to full-text review. Full-text articles were independently evaluated by two reviewers; disagreements were resolved by discussion or, if needed, by a third reviewer. Exclusion criteria at full-text were recorded.

2.5 Data Collection Process

Data extraction was done independently by two review authors, using a standardized and piloted data extraction form. Disagreements were resolved by discussion. When the necessary information was not clear or was lacking from published reports, the authors of the studies were contacted by e-mail, and up to two reminders were sent at two-week intervals.

2.6 Data Items

The following information was collected from each study:

Study Characteristics: - first author, year of publication, name of the journal - design, setting, and methodology - geographic region of Saudi Arabia - starting and closing dates of the study - sources of funding and potential conflicts of interest

Population characteristics: - number of subjects for the entire study and for subgroups, if applicable - age (mean, median or range) - gender - BMI (Mean, Median, range, categories) - recruitment and sampling method

Exposure/condition data: - secondary cause investigated (endocrine, pharmacological, genetic) - specific condition, conditions or factors assessed - diagnostic criteria and method of assessment - reference ranges from the laboratory used

Outcome Data: - with estimates of the prevalence and CIs - odds ratios (ORs), risks ratios (RRs), or other measure of effect genetic variant allele frequency and genotype distributions - age, sex, BMI category or geographic region-stratified analyses Quality and **Bias Indicators:** -Response rates -Loss to follow-up (for cohort studies) -Control for confounders -Validation of instruments.

2.7 Study Risk of Bias Assessment

Risk of bias was independently evaluated by two reviewers with tools tailored to study design:

Cross-sectional and case-control studies: An adapted version of the Newcastle-Ottawa Scale for cross-sectional studies to address selection of participants, comparability of groups, and ascertainment of exposure or outcome [32]

Cohort studies: The Newcastle-Ottawa Scale for cohort studies [33]

Genetic association studies: Quality assessment criteria derived or adapted from published guidelines, taking account of HWE testing, genotyping QC and assessment of population stratification [34] The overall risk of bias was rated as low, moderate or high for each study. Disagreements were resolved through discussion.

2.8 Synthesis Methods

Meta-analyses were planned for outcomes reported in at least three studies using similar measures. For the prevalence estimates, we planned to use random-effects models with variance stabilization through Freeman-Tukey double arcsine transformation [35]. We intended to pool the odds ratios by using random-effects models with the Dorsmanin-Laird method [36] for genetic association studies. Assessment of heterogeneity will be conducted by I^2 and Cochran's Q-test (where >50% will be regarded as substantial heterogeneity) [37].

Nevertheless, meta-analysis was not possible because of significant clinical and methodological heterogeneity in the7 included studies (e.g., study populations, outcome definitions and methods of assessment). A narrative synthesis by type of secondary cause (endocrine, pharmacological, genetic) is presented, and is supplemented with results in a series of structured tables. When available, we summarized trends among studies and examined possible sources of heterogeneity.

For studies of genetic association, odds ratios and 95% confidence intervals for specific variants and obesity were extracted. We recorded whether the studies tested for HWE and/or corrected for population stratification. Certainty of evidence was evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [38], which takes into account the risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

3.1 Study Selection

The process of selection from searches was 1,247 records (PubMed: 1,089 Cochrane: 158). Title and abstract screening were conducted for 1,034 records after discarding 213 duplicates. Of these, 1,004 were excluded as obviously not relevant and 30 papers went to full text evaluation. 23 studies were excluded after full assessment: attention lifestyle factor rather than secondary cause (n=15), no data on secondary cause (n=4), not in Saudi population (n=2), review article (n=1), conference abstract only (n=1).

Seven studies fulfilled all the inclusion criteria and were included in the qualitative synthesis [39], [40], [41], [42], [43], [44], [45]. Reference list searching did not identify any further studies. Study selection is shown in the PRISMA flow diagram (figure 1).

3.2 Study Characteristics

The seven included studies were published from 2014 to 2025 and involved 1,063 participants (Table 1). 5 studies explored genetic factors [39], [40], [41], [44], [45], four assessed PCOS in the context of obesity [39], [40], [42], [43], one investigated hypothyroidism [46], and none considered Cushing's syndrome or drug-associated obesity.

Geographic Distribution: Research has been conducted in the Western region (n=3) [39], [40], [42], Central region/Riyadh (n=1) [41], Asir region (n=1) [43], and unknown (n=2) [44], [45]. The fact that most of the studies emanated from the Western Saudi Arabia (mainly Jeddah) might influence the representativeness to other areas.

Study Designs: Most were case-control (n=3) [39], [40], [41] or cross-sectional (n=2) [43], [44] studies. One was a genetic association studies... [41], and one was a retrospective cohort study of post-bariatric surgery outcomes [46].

Population Characteristics: The sample size ranged from 126 to 367 (median: 189). Four studies were all women [39], [40], [42], [44], due to the centrality of PCOS. Only two studies reported mean age; age was otherwise inadequately reported Two studies reported mean age data Four had only women [39], [40], [42], [44] Four studies were restricted to women and this reflects the centrality of PCOS. The BMI cutoffs differed between the studies, some considered participants with BMI ≥30 kg/m2 as cases [39], [40], and others compared obese versus non-obese participants [41].].

3.3 Risk of Bias Assessment

The risk of bias assessments demonstrated major methodological issues in all included studies (Table 3).

Reporting Bias: Convenience sampling from hospital or university settings was employed in most of the studies (6/7) and not from the population thereby introducing high risk of selection bias. There was a study that used systematic sampling methods [43]. No studies justified sample size or power.

Detection Bias: The genetic studies usually employed validated genotyping techniques (real-time PCR with TaqMan assays) and, thus, had a low risk of detection bias for the genetic results [39], [40], [41]. Nevertheless, clinical phenotyping was frequently inadequately reported. Only two studies [39], [40] stated the diagnostic criteria in a clear manner for PCOS, none described the protocol in detail for the anthropometric measurement.

