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High Hemoglobin Levels and Polycythemia as Markers of Cardiometabolic Risk and Metabolic Syndrome in Adults: A Focused Systematic Review and Evidence Update Through August 2026

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ABSTRACT

Metabolic syndrome (MetS) increases the risk of type 2 diabetes mellitus and cardiovascular disease. Although hemoglobin concentration is routinely measured in clinical practice, its utility as an indicator of cardiometabolic risk remains uncertain. This systematic review examined the associations between elevated hemoglobin concentrations, including high-normal levels and polycythemia, and MetS and cardiometabolic outcomes in adults, with particular attention to temporal patterns and differences by sex and age. A systematic literature search was conducted in PubMed/MEDLINE, PubMed Central, and ScienceDirect for studies published between 2013 and August 22, 2026, supplemented by citation tracking. Risk of bias was assessed qualitatively, and findings were synthesized narratively because of heterogeneity in exposure and outcome definitions and overlapping study cohorts. Eighteen publications representing approximately 15 distinct cohorts were included. Higher hemoglobin concentrations were generally associated with a greater prevalence of MetS and less favorable adiposity, blood pressure, lipid, and glycemic profiles. Among middle-aged Japanese men, polycythemia was associated with significantly higher odds of MetS (adjusted odds ratio [aOR] = 2.39; 95% confidence interval [CI]: 2.02–2.85). Longitudinal studies also identified associations between higher hemoglobin concentrations and incident MetS, although the magnitude and direction of these associations varied by sex and age. Population-based biobank analyses revealed U-shaped associations between hemoglobin concentrations and diabetes risk, highlighting potential nonlinear relationships. Overall, hemoglobin concentration may serve as a complementary marker in cardiometabolic risk assessment. However, the available evidence remains insufficient to establish causality or justify its use as a standalone screening biomarker. Further prospective studies and external validation are needed to determine whether hemoglobin provides incremental predictive value beyond established cardiometabolic risk factors.

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of interrelated cardiometabolic risk factors, typically characterized by abdominal obesity, elevated blood pressure, impaired glucose regulation, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol (HDL-C) concentrations. The coexistence of these abnormalities is associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Internationally harmonized diagnostic criteria define MetS as the presence of at least three of these five components, with population- and ethnicity-specific waist circumference thresholds (Alberti et al., 2009). From a pathophysiological perspective, insulin resistance, visceral adiposity, chronic low-grade

inflammation, endothelial dysfunction, oxidative stress, and disturbances in lipid metabolism interact in the development and progression of the MetS phenotype (Fahed et al., 2022).

Routine hematological parameters are not generally included among the core diagnostic criteria for MetS (Liu et al., 2025; Najafzadeh et al., 2023). Nevertheless, complete blood counts provide inexpensive, standardized, and widely accessible clinical information that may offer additional insights into cardiometabolic health. Hemoglobin (Hb) is primarily responsible for oxygen transport; however, its circulating concentration is influenced by several physiological and pathological factors, including erythropoiesis, iron and heme metabolism, plasma volume, hypoxic exposure, smoking, sex, age, and underlying medical conditions. Because hematocrit and erythrocyte mass influence the rheological properties of blood, elevated Hb concentrations may be associated with increased blood viscosity and alterations in microvascular perfusion. These physiological processes could potentially interact with insulin resistance, endothelial dysfunction, and cardiovascular disease development, although the underlying causal mechanisms remain incompletely understood (Gyawali et al., 2014; Minato et al., 2017).

Interest in the relationship between Hb concentrations and metabolic health has increased following population-based studies demonstrating that individuals with higher Hb concentrations, including those within the upper normal reference range, tend to exhibit higher body mass index (BMI), blood pressure, triglyceride concentrations, blood glucose levels, and measures of insulin resistance. Subsequent longitudinal investigations conducted in China, Japan, and Finland provided additional evidence suggesting that these associations may extend beyond cross-sectional correlations (Auvinen et al., 2021; Hashimoto et al., 2015; He et al., 2021; Tanaka et al., 2020; Tapio et al., 2021; Wu et al., 2013). However, the observed relationships have not been entirely consistent across populations. Some prospective studies identified stronger or more consistent associations among men (Hashimoto et al., 2015; Tanaka et al., 2020), whereas other investigations reported significant associations in both sexes (He et al., 2021; Timoteo et al., 2022). More recent studies focusing specifically on women have also identified substantial associations between high-normal Hb concentrations and adverse cardiometabolic profiles (Tokugawa et al., 2025). These variations suggest that sex, age, and population characteristics may modify the relationship between Hb concentrations and metabolic risk.

