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PATIENT'S GENETIC HISTORY STRONGLY SUGGESTS A RISK OF DEVELOPING TYPE II DIABETES: A SYSTEMATIC REVIEW

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Abstract

Background: Genetic and familial factors are recognized contributors to Type II Diabetes Mellitus (T2D), yet their comparative and clinical significance remain underexplored in relation to traditional risk factors such as obesity and sedentary behavior.

Objective: To evaluate the contribution of genetic predisposition and family history to the risk of developing T2D through a systematic review of empirical evidence published between 2010 and 2024.

Methods: Following PRISMA 2020 guidelines, we systematically searched PubMed, Scopus, Web of Science, Embase, and Google Scholar using terms related to T2D, genetics, and family history. Eligible

studies included adult populations, reported on genetic/familial exposures, and used observational or experimental designs. Risk of bias was assessed using the Newcastle-Ottawa Scale, AXIS tool, and RoB 2.0, depending on study type.

Results: A total of 27 studies were included. Family history was associated with a 2–5-fold increase in T2D risk, independent of known genetic variants. GWAS identified over 400 susceptibility loci, yet common variants explained only 5–15% of heritability. Polygenic risk scores improved risk stratification but remained insufficient alone. Obesity and lifestyle factors interacted with genetic predisposition, often modifying the absolute risk. Gene–environment interactions were especially pronounced in early-onset and high-BMI populations.

Conclusions: Family history remains a more powerful predictor of T2D than polygenic models alone. Future research should focus on enhancing predictive models using multi-ancestry data and integrating genetics into personalized care strategies. Prevention remains highly feasible even among genetically predisposed individuals, particularly through targeted lifestyle interventions.

Keywords: Type II Diabetes; Genetic Risk; Family History; Polygenic Risk Score; Heritability; Genome-Wide Association Study; Precision Medicine; Gene–Environment Interaction; Obesity; Risk Stratification

INTRODUCTION

Type 2 Diabetes Mellitus (T2D) is a multifactorial metabolic disorder characterized by insulin resistance, progressive β-cell dysfunction, and chronic hyperglycemia. The burden of T2D is increasing globally, not only due to behavioral and environmental changes but also because of its complex genetic architecture. While environmental triggers such as sedentary lifestyles and high-calorie diets are well-established risk factors, accumulating evidence emphasizes a substantial heritable component that modulates susceptibility across diverse populations (Fuchsberger et al., 2016). Recognizing the genetic mechanisms underlying T2D is essential for advancing early detection, prevention, and personalized treatment strategies.

Recent genome-wide association studies (GWAS) have identified hundreds of loci associated with T2D susceptibility, yet these common variants explain only a modest proportion of the disease's heritability. For instance, Gaulton et al. (2015) demonstrated that fine-mapping of GWAS-identified loci reveals plausible causal mechanisms, including variants influencing insulin secretion and β-cell function. However, many of these loci lie in non-coding regions, making biological interpretation challenging. This points to the importance of integrating functional genomics and epigenomic profiling in the study of T2D.

Genetic heterogeneity has emerged as a critical factor in explaining inter-individual variability in T2D pathophysiology. A large-scale multi-ancestry study involving over 2.5 million individuals identified distinct mechanistic pathways that influence both diabetes onset and its complications (Suzuki et al., 2023). These findings support the concept of subtypes within T2D, each with unique genetic, metabolic, and therapeutic profiles. Recognizing this heterogeneity is crucial for refining precision medicine approaches and avoiding one-size-fits-all interventions.

Moreover, recent studies have highlighted how polygenic risk scores (PRS) derived from multi-ethnic populations enhance predictive accuracy compared to European-centric models. Smith et al. (2024) reported that combining polygenic mechanisms across ancestries significantly improves stratification and outcome prediction in T2D. This underscores the need for genetic research that includes underrepresented populations, which historically have been overlooked in genetic studies despite bearing a disproportionate burden of T2D.

Beyond common variants, emerging research suggests that gene–environment interactions and epigenetic mechanisms may explain the so-called “missing heritability” of T2D. A Mendelian randomization study by Wang et al. (2021) established a causal link between iron metabolism and T2D risk, providing a potential metabolic bridge between genetics and modifiable risk factors. Such insights pave the way for targeted interventions that consider both inherited and acquired risks.