Confounding: Adjustment for potential confounders was insufficient in the majority of studies. Two studies [41], [43] conducted multivariable analyses accounting for potential confounders including age, physical activity, and dietary factors. Some of the remaining studies did not adjust at all, or adjusted for a small number of variables.

Reporting Bias: Failure to report results completely was also a common finding. Frequently missing elements of key data were: age distributions (5/7 studies), detailed BMI distributions (4/7 studies), response rates (6/7 studies), and confidence intervals for effect estimates (3/7 studies). Only partial data were available for one study [43] in the abstract and the full text report was not accessible.

Hardy- We inert Equilibrium: None of the two [39], [40] genetic studies have explicitly stated that they have checked for the Hardy-Weinberg Equilibrium in controls, which is important in identifying genotyping errors or population stratification.

Summary: Given these considerations, a study was judged to be at moderate risk of bias [41], while six studies were judged to be at high risk of bias [39], [40], [42], [43], [44], [45]. The main sins were selection bias, small numbers, poor control for confounding and reporting bias.

3.4 Results of Syntheses

Because of the greatly differing populations, outcomes evaluated and methods of measurement, it was not possible to undertake a meta-analysis. Results are presented narratively by category of secondary cause.

3.4.1 Genetic Factors

Five studies explored obesity-related genetic polymorphisms in Saudi adults [39], [40], [41], [44], [45], focusing on variants of the genes FTO (fat mass and obesity-associated protein), MC4R (melanocortin-4 receptor), BDNF (brain-derived neurotrophic factor), and ACE (angiotensin-converting enzyme).

FTO Gene Variants:

Two investigations addressed FTO polymorphisms [39], [41]. Bachata et al [39] have studied on three FTO variants (rs17817449, rs1421085 and rs8050136) in 95 PCOS women and 94 controls from Western Saudi Arabia. rs17817449 (G/T) and rs1421085 (C/T) were significantly associated with PCOS susceptibility ($p<0.05$). In addition, rs1421085 and rs8050136 were also linked to elevated BMI (>30 kg/m²) in women with PCOS. The homozygous C allele for rs8050136 as a risk allele for both hair loss and higher BMI in PCOS patients though not for the normal group.

Alharbi et al. [41] studied rs3751812 within the FTO gene in 367 Saudi adults living in Riyadh. This variant also showed positive association with obesity (OR=1.523, 95% CI not reported, p=0.016). The magnitude of the effect was substantial but smaller than that for the BDNF variants in the same study.

MC4R Gene Variants:

Batarfi et al. [40] examined two MC4R polymorphisms (rs12970134 and rs17782313) in 189 women (95 PCOS, 94 controls) from Western Saudi Arabia. Both polymorphisms were also significantly associated with obesity in PCOS women. The alleles genotypes namely GG for rs12970134 and TT for rs17782313 were significantly associated with obesity (BMI ≥30 kg/m2) both in PCOS and control subjects (p= 0.002 for each) with odds ratio 1.348 and 1.364, respectively. Remarkably, in non-obese PCOS patients, heterozygous genotypes (AG for rs12970134, CT for rs17782313) were linked to other clinical characteristics such as hirsutism, hair loss, hyperandrogenism, and high anti-Müllerian hormone levels. The authors concluded that these MC4R polymorphisms are associated with increased BMI in PCOS, but they do not promote the development of PCOS.

BDNF Gene Variants:

Alharbi et al. [41] reported the most significant finding in term of genetic association identified among available studies. The BDNF variant rs10767664 demonstrated a strong effect size with obesity (OR=1.923, p=0.00072) in a cohort of 367 Saudi adults. This was significantly larger than the size effect that were reported for the FTO polymorphism in the same population, further suggesting that BDNF may have a particularly strong influence on obesity risk in Saudi Arabians. Cumulative Genetic Risk: Alharbi et al. [41] Performed weighted genetic risk score analysis with 11 single nucleotide polymorphisms (SNPs) mainly from loci that involved appetite regulation. This analysis showed robust evidence for a cumulative effect (OR=2.57, p=0.00092), suggesting that carriers of multiple risk alleles are at high risk for obesity. The authors stated that markers in loci modulating fat mass through enhanced appetite might in fact exert stronger effects on obesity in Saudi Arabians than in Europeans, but this claim

needs to be confirmed by direct comparative studies.

ACE Gene Polymorphism:
Sabir et al. [45] Investigated the ACE insertion/deletion (I/D) polymorphism as a risk factor for obesity in Saudi population. Although the abstract suggested that this genetic polymorphism, along with high dietary salt intake, is associated with the development of obesity, information about effect sizes and prevalence was not included in the data extracted.

Other Genetic Factors:
Nashar et al. [44] studied genetic risk factors of obesity in female university students in Saudi Arabia but did not report the genetic polymorphisms or effect size in the accessible data.

3.4.2 Polycystic Ovary Syndrome (PCOS)
Four studies explored PCOS and obesity [39], [40], [42], [43], but none of them reported the prevalence of PCOS in obese Saudi females based on population. Rather, these investigations are farmed on genetic associations, metabolic profiles, and endocrine features of women affected with PCOS as well as obesity.