Wakabayashi (2022) made an important contribution to this body of evidence by specifically examining the association between polycythemia and cardiometabolic risk factors among 11,261 Japanese men. In that study, polycythemia was operationally defined as an Hb concentration ≥16.5 g/dL and was associated with less favorable blood pressure, lipid, adiposity, glycated hemoglobin (HbA1c), cardiometabolic index (CMI), and MetS profiles. After adjustment for age, smoking status, alcohol consumption, physical activity, and relevant medication use, polycythemia was associated with higher odds of an elevated CMI (adjusted odds ratio [aOR] = 2.18) and MetS (aOR = 2.39). Similar associations were observed among nonsmokers, suggesting that smoking alone did not fully explain the observed relationships (Wakabayashi, 2022). These findings extend the research focus beyond differences in mean Hb concentrations between individuals with and without MetS toward evaluating whether high-normal Hb concentrations and polycythemia may serve as clinically informative markers of cardiometabolic risk.

In 2024, Mahmood et al. published a meta-analysis encompassing 51 studies and approximately 170,000 participants, reporting significantly higher mean Hb concentrations among individuals with MetS than among those without MetS (standardized mean difference [SMD] = 0.24; 95% confidence interval [CI]: 0.18–0.31) (Mahmood et al., 2024). Although this meta-analysis provided substantial evidence of an association between hematological characteristics and MetS, its broad scope encompassed multiple erythrocyte and platelet parameters rather than focusing specifically on high-normal Hb concentrations and polycythemia. Furthermore, it did not comprehensively address Hb thresholds, the temporal relationship between elevated Hb and incident MetS, potential effect modification by sex and age, or evidence emerging from studies published during 2025–2026. Consequently, a focused systematic review incorporating recent evidence is warranted to clarify the potential role of elevated Hb concentrations as cardiometabolic risk markers while distinguishing Hb-specific associations from those involving other hematological parameters.

Accordingly, this systematic review aimed to evaluate the consistency and strength of associations between elevated Hb concentrations, including high-normal levels and polycythemia, and MetS and its individual cardiometabolic components. It also sought to examine longitudinal evidence regarding temporal relationships, identify potential differences in associations according to sex and age, and explore plausible biological mechanisms linking elevated Hb concentrations to cardiometabolic dysfunction. Furthermore, the review assessed whether the available evidence supports the potential use of Hb concentration as an additional biomarker in clinical cardiometabolic risk assessment or whether its current utility remains primarily epidemiological. By integrating evidence published through August 2026, this review aimed to provide an updated understanding of the clinical relevance, limitations, and future research priorities associated with elevated Hb concentrations as potential indicators of cardiometabolic risk.

METHOD

Reporting Design and Guidelines

This study was conducted as a focused systematic review with a narrative synthesis and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). A new meta-analysis was not performed because of substantial heterogeneity in exposure definitions (continuous hemoglobin concentrations, quartiles or deciles, high-normal hemoglobin levels, polycythemia, hematocrit, and composite indices), outcome measures, study designs, and sex- and age-specific subgroups. Additionally, several publications included identical or substantially overlapping Japanese occupational health cohorts. A narrative synthesis was therefore adopted to minimize the risk of participant double-counting and avoid generating pooled effect estimates that could be statistically precise but methodologically misleading.

PECO Review Questions and Framework

The main question of the review was: in adults, do higher Hb levels, high-normal Hb, or polycythemia compared to lower/normal Hb levels relate to the prevalence or incidence of MetS and poorer cardiometabolic outcomes?

Table 1. PECO framework and study design limitations.

Components	Operational definition
Population	Adults (≥18 years), general population, community, occupational health, or relevant clinical cohort.
Exposure	Hb levels, categories/quartiles/deciles Hb, Hb high-normal, polycytemia/erythroccytosis; hematocrit is considered when analyzed with Hb.
Comparator	Lower/normal Hb category or group without polythemia.
Outcomes	Primary: MetS. Secondary: obesity/waist circumference, hypertension, triglycerides/HDL/LDL, glucose/HbA1c, insulin/HOMA-IR, diabetes, NAFLD/liver fat, CMI, mortality/CVD.
Study designs	Prospective/retrospective, cross-sectional, population/biobank analysis, and secondary intervention analyses linking Hb changes to metabolic outcomes.

Sources of Information and Search Strategies

Structured searches were conducted through PubMed/MEDLINE, PubMed Central, ScienceDirect/publisher-indexed records, as well as backward and forward citation searches from the Wakabayashi anchor study (Wakabayashi, 2022) and other key studies. The search focused on the 2013 publication to 22 August 2026 to provide a contemporary update of the evidence of the last decade, while older sources may be used in the discussion of mechanisms where relevant.

The core strategy used was a combination of terms: ("hemoglobin" OR "haemoglobin" OR "hematocrit" OR "polycythemia" OR "erythrocytosis") AND ("metabolic syndrome" OR "cardiometabolic" OR "insulin resistance" OR "obesity" OR "hypertension" OR "dyslipidemia" OR "diabetes"). Additional searches used author/study name, terms "high-normal hemoglobin", "incident metabolic syndrome", "cardiometabolic index", and "hematometabolic index". The identity of the article was verified at the level of title, author, year, journal, DOI/PMID, population, and main outcomes.