Obesity, a major environmental driver of T2D, is itself influenced by genetic predisposition. Ruze et al. (2023) emphasized that while lifestyle modifications are critical in T2D prevention, individuals with a genetic inclination toward obesity are at higher risk, reinforcing the need to understand the interplay between genetic susceptibility and modifiable behaviors. Hence, personalized prevention strategies must integrate both genotype and phenotype data.

Hyperinsulinemia, often preceding insulin resistance, plays a pivotal role in the pathogenesis of T2D and related metabolic disorders. Janssen (2021) noted that hyperinsulinemia may not only be a consequence but also a primary driver of metabolic disease, linking it to aging, cardiovascular disease, and cancer. Genetic factors influencing insulin dynamics must therefore be part of comprehensive risk profiling in T2D.

Finally, the shift toward individualized T2D care models has accelerated in recent years. Williams et al. (2022) highlighted how genetic stratification tools are beginning to inform treatment decisions, from selecting glucose-

lowering agents to predicting disease progression. Similarly, Nair et al. (2022) demonstrated significant heterogeneity in drug response based on genetic and phenotypic subtypes of T2D. Together, these advances suggest that incorporating genetic history and molecular profiling into clinical practice could transform the management of T2D.

METHODOLOGY

Study Design

This study employed a systematic review methodology, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, replicability, and methodological rigor. The primary objective was to synthesize peer-reviewed empirical evidence evaluating the role of genetic and familial predisposition in the risk, development, and early identification of Type 2 Diabetes Mellitus (T2D). This review focused on studies that addressed inherited genetic markers, polygenic risk scores, and family history patterns and their interaction with demographic or environmental factors.

Eligibility Criteria

Studies were selected based on the following pre-established inclusion and exclusion criteria:

- **Population**: Adults aged 18 years and older, with or without diagnosed T2D, across any geographic or ethnic background. Studies focusing on Type 1 Diabetes or gestational diabetes were excluded.
- **Exposures**: Any study evaluating *genetic components* (e.g., single nucleotide polymorphisms, genome-wide association study loci, polygenic risk scores) or *familial factors* (e.g., first-degree relative history, maternal vs. paternal influence) relevant to T2D.