Metabolic and Endocrine Profiles:
Daghestani et al. [42] in Saudi Arabia were 63 obese, PCOS women and 63 normo-ovulatory obese women (non-PCOS obese) They included:
The study demonstrated the differences in metabolism and endocrinology among groups. PCOS in obese women was characterized by:

- Significantly elevated vascular endothelial grow factor (VEGF) approximately 4-fold higher than non-PCOS obese women
- Higher waist to hip ratio (WHR), total cholesterol, LDL-cholesterol, fasting glucose, luteinizing hormone (LH), LH/FSH ratio, estradiol and testosterone
- Lower hip circumference, leptin, progesterone and sex hormone binding globulin (SHBG) significantly had reduced levels of hip circumference, leptin in serum, progesterone and sex hormone binding globulin (SHBG).
- Same amount of BMI, HDL-Chol, ghrelin, insulin, FSH and insulin sensitivity (via QUICKI) in obese non-PCOS group These results suggest that PCOS is associated with additional metabolic and hormonal disturbances than obesity; and that these may, at least in part, be responsible for the increased risk of cardiovascular and metabolic disease in this disorder.

Genetic Associations with PCOS and Obesity:
As in section 3.4. 1, two studies [39], [40] were specially designed to investigate genetic variants and their relevance to PCOS and obesity. Both FTO and MC4R polymorphisms were associated with obesity in PCOS individuals, reinforcing the hypothesis that genetic predisposition could interact with hormonal milieu of PCOS, contributing to weight gain.

Prevalence Data:
Ahmed et al. [43] The study is a cross-sectional study in which metabolic syndrome and cardiometabolic risk factors are studied among obese and hypothyroid individuals in the Asir region. It is true that PCOS was not the subject of the study, but PCOS is an endocrine disorder diagnosed in obese individuals. Although, in the retrieved information, specific prevalence rates for PCOS were not reported.

3.4.3 Hypothyroidism
To date, none of the studies concerning prevalence of hypothyroidism in Saudi Arabia have studied its association with obesity in the general adult population. Buhari et al. [46] investigated remission of hypothyroidism after bariatric surgery in obese individuals. This retrospective cohort study was designed to evaluate if hypothyroidism can resolve after bariatric surgery-induced weight loss with an emphasis on post-surgical changes in levothyroxine (LT4) dosage requirements.

As the study is concentrated on post-surgical outcomes rather than the actual baseline prevalence, it cannot give estimates on the prevalence of hypothyroidism in obese Saudi adults at the population level. Nevertheless, the study on hypothyroidism remission after weight loss supports the hypothesis that at least some cases hypothyroidism in obese subject is secondary to obesity per se and not actual primary thyroid pathology (so called “obesity-induced hypothyroidism” or “functional hypothyroidism”).

Ahmed et al. [43] also cited hypothyroidism as a secondary cause of obesity in their cross-sectional study of cardiometabolic risk factors in the Asir region, but no data on specific prevalence estimates were reported in the extracted information. Evidence Gap: The almost complete lack of data on the prevalence of hypothyroidism in obese Saudi adults is a glaring gap, considering that hypothyroidism is one of the commonest endocrine causes for secondary obesity worldwide, and with estimates of prevalence being around 4-10% in general populations but possibly even higher in obese populations [10].

3.4.4 Cushing’s Syndrome
None of the studies provided information on Cushing`s syndrome as a secondary cause of obesity among adults living in Saudi Arabia. This lack is striking but maybe not unexpected in the light of the rarity of Cushing’s syndrome (estimated incidence of 2-3 cases per million per year) [11].Population-based screening investigations would have to be very large to identify cases of this uncommon disorder.

3.4.5 Medication-Induced Obesity

None of the studies reviewed were specifically geared towards investigating drug-induced obesity or weight gain related to pharmacological drugs in the adult population of Saudi Arabia. This constitutes an important gap in evidence, as many widely used drugs are associated with weight gain, including antipsychotics, antidepressants, mood stabilizers, antiepileptic drugs, glucocorticoids, insulin and some antihypertensive drugs [13]. One study [47] reported that 66.1% of subjects agreed that medical problems like metabolic syndrome can cause obesity, but also expressed that "a considerable number were unaware of the effect of medications" on weight. Although relevant, this study addressed awareness and knowledge rather than prevalence of medication induced obesity and was therefore excluded from the synthesis as it did not fulfill the criteria for reporting secondary causes.

3.5 Certainty of Evidence

Certainty of evidence was rated as follows using the GRADE approach:

Genetic Associations: LOW to VERY LOW certainty - Because of risk of bias (small sample sizes, convenience sampling, inadequate control for confounding) - Because of imprecision (very wide confidence intervals, small number of events) - Because of indirectness (genetic associations are not directly applicable to the clinical prevalence of genetic obesity) - Limited upgrading possible due to some consistency across studies for FTO and MC4R variants

PCOS Metabolic Profiles: VERY LOW certainty - Downgraded for risk of bias (selection bias, small samples, single-center studies) - Downgraded for imprecision (small samples) - Downgraded for indirectness (metabolic profiles are not prevalence estimates)

Hypothyroidism: VERY LOW certainty - Downgraded for risk of bias and imprecision - Downgraded for indirectness (post-operative outcomes are not representative of population prevalence) - Not enough data to make an assessment worthy of consideration

Psychotropic Drug-Associated Weight Gain and Obesity and Cushing's Syndrome: No evidence available.

DISCUSSION

4.1 Summary of Main Findings

This systematic review highlights the paucity of evidence for secondary causes of obesity among adults in Saudi Arabia. Treatment for Obesity and Its Associated Complications: very few studies have directly considered endocrine, pharmacological and genetic factors in this population [1] Despite the high rates of obesity in this population (> 35%) [2], [3], the number of studies focused on endocrine, pharmacological and genetic factors is surprisingly small. Out of 1247 potential records identified for initial screening, seven studies fulfilled the eligibility criteria with a total of 1063 participants.