Inclusion and Exclusion Criteria

Studies are included when all of the following criteria are met: adult human studies; evaluate Hb or polycythemia as a primary exposure or one of the separately analysed haematological exposures; report MetS or cardiometabolic components/outcomes; provide quantitative results or extractable analytical conclusions; and are peer-reviewed publications in English. Studies with a combination of indices (e.g. hematometabolic index / HMI) are included as supporting evidence where Hb is an explicit component and MetS-related results are reported.

Studies excluded from primary synthesis only address HbA1c without blood Hb, focus on anemia as a single exposure, include polycythemia vera/myeloproliferative neoplasms as the primary population, constitute pediatric/adolescent studies, case reports, editorials, reviews, or meta-analyses. Previous reviews and meta-analyses are still used to map context and novelty, but are not counted as primary studies.

Data Extraction, Cohort Overlap, and Quality Assessment

The extracted data included the most informative country, sample size, age/sex, design, definition / representation of Hb, outcome, duration of follow-up, key covariates, and most informative effect estimates. The 2022 Wakabayashi publication, 2022/2023 age analysis, 2023 HMI development, and 2025 HMI prognosis study originated from Japan's partially

overlapping population occupational health screening ecosystem; therefore the study was not treated as four independent cohorts in the reasoning of the strength of the evidence.

Risk of bias was assessed qualitatively with domains that align with the critical appraisal of observational studies: representativeness/selection, validity of Hb measurements, definition of outcomes, confounding handling, temporality, and completeness of follow-up. Overall categories were summarized as low-medium, medium, or medium-high. Numerical scores were not forced because the designs were very diverse and some reports were secondary analyses of the same cohort.

Data Synthesis

The synthesis was conducted based on four themes: (1) the cross-sectional/dose-response relationship of Hb with MetS; (2) longitudinal evidence and long-term outcomes; (3) modification of relationships by sex and age; and (4) biological mechanisms and biomarker utility. Effect estimates were selectively reported for the most informative studies, with special attention to adjusted OR/RR/HR and confidence intervals.

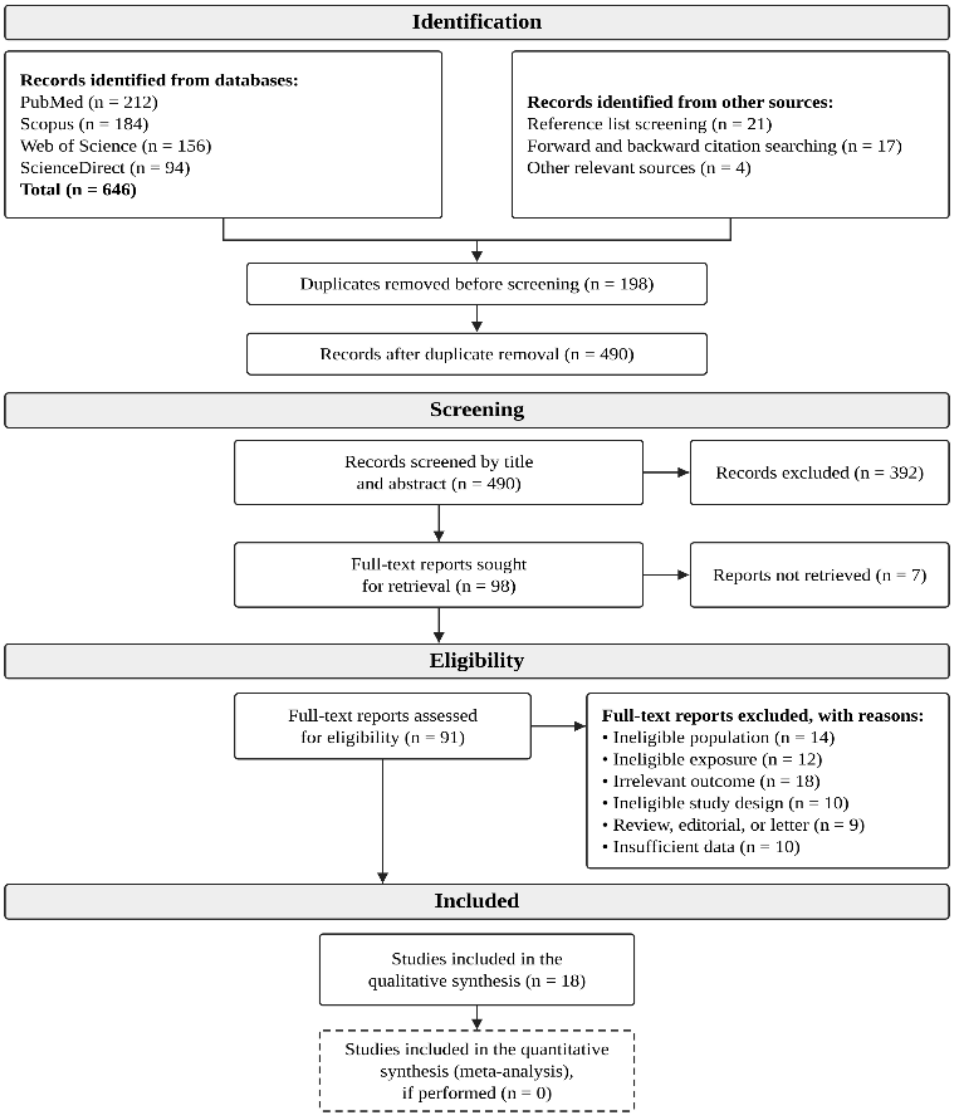


Figure 1. Framework of the study selection process compatible with the principles of PRISMA 2020