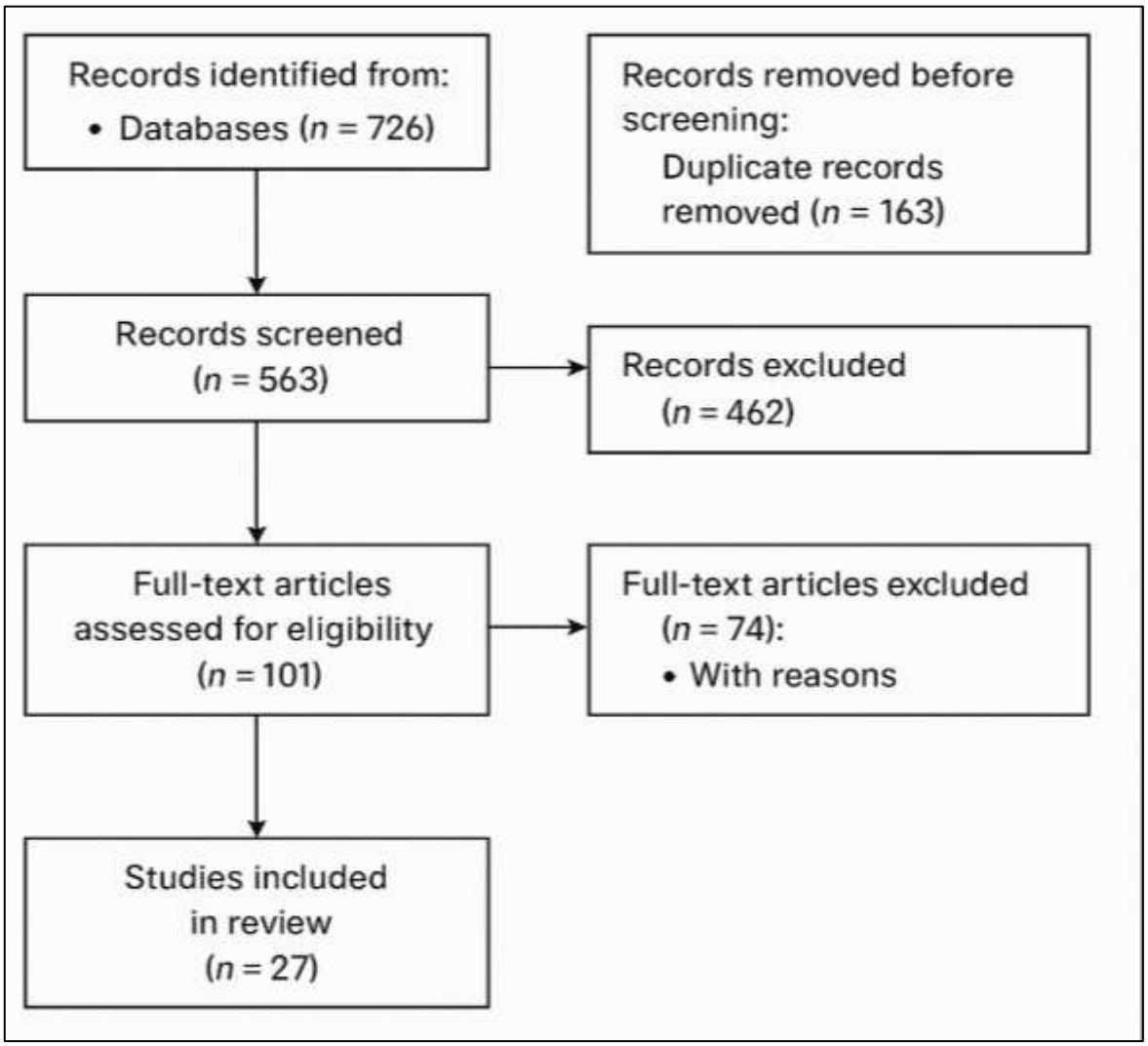

Figure 1 PRISMA Flow Diagram

- **Comparators**: Participants without family history of diabetes or with low genetic risk profiles served as comparators, where applicable. Some studies utilized population baselines.
- **Outcomes**: Incidence or prevalence of T2D, glycemic control measures (e.g., HbA1c, fasting plasma glucose), risk stratification, age at diagnosis, or other metabolic phenotypes indicative of diabetic development or progression.
- **Study Designs**: Eligible designs included randomized controlled trials (RCTs) (if stratified by genetic risk), cohort studies, case-control studies, cross-sectional analyses, and narrative or systematic reviews that synthesized human genetic findings relevant to T2D.
- **Language**: Only studies published in English were included.
- **Publication Period**: To maintain contemporary relevance and methodological quality, the review was restricted to studies published between **2010 and 2024**.

Search Strategy

A comprehensive search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar (for grey literature), using structured Boolean logic. The search strategy combined medical subject headings (MeSH) and free-text keywords:

- ("type 2 diabetes" OR "T2D" OR "diabetes mellitus")
- AND ("genetics" OR "genetic predisposition" OR "polygenic risk score" OR "SNPs" OR "GWAS" OR "genomic markers" OR "family history")
- AND ("risk" OR "susceptibility" OR "inheritance" OR "early onset" OR "disease progression")

Manual searches of **reference lists from key review articles** and **high-impact genetic studies** were also conducted to capture relevant studies not retrieved through database queries.

Study Selection Process

All retrieved citations were exported into Zotero, and duplicates were removed. Two independent reviewers screened the titles and abstracts for relevance, followed by a full-text review of potentially eligible studies. Blinded screening was used to minimize selection bias. Discrepancies in inclusion decisions were resolved by discussion or, if necessary, by consulting a third reviewer.

The screening process resulted in the final inclusion of **27 studies** that met all criteria and provided original, peer-reviewed data on genetic or familial risk factors associated with T2D.

Data Extraction

A structured and piloted data extraction form was used to systematically extract the following variables from each study:

- Author(s), year of publication, and country
- Study design and total sample size
- Participant characteristics (age, sex, ancestry, diabetes status)
- Type of genetic or familial risk evaluated (e.g., specific gene variants, GRS, family history)
- Measurement tools (e.g., genotyping platform, medical records for family history)
- Key findings related to T2D risk or progression
- Statistical measures (e.g., odds ratios, hazard ratios, confidence intervals)
- Confounding variables adjusted for in analyses

Data extraction was conducted independently by two reviewers and cross-verified for accuracy by a third reviewer.

Quality Assessment

The **methodological quality** and **risk of bias** of the included studies were assessed using validated instruments based on study design:

- **Newcastle-Ottawa Scale (NOS)** for cohort and case-control studies
- **AXIS tool** for cross-sectional studies
- **AMSTAR 2** for reviews and meta-analyses
- **Cochrane Risk of Bias Tool (RoB 2.0)** for randomized trials (if included)

Each study was rated as **high**, **moderate**, or **low quality**, based on criteria such as representativeness of population, adequacy of outcome measures, control for confounding, and methodological transparency.