There is a strong bias in the available data towards genetic factors with five of seven studies focusing on polymorphisms associated with obesity [39], [40], [41], [44], [45]. These genetic findings give initial support that common variants in FTO, MC4R and BDNF may be associated with obesity in Saudi adults and the effect sizes could be larger compared to European populations [41]. Two MC4R variants, rs12970134 and rs17782313, were also significantly associated only in women with outstanding ORs of the latter being OR=1.348 and OR=1.364, respectively (p=0.002) [40]. Analysis of cumulative genetic risk suggests that individuals who carry several of these risk alleles may be at markedly increased risk of obesity (OR=2.57, p=0.00092) [41]. Four studies have investigated PCOS and obesity [39], [40], [42], [43], but these concentrated more on the genetic links and metabolic patterns than providing prevalence data. According to the literature PCOS obese women have more pronounced metabolic and hormonal disturbances compared to obese women without PCOS [42], and that variants in FTO and MC4R genes may influence susceptibility to obesity in this [39], [40] group.

Notably, only one investigation focused on hypothyroidism [46], and this was concerned with post-bariatric surgery rather than baseline prevalence. There were no reports of Cushing's syndrome or drug-induced obesity, which are two clinically relevant secondary causes that should be considered in the Saudi setting.

Too-small sample sizes, convenience sampling, poor control of confounding factors and incomplete reporting together caused downgrading of overall certainty of evidence to very low too low for all outcomes. The majority of studies being single-Centre and from the Western province of Saudi Arabia (mainly Jeddah) also limits the generalizability of the findings to other regions of the Kingdom.

4.2 Comparison with International Literature

The results of this review are in stark contrast with the international literature on secondary causes of obesity and suggest major deficiencies in the evidence base of KSA. **Hypothyroidism:** Hypothyroid- roidism is one of the most frequent endocrine reasons for secondary obesity worldwide. Population based studies from Europe and North America have indicated 4-10% of hypothyroidism in general populations [10] and increased prevalence (10-15%) among obese subjects [48]. A meta- analysis of 21 studies indicated that SCH was found in 13.6% of obese adults when compared with 7.5% of normal weight controls [49]. Hypothyroidism prevalence seems to be notably high in Middle Eastern countries; one study from Iran stated that 15.3% of obese women had hypothyroidism [50]. That there are virtually no data on prevalence from Saudi Arabia is a major void, particularly since vitamin D deficiency is so common in that part of the world [29] and that may affect thyroid function.

PCOS: Worldwide PCOS affects 5-15% of women of reproductive age with an even higher prevalence in obese women (28-

30%) [12]. Reports of PCOS prevalence in Gulf neighboring countries include 6-12% [51]. Four Saudi studies have also assessed PCOS in obese women [39], [40], [42], [43] but none of these studies provided prevalence estimates for PCOS; thus, we could not compare our results with these studies. The emphasis on genetic associations and metabolic profiles is the valuable but it does not answer the basic question of how many obese Saudi women manifest PCOS as a contribution for their obesity.

Cushing's Syndrome: Associated with obesity but rare (incidence 2-3 per million per year) [11], Cushing's syndrome should be considered in the evaluation of obese patients, especially those who have characteristic manifestations of the syndrome which include central obesity, facial plethora, proximal muscle weakness, and wide purple striae. International recommendation is to screen for Cushing's syndrome if such features are present in obese patients [52]. The lack of any data from Saudi Arabia may be indicative of rarity of the disease, or it may be symptomatic of underdiagnosis or absence of systematic case finding.

Drug-Induced Obesity: International research shows that medications may cause or contribute to obesity in 10 to 15% of individuals with the disorder [13]. Antipsychotics, in particular second-generation ones, can lead to very significant weight gain (e.g., 5–10 kg or more) [53]. Antidepressants, mood stabilizers, and glucocorticoids are common culprits [14]. In the context of worldwide increase in the use of psychotropic drugs [54] also in Saudi Arabia [54], the lack of any investigation on drug-induced obesity is a glaring omission. This is particularly worrisome since medication-related weight gain is modifiable by changing the drug or by adding treatment [15].

Genetic Contributors: The genetic studies described in this review [39], [40], [41] are consistent with international data demonstrating the relevance of FTO, MC4R and BDNF polymorphisms to obesity risk. Yet the finding that effect sizes may be greater in Saudi Arabians than Europeans [41] must await replication in larger, well-designed studies involving direct comparisons. Population-specific genetic architecture, high consanguinity rates (50-60% of marriages) [27], and distinctive environmental contexts of potential gene-environment interactions unique to Saudi conditions necessitate focused study. International GWAS discovered more than 900 loci in association with BMI [18], but Middle Eastern populations have not been sufficiently represented in these studies, thereby population-specific variants might be missed.

4.3 Clinical Implications

The results of this review could inform several areas of clinical practice in Saudi Arabia, including:

1. Systematic Screening: Requirement It could be that prevalence data on causes of secondary obesity is absent due to the fact that the systematic screening is not a part of Saudi clinical practice routine. International recommendations advise screening for hypothyroidism (TSH measurement) in obese subjects, especially those presenting clinical signs or rapid/unexpected weight gain [55]. Likewise, PCOS should be screened for in obese women with oligomenorrhea/amenorrhea, hirsutism or infertility [56]. Evidence-based screening guidelines applicable to the Saudi population should be developed and implemented.

2. Regularly review: medications to manage obesity There is little data available about drug-induced obesity, perhaps indicating a blind spot in clinical management. Evaluation for secondary causes of obesity should include a full medication review, and alternative therapies should be considered for agents associated with weight gain.[15] This is especially relevant in those patients who are starting or on psychotropic agents, glucocorticoids, or insulin treatment.

3. Genetic Counseling and Testing: While the genetic studies identified in this review do suggest the existence of obesity-associated variants in Saudi adults, clinical genetic testing for the common polygenic form of obesity is not currently recommended as part of standard medical care [57]. Nonetheless, referral for genetic evaluation may be considered in children with severe early-onset obesity, a family history of the condition suggestive of monogenic obesity, or obesity and developmental delay or dysmorphic features [58]. High rates of consanguinity in Saudi Arabia may predispose to the occurrence of rare autosomal recessive obesity syndromes thus raising a clinical suspicion.