RESULTS AND DISCUSSION

General Characteristics of Evidence

Eighteen relevant primary publications were synthesized, representing approximately 15 different analytical cohorts after considering population overlap. Evidence came mainly from Japan, China, Taiwan, South Korea, Finland, Italy, Iran, and the UK Biobank. Sample sizes ranged from 64 participants on the secondary intervention analysis to more than 386,000 participants on the UK Biobank. The design included a cross-sectional, longitudinal cohort of 3-20 years, a large-scale biobank, a supportive randomization/experimental Mendelian analysis, and one secondary analysis of randomized behavioral intervention.

In general, the direction of the association is consistent: higher Hb is associated with higher prevalence of MetS and a less favorable profile of adiposity, blood pressure, triglycerides, glucose, or insulin resistance. However, the magnitude of the effect varies according to the definition of Hb and population characteristics. Studies that use Hb as a continuous variable tend to show a risk gradient, while extreme category studies often show a larger OR. Diabetes outcomes are an important exception because U-shaped relationships were reported in analyses of two large biobanks (Timoteo et al., 2022).

Table 2. Characteristics and main results of the synthesised study. CMI: cardiometabolic index; HMI: hematometabolic index; LAP: lipid accumulation product; MetS: metabolic syndrome; MR: Mendelian randomization.

Study	Population	Design	Hb Exposure	Outcome	Key findings
Kawamoto et al. (2013)	Japan; n=1,696	Cross-sectional community	Hb/Hct/RBC quartile	HOMA-IR, MetS	Hb/Hct/RBC was associated with HOMA-IR and MetS; Hct Q4 vs Q1 OR insulin resistance 3.78.
Laudisio et al. (2013)	Italy; n=1,036; ≥65 th	6-year cohort	Hb continuous/ median	MetS; Hb changes	Baseline MetS is associated with higher Hb; OR Hb above median 1.65.
Wu et al. (2013)	China; n=6,453	Longitudinal cohort	RBC/Hb/Hct Quartile	MetS incidents & components	Hb Q4 vs Q1 RR MetS 3.01; dose-response; Hb is also hyperglycemia.
Hashimoto et al. (2015)	Japan; n=2,695	8-year cohort	Quartet Hb	MetS Incident	Male: Hb ≥157 g/L vs <145 g/L OR 2.24; insignificant in females.
Ahmadzadeh et al. (2018)	Iran; n=11,114 males	Cross-sectional work	Quartile Hb/Hct	MetS & total components	Hb and Hct increase with the number of MetS components; the top quartile is associated with MetS.
Tanaka et al. (2020)	Japan; 20,162 cross-sectional;	Cross-sectional + cohort ~3.2 th	Hb continuous + MCV	Prevalence & incidence of MetS	Hb was associated with the prevalence of MetS in both sexes; significant incidence in males

	11,110 longitudinal				(aHR 1.12 per 1 g/L), not in females.
He et al. (2021)	China; n=9,960	3-year cohort	Quartet Hb	MetS incidents & components	High Hb predicts MetS in males and females; component patterns differ by gender.
Auvinen et al. (2021)	Finland; human n=7.175; MR n=173.480	Observational + MR + supporting experiments	Normal variation of Hb	Metabolic profile	Lower-normal Hb is associated with better BMI, glucose, blood pressure and inflammation; human causality is not fully proven.
Tapio et al. (2021)	Finland; n=967	Cohort ≥20 years	Quartet Hb	Metabolic, T2D, mortality	Hb Q4: liver fat OR 1.63; total mortality HR 1.48; CVD mortality HR 2.08; T2D follow-up was higher.
Wakabayashi (2022)	Japan; n=11,261 males	Cross-sectional work	Polycythemia Hb ≥16.5 g/dL	CMI, MetS & components	Polythemia: high OR CMI 2.18; MetS 2.39; independent of smoking.
Timoteo et al. (2022)	Taiwan n=67,237; UK n=386,477	Cross-sectional biobank	Desil Hb	MetS & components	Highest decile Hb: OR MetS 1.89-3.17 males and 2.35-3.11 females; diabetes shows U-shape.
Wakabayashi, 2022/2023 (Wakabayashi, 2023)	Japan; n=11,261 males	Age analysis; overlap cohort	Polycythemia Hb ≥16.5	MetS, LDL/HDL	The relationship was stronger at age 30-39 (OR MetS 3.49) and weakened with age, remaining apparent at 60-65 (OR 1.88).
Wakabayashi and Daimon (2023)	Japan; n=11,140 males	Cross-sectional; Cohort overlap	Hb + leukocyte (HMI)	CMI, MetS	HMI differentiates risk; age 30-39 AUC MetS 0.707; HMI cutoff 9.850.
Li et al. (2023)	China; n=7,726	Cross-sectional	Hb + WBC/neutrophil	MetS & components	Hb is higher on MetS and increases with the number of components; predictive performance is especially <40 years.
Tokugawa et al. (2025)	Japan; n=18,410 females	Cross-sectional work	quartile Hb; anemia removed	CMI, LAP, MetS	Q4 vs Q1: OR CMI 2.26; LAP 3.05; MetS 3.71; polycythemia only 0.14%, confirming the risk at high-normal.