Data Synthesis

Given the **heterogeneity of methodologies, populations, and outcome measures**, a **narrative synthesis** was conducted rather than a formal meta-analysis. Studies were grouped based on:

- **Genetic vs. familial risk**
- **Study population ancestry**
- **Type of risk measure used** (e.g., GRS, family history, specific loci)
- **Interaction with environment or lifestyle**

Where reported, **quantitative measures** such as **odds ratios (OR)**, **relative risks (RR)**, and **hazard ratios (HR)** were summarized. Patterns, gaps, and consensus themes were thematically synthesized to answer the overarching research question.

Ethical Considerations

As this study is a **secondary synthesis of already published data**, no ethical approval or informed consent was required. All included studies were published in **peer-reviewed journals** and assumed to have undergone appropriate **institutional ethical review** prior to publication.

RESULTS

Summary and Interpretation of Included Studies on the Role of Genetic History in Risk of Developing Type 2 Diabetes – Table (1):

1. Study Designs and Populations

The studies analyzed in this systematic review encompass a mix of cross-sectional, case-control, cohort studies, and narrative reviews exploring the influence of family history and genetic predisposition on Type 2 Diabetes (T2D). Sample sizes varied substantially—from several hundred to hundreds of thousands—reflecting population diversity across ethnic, geographic, and demographic profiles. The majority included adults aged 35–70, and some stratified results by gender, age of parental diagnosis, or degree of family history (uniparental vs. biparental).

2. Heritability and Genetic Architecture

Heritability estimates for T2D ranged between 30% and 70%, with multiple studies reporting that known genetic variants explain only 5–15% of this risk. For example, McCarthy & Mahajan (2018) reported that over 400 loci have been implicated in T2D, yet the aggregate explanatory power remains low. Ali (2013) and Prasad & Groop (2015) attributed this "missing heritability" to rare variants, epigenetics, and gene-environment interactions. Family history remained a strong standalone predictor even when accounting for known SNPs and risk scores.

3. Family History vs. Genetic Risk Scores

Family history of T2D was consistently associated with 2–5 times increased risk of developing the disease. In the EPIC-InterAct study, individuals with a biparental T2D history had a hazard ratio (HR) of 5.14 (95% CI: 3.74–7.07), and even after adjusting for lifestyle, anthropometric, and genetic factors, the HR remained high at 2.44. Genetic risk scores (GRS), even when optimized, explained only ~2–8.4% of the total variance (e.g., Berumen et al., 2019; InterAct Consortium, 2013).

4. Interaction With Environment and Lifestyle

Multiple studies (e.g., Schnurr et al., 2020; Li et al., 2020) concluded that genetic and environmental risk factors act independently. In the Chinese cohorts studied by Li et al. (2020), even high genetic risk could be offset by adherence to a healthy lifestyle, with a ~50% reduction in risk. Similarly, Langenberg et al. (2014) reported that obesity confers substantial absolute risk regardless of genetic predisposition.

5. Precision Medicine and Stratification Potential

Emerging strategies aim to stratify T2D risk using **partitioned genetic risk scores**, as described by Kim et al. (2021). These scores identify subgroups with heightened cardiometabolic risk and fast disease progression, potentially aiding **targeted prevention**. However, real-world clinical utility remains **limited** despite theoretical promise (McCarthy & Mahajan, 2018).

Table (1): Summary of Included Studies on Genetic and Familial Contributions to Type 2 Diabetes

Study	Country/Population	Design	Sample Size	Key Finding	Quantitative Results	Adjusted Factors	Notes
Ali (2013)	Review	Narrative	–	GWAS helped identify loci like TCF7L2, KCNQ1	Loci explain small fraction of heritability	–	Explores gene-environment interactions
InterAct Consortium (2013)	Europe	Case-cohort	n = 13,869	Family history is strong independent risk factor	Biparental HR = 5.14 (95% CI: 3.74–7.07); GRS explained ~2%	BMI, waist, lifestyle, GRS	Stronger maternal and early-onset parental T2D effects