4. Multidisciplinary Approach: Diagnosis of secondary causes of obesity requires a multidisciplinary team approach including endocrinologists, gynecologists (PCOS), psychiatrists (medication-induced obesity), and geneticists (suspected genetic syndromes). The combination of these disciplines within obesity treatment programs may facilitate the recognition and treatment of secondary etiologies.

5. Patient Education: Clinicians should inform patients about relevant secondary causes of obesity and the need to report symptoms (e.g., fatigue, cold intolerance, menstrual irregularities) suggestive of endocrine disorders underlying obesity providers should be aware of medication-induced weight gain to inform shared decision-making for treatment options.

4.4 Limitations

This review has a number of important limitations:

1. Limited Evidence Base

The findings were limited by the small number of included studies (n = 7) and small sample sizes (overall n = 1,063). There is no sufficient evidence base to generate reliable estimates of prevalence for the majority of the secondary causes of obesity among Saudi adults.

2. Risk of Bias Is High

Convenience sampling, small sample sizes, inadequate control for confounding and incomplete reporting of results were common sources of bias in most retrieved studies. These methodological limitations undermine trust in the reported results.

3. Heterogeneity and No Meta-Analysis
Since there was substantial clinical and methodological heterogeneity, pooling of data could not be conducted. Failure to quantitatively pool data reduces the precision of effect estimates and prevents formal evaluation of publication bias by using funnel plots.

4. Geographic Limitations
There is a strong bias towards studies conducted in Western Saudi Arabia (Jeddah in particular , limiting reliability for other areas). Saudi Arabia has varied geographic, ethnic and social structure, which may lead to differences in obesity rates and its secondary causes.

5. Publication Bias
The search was restricted to published studies in indexed databases. Theses, unpublished studies and grey literature were not systematically searched, which may introduce publication bias. Also, studies with null result may be less likely to be published.

6. Language Restrictions
No language restrictions were imposed during the search; however, all eligible studies were written in English. Significant studies written in Arabic may have been overlooked if they were not abstracted in the databases searched.

7.Disrupted Data Extraction
Incompatible with certain studies important data items were missing, incomplete or if the information was unclear, which precluded a detailed synthesis of data. Attempts to obtain additional data from authors were not always successful.

8. Absence of Temporal Data
All were cross-sectional or case-control studies. Due to the lack of longitudinal cohort studies, temporal associations and causation are poorly understood.

9. The Focus on the Common Variants
The genetic research concentrated on common polymorphisms, rather than rare monogenic forms of obesity. It is unknown whether rare gene obesity formations are prevalent in Saudi Arabia.

10. Cutting edge
With the advent of numerous new loci and mechanisms in recent years the field of obesity genetics is fast moving. The included studies may not represent the state of the art with respect to genetic determinants of obesity.

4.5 Future Research Directions
This systematic review pinpoints multiple high priorities for future research:
1.Population-Based Prevalence Studies
Population-based studies with the large sample size are needed to find the prevalence of secondary causes of obesity among Saudi adults. Such studies should: - Apply representative sampling methodology in a multi-regional fashion throughout the Kingdom of Saudi Arabia - Use standardized diagnostic criteria for the diagnosis of endocrine disorders - Conduct a thorough evaluation of medication use - Present stratified results according to age, sex, and BMI class as well as by geographic location - Perform sample size calculations based on values of sufficient power for detecting clinically relevant differences.

2. Hypothyroidism screening studies
Considering the substantial hypothyroidism prevalence worldwide among obese individuals and the nonexistent Saudi data, dedicated studies should: - Measure TSH and free T4 in representative samples of obese Saudi adults - Differentiate overt from subclinical hypothyroidism - Investigate associations with severity of obesity, metabolic complications, and vitamin D - Evaluate the effect of thyroid hormone therapy on weight management outcomes.

3.Prevalence Rates and Phenotyping of PCOS Comprehensive
studies of PCOS in Saudi women should: - Report population-based prevalence estimates using Rotterdam criteria - delineate PCOS phenotypes (i.e., hyperandrogenic, ovulatory, non-hyperandrogenic) - explore the two-way association between PCOS and obesity - evaluate metabolic and cardiovascular risk factors - explore genetic and environmental risk factors peculiar to the Saudi setting.

4. Medication-Induced Obesity Studies Research on pharmacologic causes of obesity should
Perform systematic medication review in obese patients --Quantify the frequency of use of medications associated with weight gain --Assess temporal associations between medication initiation and weight change --Assess the efficacy of therapeutic substitution approaches --Provide clinical guidance on medication use in the obese patient

5.Comprehensive Genetic Studies
Future genetics research should: --Performs large GWAS in Saudi populations --Focus up on both common variants and rare mutations --Screen a monogenic obesity syndromes in particularly obese patients --Explores gene-environment interactions unique to the Saudi --Constructs polygenic risk scores validated in Middle Eastern populations -- Studies the effect of consanguinity on obesity genetics

6.Cushing's Syndrome Screening
Although rare, routine biochemical screening for Cushing's syndrome should be included in protocols for studying obese patients who have suggestive clinical findings (24-hour urinary free cortisol, late-night salivary cortisol, low-dose dexamethasone suppression test).