Wakabayashi et al. (2025)	Japan; n=7,254 males	5-year cohort; related cohort	Quartile HMI	MetS Incident	Q4 vs Q1 HMI crude OR 3.02; association persists after adjustment; evidence for composite indices, not a single Hb.
StuRat (talk) 21:21, 21 January 2010 (UTC)	South Korea; n=1,680 men ≥60	Cross-sectional KNHANES	Tertile Hb normal 13-17 g/dL	MetS & components	Tertile highest OR MetS 1.78; abdominal obesity 2.03; FPG 1.71; TG 2.30.
Gassner et al. (2026)	Finland; n=64 MetS	Secondary analysis of 6-month RCTs	Hb baseline & changes	Insulin sensitivity, liver fat, fitness	Higher Hb is associated with lower insulin sensitivity and higher liver fat; changes in Hb correlate with changes in several metabolic markers.

The Relationship of High Hb and Polycytemia with MetS

The Wakabayashi (2022) study provides the most direct evidence for the polycythemia category in middle-aged men. Compared to the non-polycythemia group, the Hb ≥16.5 g/dL group had central adiposity, higher blood pressure, triglycerides, LDL-C, CMI, and HbA1c as well as lower HDL-C. The Adjusted OR for MetS 2.39 (95% CI 2.02-2.85) suggests that the association is not only statistically small, and the nonsmoking analysis reduces the likelihood that the entire association is explained by smoking's effects on Hb.

These results are consistent with the biobank study of Timoteo et al. (2022). In the Taiwan Biobank, the highest Hb decile was associated with a MetS OR of 3.17 in males and 3.11 in females; in the UK Biobank, the OR was 1.89 and 2.35, respectively. Replication in two large populations with different ethnic backgrounds reinforces the generalization that the high side of the Hb distribution is related to MetS. However, due to the cross-sectional design, the relationship remains unable to distinguish whether Hb plays a role in pathogenesis, is a response to the metabolic environment, or is a marker of a third determinant.

Women's evidence is gaining significant traction by 2025. Tokugawa et al. (2025) exclude Hb <11 g/dL and anemia therapy, so the problem of confounding by anemia is reduced. Although the prevalence of polycythemia (>16.0 g/dL) is only 0.14%, women in the highest Hb quartile have an OR MetS of 3.71 compared to the lowest quartile, along with an increase in CMI and LAP. These findings confirm that cardiometabolic signaling does not require pathological Hb; high-normal Hb can carry risk information.

In Korean men aged ≥60 years with Hb still in the range of 13-17 g/dL, Park (2026) found that the prevalence of MetS increased from 33.8% to 48.8% between tertiles and adjusted OR 1.78 for the highest tertil. Thus, although the Wakabayashi (2023) study showed the association of polycythemia tends to weaken with age, the association of high-normal Hb with MetS did not disappear in the elderly population.

Longitudinal and Temporality Evidence

The strongest evidence for temporality came from the longitudinal cohort. Wu et al. (2013) followed 6,453 participants and found the highest quartile Hb associated with MetS risk was about three times greater than that of the lowest quartile (RR 3.008; 95% CI 1.481-6.109), with a dose-response bias. Hashimoto et al. (2015) over eight years also found that males in the highest Hb quartile (≥157 g/L) had an adjusted OR of 2.24 (95% CI 1.34-3.85) for MetS incidence compared to the lowest quartile, but a similar relationship was not seen in females.

Tanaka et al. (2020) combined a large cross-sectional analysis with a longitudinal cohort and found that Hb was associated with the prevalence of MetS in both sexes, but with the incidence of MetS only in men. In contrast, He et al. (2021) in a cohort of 9,960 people over three years reported an association between high Hb and the incidence of MetS in both men and women, although the components driving the association were different: in women there was a greater pronouncement of high triglycerides and low HDL-C, while in men there was an association between abdominal obesity and low HDL-C.

Tapio et al. (2021) expanded on the long-term consequences of simply MetS. At follow-up of at least 20 years, higher Hb was associated with a less favorable metabolic profile, type 2 diabetes at follow-up, liver fat, total mortality, and cardiovascular mortality. Although the sample size was smaller than that of the biobank, the duration of follow-up signaled that high-normal Hb could identify a long-term risk phenotype.

The 2025 HMI study (Wakabayashi et al., 2025) showed that the combination of Hb and leukocytes could predict the occurrence of MetS over five years. These results are relevant to the hypothesis that erythrocyte information can be amplified by inflammatory indicators, but HMI should not be considered independent evidence that a single Hb is causal.