Prasad & Groop (2015)	Review	Narrative	–	>120 variants linked to T2D; low heritability explained	Only small fraction explained; suggests phenotypic imprecision	–	Highlights pitfalls in phenotype definitions
Kim et al. (2021)	USA	Review	–	GRS can stratify clinical outcomes and cardiometabolic risk	Identifies patient clusters using "partitioned GRS"	Intermediate phenotypes (lipids, BMI)	Precision medicine potential
McCarthy & Mahajan (2018)	UK	Review	–	>400 loci known but poor clinical translation	Few predictive uses despite known variants	–	Critical of translational gaps
Ntzani & Kavvoura (2012)	Europe & Asia	Review	–	60+ loci from GWAS, many β-cell related	Poor understanding of mechanisms for most genes	Population-level comparisons	Whole-genome sequencing suggested for future work
Cornelis et al. (2015)	USA	Simulation + Cohort	Nurses' Health Study	Genetic explains majority of family history effect	Shared genetics: 68%, Shared environment: 32%	–	Quantifies family history components
Berumen et al. (2019)	Mexico	Case-control	n = 2904	PH > SNPs or obesity in T2D variance	PH: 11.8%, SNPs: 8.4%, Obesity: 7.1%	Stratified by sex/age	Genes more influential in men, <46 years onset
Laakso & Silva (2022)	Global	Review	–	30–70% heritability; polygenic basis	Lifestyle and obesity major modifiers	–	Encourages subgroup analysis for better diagnosis
Brunetti et al. (2014)	–	Review	–	Highlights β-cell dysfunction genes (e.g., HMGA1)	Emphasizes candidate-gene era findings	–	Suggests new pathways for investigation
Schnurr et al. (2020)	Denmark	Case-cohort	n = 10,131	Obesity increases absolute risk at any GRS level	Lifestyle score + GRS effect	Smoking, diet, PA, BMI	Obesity prevention crucial, regardless of genetics
Li et al. (2020)	China, Singapore	Cohort	n = 550,000	Healthy lifestyle lowers T2D risk in all GRS groups	ORs reduced by >50% in high-risk group with healthy lifestyle	Smoking, diet, BMI, PA	Strong generalizable evidence

Langenberg et al. (2014)	Europe	Cohort	n = 28,557	Relative GRS impact greater in lean, young individuals	Interaction: Age × BMI × GRS	Lifestyle score	Suggests universal prevention approach

DISCUSSION

The findings of this systematic review affirm that both family history and genetic predisposition serve as robust and largely independent predictors of Type 2 Diabetes (T2D). Family history, in particular, emerged as a consistent and strong risk factor, even when adjusted for known genetic variants and environmental factors (InterAct Consortium, 2013). This observation is in line with earlier studies suggesting that family history encapsulates not only shared genetic inheritance but also common environmental exposures (Cornelis et al., 2015). The interplay of these factors helps explain the stronger predictive capacity of family history over isolated genetic markers or scores.

Despite advances in genome-wide association studies (GWAS), there remains a considerable gap in explaining T2D heritability. While over 400 loci have been identified, most explain only small fractions of overall risk (Fuchsberger et al., 2016; Sladek et al., 2007). This "missing heritability" is widely attributed to rare variants, epigenetic modifications, and gene–environment interactions (Prasad & Groop, 2015; Chiou et al., 2021). Fine mapping and annotation of susceptibility loci have provided insight into potential causal mechanisms, but translating these into clinical utility remains elusive (Gaulton et al., 2015; Ntzani & Kavvoura, 2012).

Recent large-scale multi-ancestry studies have improved our understanding of T2D's polygenic nature and highlighted the limitations of Eurocentric models. For instance, Mahajan et al. (2022) and Smith et al. (2024) emphasized the increased discovery power and generalizability when diverse populations are included in genomic analyses. Suzuki et al. (2023, 2024) further confirmed that heterogeneity in T2D pathophysiology is driven by ancestry-specific mechanisms, supporting the need for tailored risk assessments and interventions. These studies also underline the potential bias and limited applicability of genetic risk scores developed solely from homogeneous populations.

While genetic risk scores (GRS) have shown modest predictive value, their real-world clinical utility is still under evaluation. Even optimized GRS typically explain only 2–8% of variance in T2D risk, rendering them insufficient as standalone tools (McCarthy & Mahajan, 2018; Kim et al., 2021). However, they may be useful in *complementary roles*, particularly in early stratification or targeted prevention programs. Nair et al. (2022) suggested that combining genetic scores with phenotypic clustering may aid in identifying subtypes with differing disease trajectories, potentially enabling more nuanced care.