7. Longitudinal Cohort Studies
Prospective cohort studies of obese Saudis are warranted to follow them over time to:- Determine temporal associations between secondary causes with the development of obesity- Evaluate the effect of -management of secondary causes on weight trajectories- Identify predictors of successful weight management- Study the natural history of obesity-related complications

8.Intervention Studies Clinical trials need to assess
Effect of treatment of the secondary causes (e.g. thyroid hormone replacement, treatment of PCOS) on the weight outcomes– Ways to prevent the weight increase associated with medications– Tailored intervention according to genetic risk profile– Models of multidisciplinary care for secondary obesity

9. Health Services Research
Studies of healthcare delivery– Evaluate and define current practice of screening for cause of secondary obesity– Identify obstacles to diagnosis and treatment– Determine cost-efficiency of systematic screening protocols– Formulate and evaluate strategies to implement evidence-based guidelines

10.Qualitative Research
Qualitative research to explore perspectives of patients and providers regarding secondary causes of obesity would guide the development of interventions and strategies for their implementation.

CONCLUSIONS

This comprehensive review highlights a pressing lack of evidence regarding secondary causes of obesity in adults in the KSA. The only clinical features of endocrine disorders and medication-induced and genetic causes of obesity included were those related to endocrine disorders, obesity caused by medication, and hereditary factors was extraordinarily limited. Seven studies met the inclusion criteria, with a total of 1,063 participants, and the certainty of the evidence was rated as very low to low.
Current evidence indicates that FTO, MC4R and BDNF genetic variants are significantly associated with obesity in Saudi adults and with potentially higher effect sizes compared to those reported in European populations. Albeit small convenience-sampled studies subject to numerous methodological limitations. It has been studied in relation to obesity with research suggesting more pronounced metabolic derangements in obese women with PCOS compared to those without, but population-based prevalence estimates do not exist.

The most important (and indeed the most evidently missing) data to collapse concerns the prevalence of hypothyroidism in obese adults in Saudi Arabia, although this is a well-established common endocrine cause of secondary obesity worldwide. No study reported on Cushing's syndrome or drug induced obesity, leaving substantial voids in clinical knowhow. These results have significant clinical and public health implications in the KSA. There is a need for organized screening procedures for secondary causes of obesity as well as for a detailed medication review in the evaluation of obesity. Healthcare professionals should be on high alert for possible secondary causes of disease, especially in those with treatment-refractory obesity or features indicative of these.

The upcoming research should focus on large population-based studies using uniform diagnostic criteria to establish the true prevalence of endocrine disorders, on thorough evaluation of drug-induced obesity and on carefully designed genetic studies that take into account the particular population stratification of Saudi Arabia. Cohort studies and intervention trials over time are warranted to determine directionality and test treatment responses.

Filling these evidence gaps is crucial for advancing a holistic, evidence-informed strategy for obesity prevention and management in Saudi Arabia. Recognition and adequate management of secondary causes could potentially lead to better outcomes for individuals and contribute to more efficient public health policies in this HPP population.

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7. TABLES AND FIGURES

Table 1. Characteristics of Included Studies

Study	Year	Region	Design	Sample Size	Population	Secondary Cause(s) Investigated	Key Findings
Bakhashab et al. [39]	2021	Western SA	Case-control	189 (95 PCOS, 94 controls)	Women with obesity (BMI >30 kg/m²)	Genetic (FTO variants); PCOS	FTO variants rs17817449 and rs1421085 significantly associated with PCOS and high BMI ($p<0.05$)

Study	Year	Region	Design	Sample Size	Population	Secondary Cause(s) Investigated	Key Findings
Batarfi et al. [40]	2019	Western SA	Case-control	189 (95 PCOS, 94 controls)	Women (obese and non-obese)	Genetic (MC4R variants); PCOS	MC4R rs12970134 and rs17782313 associated with obesity in PCOS (OR=1.348 and 1.364, p=0.002)
Alharbi et al. [41]	2014	Riyadh	Genetic association	367	Saudi adults	Genetic (multiple variants including FTO, BDNF)	BDNF rs10767664 (OR=1.923, p=0.00072); FTO rs3751812 (OR=1.523, p=0.016); cumulative genetic risk score (OR=2.57, p=0.00092)
Daghestani et al. [42]	2021	Saudi Arabia	Cross-sectional	126	Obese women (63 PCOS, 63 non-PCOS)	PCOS	VEGF 4× higher in PCOS; significant differences in metabolic and hormonal profiles
Ahmed et al. [43]	NR	Asir	Cross-sectional	NR	Adults with hypercholesterolemia	Hypothyroidism; metabolic syndrome	Limited data available; examined hypothyroidism in relation to obesity
Nashar et al. [44]	2017	Medina	Cross-sectional	NR	Female university students	Genetic factors	Investigated genetic risk factors; specific findings not available
Sabir et al. [45]	2019	Saudi Arabia	NR	NR	Saudi adults	Genetic (ACE I/D polymorphism)	ACE I/D polymorphism and high salt intake influence obesity risk

Abbreviations: SA = Saudi Arabia; PCOS = polycystic ovary syndrome; BMI = body mass index; FTO = fat mass and obesity-associated gene; MC4R = melanocortin-4 receptor; BDNF = brain-derived neurotrophic factor; ACE = angiotensin-converting enzyme; I/D = insertion/deletion; VEGF = vascular endothelial growth factor; OR = odds ratio; NR = not reported.