Gender and Age as Modifier

Sex differences are a major source of heterogeneity. Hashimoto et al. (2015) and Tanaka et al. (2020) found a clearer prediction of MetS incidence in men. Possible explanations include physiologically distinct Hb distributions, menstruation and menopausal status, differences in iron reserves, sex hormones, as well as differences in adiposity patterns. However, the data of He et al. (2021), Timoteo et al. (2022), and Tokugawa et al. (2025) suggest that it is inappropriate to conclude the association applies only to men. After anemia was treated more carefully, the high side of Hb distribution in women remained strongly associated with metabolic risk.

Age also modifies the signals. In Wakabayashi's analysis (Wakabayashi, 2023), polythemia had the strongest association with MetS at 30-39 years of age (OR 3.49), then diminished with age. Li et al. (2023) also reported better predictive performance of hematologic combinations in participants aged <40 years. In contrast, Park's (2026) study proved that high-normal Hb associations remained detected in men ≥60 years of age. Clinically, this means that one cutoff and one effect size should not be assumed to be the same across all age ranges.

Nonlinearity and Glycemic Outcomes

The association of Hb with diabetes does not always follow the same linear gradient as MetS. Timoteo et al. (2022) show that both the highest and lowest Hb deciles can be related to higher odds of diabetes, forming a U-shaped pattern. This makes sense because low Hb can signal chronic disease, deficiency, kidney disorders, or inflammation, while high Hb can reflect different factors such as hypoxia, hemoconcentration, iron/heme status, or metabolic

phenotype. Therefore, the use of Hb as a cardiometabolic marker should maintain a clinical context and not assume 'the lower the better' for all outcomes.

Summary of Quality Assessment and Risk of Bias

Table 3. Summary of qualitative quality/risk of bias assessment based on the domains of selection, measurement, outcome, confounding, temporality, and follow-up.

Study	Overall risk of bias	Key considerations
Kawamoto 2013	Medium	Cross-sectional; single community; objective measurement and adjustment are good, but temporality is absent.
Theme 2013	Medium	Elderly cohorts with follow-up; attrition and direction of complex Hb-MetS analysis.
Wu 2013	Low-Medium	Large cohorts and repeated checks; selection from health-check population and some confounders are not available.
Hashimoto 2015	Low-Medium	8-year-old, broad-adjusted, sex-stratified; health-check population may limit generalization.
Ahmadzadeh 2018	Medium	Very large but cross-sectional and only male driver.
Tanaka 2020	Low-Medium	Large samples, longitudinal sections; differences in sex effects and population-specific cut-offs.
It's 2021	Low-Medium	Large cohort of 3 years, both sexes; residual confounding remains possible.
Auvinen 2021	Low-Medium	Observational/MR/experimental triangulation is strong; Hb as a proxy for hypoxia and causal inference are inconclusive.
Tapio 2021	Medium	Follow-up >20 years; smaller sample size and potential survivor/attrition bias.
Wakabayashi 2022	Medium	Very large and adjustment good; cross-sectional and men's only.
Copyright © 2022	Low-	Two biobanks are very large and sex-specific; cross-
Copyright © 2022	Medium	sectional and selection/residual confounding.
Wakabayashi age 2022/23	Medium	Informative age modifier analysis; overlap with anchor cohort and cross-sectional design.
Wakabayashi-Daimon 2023	Medium	New indices and ROC; derivations in related populations, not yet external validation.
Li 2023	Medium	Large sample; cross-sectional and prediction evaluation without temporal validation.
Tokugawa 2025	Medium	Large females and anemia excluded; cross-sectional, incomplete menopause/nutritional status.
Wakabayashi et al. 2025	Low-Medium	5-year cohort; Composite and overlapping HMI of the Japanese cohort ecosystem.
Park 2026	Medium	National representative; cross-sectional, only elderly Korean men.
Gassner 2026	Medium	In-depth metabolic measurements; small n and secondary/post hoc analysis.

This review shows three main findings. First, the association between higher Hb and MetS appears consistently across different countries, designs, and categorization methods. This consistency comes not only from clinical polythemia, but also from high-normal variations of Hb. Second, some longitudinal cohorts suggest that high Hb precedes the onset of MetS, so reverse causality alone does not adequately explain all the evidence. Third, the strength and shape of the relationship are influenced by the sex, age, and outcomes analyzed; specifically for diabetes, nonlinearity must be taken into account.

These findings are in line with the meta-analysis of Mahmood et al. (2024) who found higher average Hb on MetS. The added value of the review now is to focus on the high side of the Hb distribution, polythememia category, temporality, and the 2025-2026 study. With that perspective, Hb is more appropriately positioned as a continuous risk marker rather than simply a 'normal versus abnormal' variable. The fact that Tokugawa et al. (2025) found a MetS OR of 3.71 in the high quartile of women despite polythemia being only 0.14%, and Park (2026) found an association in the normal Hb range of elderly men, supports this interpretation.