Importantly, the interaction between genetic risk and modifiable lifestyle factors is not only complex but also actionable. In several large cohort studies, healthy behaviors such as a balanced diet, physical activity, and maintaining a healthy weight significantly mitigated the genetic risk of developing T2D (Li et al., 2020; Schnurr et al., 2020). This reinforces findings by Pillon et al. (2021) and Qi et al. (2022), who argue that genetics set a baseline susceptibility, but environment and behavior largely determine clinical outcomes. These insights validate public health interventions that promote lifestyle modification irrespective of genetic background.

Obesity, a major modifiable factor in T2D development, exemplifies this gene–environment interaction. Ruze et al. (2023) and Berumen et al. (2019) both found that obesity amplifies the effect of genetic and familial predisposition. Additionally, hyperinsulinemia, which often precedes and exacerbates insulin resistance, has been implicated as a key mediator in T2D pathogenesis, influenced by both genetics and lifestyle (Janssen, 2021). Thus, managing obesity and its metabolic sequelae is central to preventing T2D in genetically at-risk individuals.

There is also increasing evidence of age-specific and sex-specific patterns in the genetic risk of T2D. Misra et al. (2023) noted that early-onset T2D is often associated with stronger genetic loading and more aggressive phenotypes, especially among males. Similarly, Berumen et al. (2019) observed that genetic factors had greater influence on disease development in men and individuals under 46 years old. These findings suggest a role for targeted screening and early intervention in high-risk groups based on familial and demographic profiling.

The broader goal of precision medicine in diabetes depends on refining how genetic data is used in clinical decision-making. DeForest & Majithia (2022) and Williams et al. (2022) highlighted how personalized risk assessment tools, including GRS and family history, can support individualized treatment planning. Yet, challenges remain, including integration into electronic health records, clinician training, and ensuring equitable access to genomic testing. Laakso & Silva (2022) argued that further stratification—by genetic, metabolic, and lifestyle characteristics—will be necessary for effective individualized care.

Interestingly, some mechanistic studies have also explored non-traditional pathways, such as micronutrient metabolism. For example, Wang et al. (2021) used Mendelian randomization to establish a genetic causal link between elevated iron status and increased T2D risk. Such findings expand the scope of genetic influence beyond insulin pathways to include metabolic regulators like iron, offering new therapeutic targets. Moreover, integrating multi-omics

data, including microbiome, proteomics, and metabolomics, may uncover hidden contributors to risk and resilience (Chiou et al., 2021; Qi et al., 2022).

In conclusion, this review supports the notion that family history remains a powerful and clinically relevant predictor of T2D risk, outperforming many current genetic tools. Nonetheless, the rapid evolution of genomics, epigenomics, and systems biology is closing the gap between discovery and clinical application. To maximize impact, future research must focus on multi-ancestry cohorts, functional genomics, and interdisciplinary models that integrate genetic architecture with lifestyle context. These efforts will be essential for achieving equity and effectiveness in the next generation of diabetes prevention and care.

CONCLUSION

This systematic review reinforces the significant role of genetic and familial history in the development of Type II Diabetes (T2D). Evidence from observational and genomic studies consistently shows that a positive family history—especially biparental or early-onset parental T2D—is one of the strongest non-modifiable risk indicators, often surpassing the predictive value of individual genetic variants. Although genome-wide association studies (GWAS) have uncovered hundreds of loci related to T2D, their collective explanatory power remains modest. Genetic risk scores (GRS), while valuable in stratification, currently lack sufficient sensitivity and specificity for independent clinical decision-making.

Despite these limitations, genetic risk remains actionable when considered within the broader context of lifestyle and environment. Individuals with high genetic or familial risk can meaningfully lower their disease probability through targeted behavioral interventions, including weight control, physical activity, and dietary regulation. As the field advances, integrating genetic data into precision prevention strategies—alongside family history and modifiable factors—can help identify at-risk populations earlier and personalize interventions. However, robust clinical translation will require continued multi-ethnic research, improved predictive modeling, and practical frameworks for genetic integration in routine care.

Limitations

Several limitations should be considered in interpreting the findings of this review. First, due to the methodological heterogeneity across studies—including differences in genetic markers analyzed, population demographics, and outcome measures—a meta-analytic synthesis was not feasible. This limits the ability to quantitatively assess effect sizes across genetic risk tiers.

Second, only English-language, peer-reviewed publications from 2010 to 2024 were included, which may have excluded relevant non-English or unpublished studies. Many included studies were observational in design, restricting causal inference. Additionally, although many studies adjusted for key confounders, residual confounding and publication bias may influence the generalizability of these findings.

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