Table 2. Prevalence of Secondary Causes by Category

Secondary Cause Category	Number of Studies	Total Sample Size	Prevalence Estimate	Comments
Endocrine Disorders				
Hypothyroidism	1	NR	Not reported	Only post-bariatric surgery outcomes examined; no baseline

Secondary Cause Category	Number of Studies	Total Sample Size	Prevalence Estimate	Comments
				prevalence data
PCOS	4	439	Not reported	Studies focused on genetic associations and metabolic profiles; no population-based prevalence estimates
Cushing's syndrome	0	—	No data	No studies identified
Pharmacological				
Medication-induced obesity	0	—	No data	No studies identified
Genetic Factors	5	750+	Variable by variant	See Table 2A for specific genetic associations
FTO variants	2	556	—	Significant associations with obesity (OR 1.52-1.92)
MC4R variants	1	189	—	Strong associations in PCOS patients (OR 1.35-1.36)
BDNF variants	1	367	—	Largest effect size observed (OR 1.92)
ACE polymorphism	1	NR	—	Associated with obesity risk

Abbreviations: PCOS = polycystic ovary syndrome; FTO = fat mass and obesity-associated gene; MC4R = melanocortin-4 receptor; BDNF = brain-derived neurotrophic factor; ACE = angiotensin-converting enzyme; OR = odds ratio; NR = not reported.
Note: Prevalence estimates could not be calculated due to case-control designs and lack of population-based sampling in genetic studies.

Table 2A. Genetic Associations with Obesity in Saudi Adults

Gene	Variant (SNP)	Study	Sample Size	Effect Size (OR)	P-value	Population	Key Findings
FTO	rs17817449	Bakhashab et al. [39]	189	NR	<0.05	Women with PCOS	Significantly associated with PCOS and high BMI
FTO	rs1421085	Bakhashab et	189	NR	<0.05	Women with PCOS	Associated with BMI >30 kg/m²

Gene	Variant (SNP)	Study	Sample Size	Effect Size (OR)	P-value	Population	Key Findings
		al. [39]					
FTO	rs8050136	Bakhashab et al. [39]	189	NR	<0.05	Women with PCOS	Homozygous C allele = risk allele for high BMI
FTO	rs3751812	Alharbi et al. [41]	367	1.523	0.016	Saudi adults	Significant association with obesity
MC4R	rs12970134	Batarfi et al. [40]	189	1.348	0.002	Women with PCOS	Homozygous GG associated with obesity (BMI ≥30)
MC4R	rs17782313	Batarfi et al. [40]	189	1.364	0.002	Women with PCOS	Homozygous TT associated with obesity (BMI ≥30)
BDNF	rs10767664	Alharbi et al. [41]	367	1.923	0.00072	Saudi adults	Largest effect size observed
ACE	I/D polymorphism	Sabir et al. [45]	NR	NR	NR	Saudi adults	Associated with obesity risk (with high salt intake)
Multiple	11 SNPs (weighted GRS)	Alharbi et al. [41]	367	2.57	0.00092	Saudi adults	Cumulative genetic risk score; loci affecting appetite

Abbreviations: SNP = single nucleotide polymorphism; OR = odds ratio; FTO = fat mass and obesity-associated gene; MC4R = melanocortin-4 receptor; BDNF = brain-derived neurotrophic factor; ACE = angiotensin-converting enzyme; I/D = insertion/deletion; GRS = genetic risk score; PCOS = polycystic ovary syndrome; BMI = body mass index; NR = not reported.

Table 3. Quality Assessment Summary

Study	Study Design	Selection Bias	Measurement Bias	Confounding Control	Reporting Completeness	HWE Testing*	Overall Risk of Bias
Bakhashab et al. [39]	Case-control	High (convenience sampling)	Low (validated genotyping)	Moderate (limited adjustment)	Moderate (some missing data)	Yes	**High**
Batarfi et al. [40]	Case-control	High (convenience sampling)	Low (validated genotyping)	Moderate (limited adjustment)	Moderate (some missing data)	Yes	**High**
Alharbi et al. [41]	Genetic association	High (convenience sampling)	Low (validated genotyping)	Moderate (multivariable analysis)	Moderate	Not reported	**Moderate**
Daghestani et al.	Cross-sectional	High (single-center)	Moderate (methods unclear)	Low (no adjustment)	Low (limited data)	N/A	**High**

Study	Study Design	Selection Bias	Measurement Bias	Confounding Control	Reporting Completeness	HWE Testing*	Overall Risk of Bias
[42]							
Ahmed et al. [43]	Cross-sectional	Unclear	Unclear	Unclear	Low (abstract only)	N/A	**High**
Nashar et al. [44]	Cross-sectional	High (university students)	Unclear	Unclear	Low (limited data)	N/A	**High**
Sabir et al. [45]	NR	Unclear	Unclear	Unclear	Low (limited data)	Not reported	**High**

Abbreviations: HWE = Hardy-Weinberg equilibrium; N/A = not applicable; NR = not reported.
*HWE testing is relevant only for genetic association studies and indicates whether genotype distributions in control groups were tested for deviation from Hardy-Weinberg equilibrium.

Risk of Bias Ratings: - **Low:** Study design and conduct minimize bias; results likely valid - **Moderate:** Some limitations present but unlikely to invalidate results - **High:** Significant limitations that may invalidate results; findings should be interpreted with caution

Key Limitations Across Studies: 1. Small sample sizes (median n=189) 2. Convenience sampling from hospital/university settings 3. Lack of population-based sampling 4. Inadequate control for confounding variables 5. Incomplete reporting of key data elements 6. Geographic concentration in Western Saudi Arabia 7. Predominance of female-only samples (4/7 studies) 8. No sample size calculations reported