Possible Biological Mechanisms

One of the most direct mechanisms is hemorrhology. Increased erythrocyte and hematocrit mass increases blood viscosity; in metabolic environments already characterized by inflammation, oxidative stress, and erythrocyte membrane changes, erythrocyte aggregation and decreased deformability can worsen microcirculation (Gyawali et al., 2014). In patients with type 2 diabetes, higher whole blood viscosity has also been associated with MetS and postprandial hypertriglyceridemia (Minato et al., 2017). In theory, less efficient tissue perfusion may worsen glucose/insulin delivery and endothelial function, but direct evidence of this causal chain in the general population is limited.

The second pathway relates to iron and heme. Hb is the dominant heme reservoir, while iron/heme homeostasis plays a role in mitochondrial respiration and redox reactions. Excess iron/heme can biologically increase the formation of reactive oxygen species and interfere with cellular homeostasis (Dutt et al., 2022). The obesity literature also shows a complex relationship between iron metabolism, inflammation, adiposity, and metabolic disorders (Qiu et al., 2022). However, Hb is not identical to ferritin, transferrin saturation, or iron overload; therefore high Hb should not be directly interpreted as an excess of iron.

The third pathway involves hypoxia and HIF responses. Auvinen et al. (2021) used normal Hb variation as a surrogate of oxygen status and found that lower-normal Hb was associated with a better metabolic profile, while animal experiments supported that hypoxia pathway manipulation may affect metabolism. Mendelian randomization in humans does not provide completely strong causal evidence, so HIF is more appropriately viewed as a mechanistic hypothesis that explains part of epidemiological consistency, rather than a definitive mechanism.

The direction of the relationship is likely to be two-way as well. Visceral obesity, sleep-disordered breathing/intermittent hypoxia, smoking, inflammation, changes in plasma volume, kidney function, and hormonal factors can affect Hb; at the same time, high Hb/hematocrit can alter hemodynamics. Therefore, the Hb-MetS association is the result of biological and environmental networks that affect each other, not a simple one-arrow relationship.

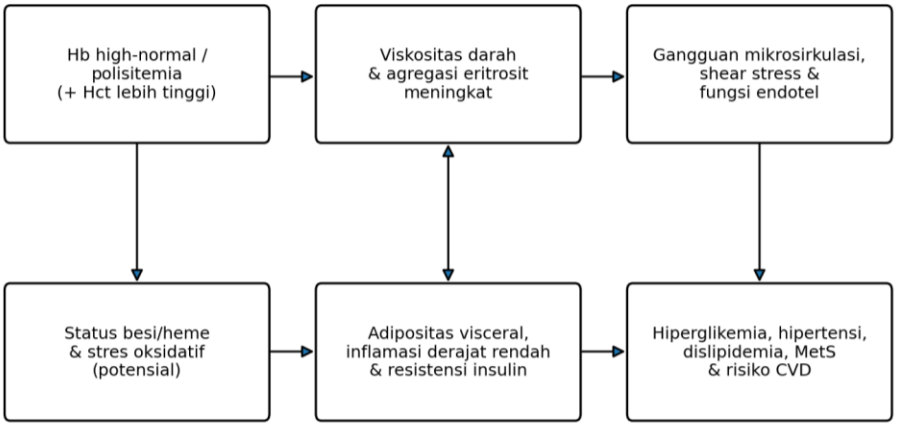


Figure 2. Conceptual models of the relationship between high-normal/polycythemia Hb and cardiometabolic risk. The diagram shows possible mechanisms and two-way relationships; not evidence of direct causality.

Clinical Meaning: Risk Markers, Not Self-Diagnosis

The advantage of Hb as a candidate marker is practical: these tests are inexpensive, automatic, and almost always available from complete blood counts. When associations with cardiometabolic risk can be replicated, Hb can serve as a 'signal amplifier' to direct attention to blood pressure, waist circumference, lipid profiles, glucose, or lifestyle factors that may not have been assessed. However, current data are not enough to recommend a new universal cutoff specifically for cardiomytabolic.

Clinical interpretation should distinguish three situations: low Hb, high-normal Hb, and pronounced erythrocytosis/polycythemia. High-normal Hb can be an epidemiological marker without implying that the patient has hematologic disease. In contrast, Hb that meets the criteria for erythrocytosis requires evaluation of secondary/primary causes in the clinical context, not simply considered as a consequence of MetS. Variables such as hydration status, smoking, elevation of residence, sleep breathing disorders, lung disease, androgen/testosterone therapy, and renal factors can shift Hb and become confounders.

Before Hb is used in prediction models, studies need to show incremental values above simple predictors such as age, sex, BMI/waist circumference, blood pressure, triglycerides, HDL-C, and glucose. The AUC of HMI of about 0.707 in young men (Wakabayashi & Daimon, 2023) is interesting, but derivation and validation should be separated and tested in external populations.