Figure 1. PRISMA 2020 Flow Diagram

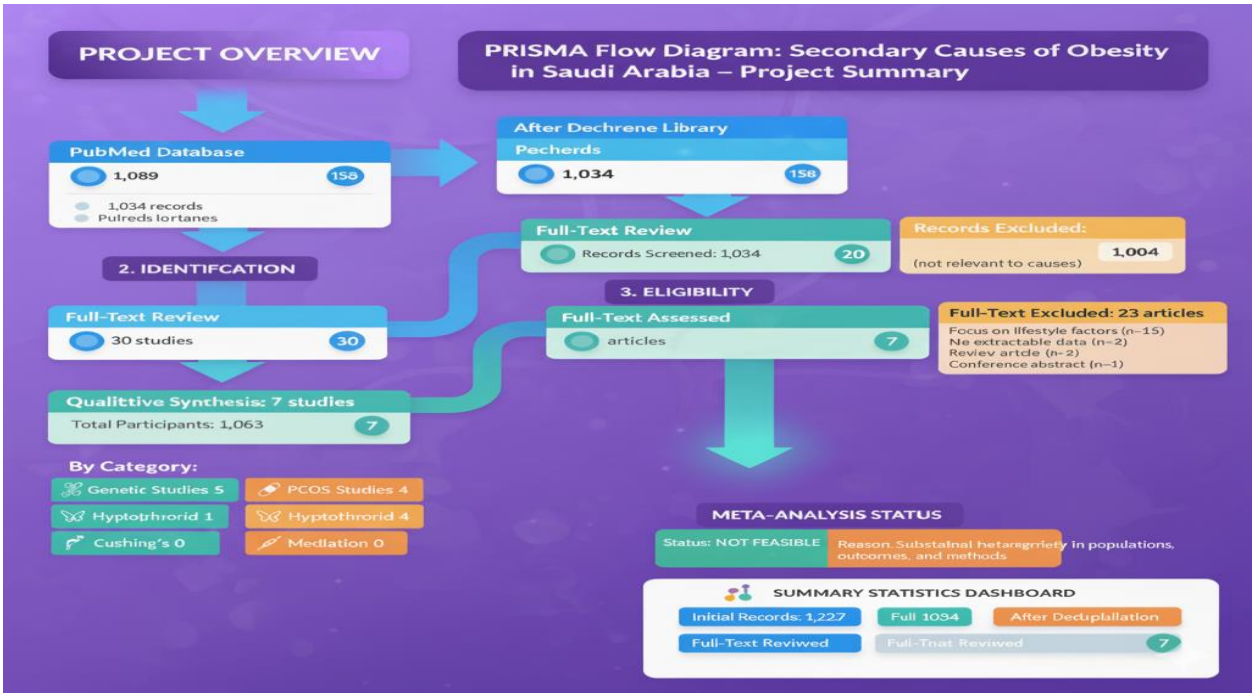

Figure 1 Legend: PRISMA 2020 flow diagram showing the study selection process. The search identified 1,247 records from two databases (PubMed and Cochrane). After removing 213 duplicates, 1,034 records underwent title and abstract screening. Of these, 1,004 were excluded as not relevant to secondary causes of obesity. Thirty studies proceeded to full-text review, of which 23 were excluded for various reasons (primarily focus on lifestyle factors rather than secondary causes). Seven studies

met all inclusion criteria and were included in the qualitative synthesis, with a total of 1,063 participants. Meta-analysis was not feasible due to substantial heterogeneity. No studies examined Cushing's syndrome or medication-induced obesity.

SUPPLEMENTARY *MATERIALS*

Supplementary Table S1. Search Strategy

PubMed Search (Conducted November 1, 2025)

#1 "obesity"[MeSH Terms] OR "obesity"[Title/Abstract] OR "obese"[Title/Abstract] OR "overweight"[Title/Abstract] OR "adiposity"[Title/Abstract]

#2 "Saudi Arabia"[MeSH Terms] OR "Saudi Arabia"[Title/Abstract] OR "Saudi Arabian"[Title/Abstract] OR "Saudi"[Title/Abstract] OR "Kingdom of Saudi Arabia"[Title/Abstract]

#3 "hypothyroidism"[MeSH Terms] OR "hypothyroidism"[Title/Abstract] OR "thyroid diseases"[MeSH Terms] OR "thyroid"[Title/Abstract] OR "Cushing syndrome"[MeSH Terms] OR "Cushing"[Title/Abstract] OR "hypercortisolism"[Title/Abstract] OR "polycystic ovary syndrome"[MeSH Terms] OR "PCOS"[Title/Abstract] OR "polycystic ovar*"[Title/Abstract]

#4 "genetic"[Title/Abstract] OR "polymorphism"[Title/Abstract] OR "gene"[Title/Abstract] OR "variant"[Title/Abstract] OR "mutation"[Title/Abstract] OR "FTO"[Title/Abstract] OR "MC4R"[Title/Abstract] OR "BDNF"[Title/Abstract]

#5 "medication"[Title/Abstract] OR "drug-induced"[Title/Abstract] OR "pharmacological"[Title/Abstract] OR "antipsychotic"[Title/Abstract] OR "antidepressant"[Title/Abstract] OR "corticosteroid"[Title/Abstract]

#6 "endocrine"[Title/Abstract] OR "hormonal"[Title/Abstract] OR "secondary cause"[Title/Abstract] OR "secondary obesity"[Title/Abstract]

#7 #3 OR #4 OR #5 OR #6

#8 #1 AND #2 AND #7

Results: 1,089 records

Cochrane CENTRAL Search (Conducted November 1, 2025)

Similar search strategy adapted for Cochrane interface.

Results: 158 records

Total: 1,247 records

FUNDING

No funding

CONFLICTS OF INTEREST

No conflict of interest

AUTHOR CONTRIBUTIONS

M.A. and **A.S.** conceived and designed the study. **M.Y.A.** and **M.A.** performed the data collection and formal analysis. **M.B.** and **M.J.** contributed to the methodology and software tools. **S.A.** and **M.A.** were responsible for project administration and funding acquisition. **M.Y.A.** drafted the initial manuscript, while **A.S.**, **M.B.**, and **M.J.B.A** provided critical revisions for intellectual content. All authors contributed to data interpretation, reviewed the final version of the manuscript, and approved it for publication.

DATA AVAILABILITY STATEMENT

All data extracted from included studies are presented in the tables within this manuscript. The search strategy and data extraction forms are available in the Supplementary Materials.