Gender, Menopause, and Age

Gender heterogeneity should not be considered statistical noise. Hb values are physiologically different between men and women, and in women they are affected by menstruation and menopause. Studies that include anemia in the low Hb group can artificially magnify the contrast with the high Hb group. Tokugawa et al. (2025) helped address this problem by excluding Hb <11 g/dL and anemia therapy; strong associations persisted. Future studies should report analyses of sex-at-birth stratification, menopausal status, and biologically comparable Hb ranges.

Age has the potential to influence relationships through changes in body composition, prevalence of chronic diseases, kidney function, therapy, and distribution of Hb. The strong

OR in young men in the Wakabayashi (2023) study suggests that high Hb at a relatively young age may be a marker of a more unusual and therefore more discriminating metabolic phenotype. In advanced age, the baseline cardiometabolic burden is higher so the relative effect may decrease although the absolute risk remains large.

Why New Meta-Analysis Isn't Done

Technically, combining numbers from available studies is possible, but not always valid. Exposure definitions include continuous Hb per 1 g/L, quartile, tertile, decil, polycythemia cut-off, or HMI. The definition of MetS uses different criteria; some studies only assess components, CMI, LAP, or mortality. More importantly, some Wakabayashi publications use the same or very close proximity health screening samples. Combining them all without individual participant data or overlap handling can result in excessive weight in a single population. Since the 2024 meta-analysis already shows pooled association of Hb-MetS (Mahmood et al., 2024), focused narrative synthesis is more appropriate to answer this novelty review question.

Strengths and Limitations of Reviews

The strength of this review is a clear focus on high-normal Hb/polycythemia as a marker, separation of cross-sectional and longitudinal evidence, attention to cohort overlap, and an update to August 2026 that includes studies of women, the elderly, and analysis of recent Hb changes. The use of biobank, long-term cohort, and supporting experiments/MRs allows for triangulation of evidence.

Limitations include the dominance of Asian studies and health-check/occupational cohorts, the heterogeneity of cut-offs and definitions of MetS, the large number of cross-sectional designs, and residual confounding. The review also does not have a standardized database export log to quantify all PRISMA stages; therefore, retrieval numbers are not fabricated and must be completed prior to formal submission. In addition, the quality appraisal in this draft is domain-based qualitative and should be conducted independently by two reviewers on the submission version to reduce subjectivity.

Implications for Further Research

Table 4. Research agenda to validate hemoglobin as a marker of cardiometabolic risk.

Priorities	Methodological recommendations
Display standardization	Report continuous Hb and sex-specific categories; separate high-normal from erythrocycytosis/polycytemia.
Temporalities	Prioritize the MetS-free cohort at baseline with a follow-up of ≥5 years and repeated Hb.
Confounding	Minimum: age, sex, smoking, alcohol, BMI/waist, renal function, altitude, hydration proxies, sleep apnea/hypoxia, medications/hormonal therapy.
Nonlinearity	Use restricted cubic splines and U/J-shaped tests, especially for diabetes and mortality.
Prediction	Incremental C-statistic/AUC tests, calibration, NRI/IDI or decision-curve on top of the basic clinical model.
External validation	Validation of cutoffs and models in Southeast Asian, European, African, and age/sex populations differed.
Mechanism	Combine Hb with Hct, ferritin/transferrin saturation, viscosity/deformability, inflammatory markers, hypoxia/HIF markers, and body composition.

CONCLUSION

Evidence available through August 22, 2026, indicated a relatively consistent association between elevated hemoglobin (Hb) concentrations, including high-normal levels and polycythemia, and metabolic syndrome (MetS) and increased cardiometabolic risk. The 2022 study by Wakabayashi provided evidence that polycythemia among middle-aged men was associated with higher odds of MetS and an elevated cardiometabolic index (CMI), even after accounting for smoking status. Longitudinal studies conducted in China, Japan, and Finland provided additional evidence of temporal associations between elevated Hb concentrations and cardiometabolic outcomes in certain population subgroups. Furthermore, population-based biobank analyses and recent studies extended these findings to older adults, including both women and men.

However, the available evidence remained insufficient to establish elevated Hb concentrations as a causal factor or support their use as a standalone diagnostic biomarker for cardiometabolic disorders. The presence of U-shaped associations with diabetes risk, heterogeneity across sex and age groups, and the potential influence of plasma volume, hypoxia, smoking, and underlying clinical conditions highlighted the need for contextual interpretation. Therefore, Hb concentration may be considered an inexpensive, widely available supplementary marker that could help identify individuals who may benefit from more comprehensive cardiometabolic risk assessment. Future research should prioritize prospective longitudinal designs, nonlinear association analyses, comprehensive adjustment for potential confounding factors, and external validation of the incremental predictive value of Hb beyond established cardiometabolic risk indicators. These investigations are essential before proposing new Hb thresholds for clinical cardiometabolic risk stratification.

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AUTHOR'S CONTRIBUTION

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GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

The author states that Generative Artificial Intelligence (AI) is not used to produce research data, conduct scientific analysis, or replace the author's intellectual contribution in the preparation of this manuscript. When used in the manuscript preparation process, AI is only

used to a limited extent to help improve the language and writing structure. The author remains fully responsible for the accuracy, integrity, and final content of the manuscript.

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