Supplementary Table 1: Summary of non-coding variant types and their correlation with phenotypic severity of Sickle Cell Disease (SCD) and Thalassemia.

PMID	Article Summary	Non-coding Variant Type	Phenotypic Severity Measure/Link	Observations
1379474	Haplotypes in SS patients... associated with elevated HB F.	Locus Control Region (LCR) HS−2 sequences and Gγ promoter within a hybrid haplotype.	Elevated HbF in SCD.	Links a non-coding LCR/promoter element to the key modifier HbF level in SCD.
1380206	β-thalassemia intermedia: relationship to mutations in the β-gene promoter.	Promoter mutations (−88 C→T, −87 C→A, −29 A→G).	High HbA2 beta-thalassemia intermedia phenotype	β-thalassemia intermedia (anemia severity) and high HbA2 levels.
1419783	Australian β0-thalassaemia... due to a 12 kb deletion commencing 5′ to the β-globin gene.	Large 5′ deletion removing sequences 5′ to the promoter.	Unusually high HbA2 phenotype.	Links a non-coding deletion/flanking region loss to a measure of severity.
1515647	δ-thalassemia caused by disruption of the GATA−1 site in the δ-globin gene promoter.	Promoter mutation (−77) abolishing GATA−1 binding.	Close association with the thalassemia phenotype	δ-thalassemia phenotype (impaired gene expression/synthesis).
1550780	Promoter mutations producing mild β-thalassaemia.	Promoter mutations (−87 C→T, −86 C→A).	Mild β-thalassaemia (thalassemia intermedia to late-presenting major).	Links promoter variants to the spectrum of phenotypic severity.
1577473	βs haplotypes in various world populations..	Promoter mutations (Mutations in the promoter sequences of the Gγ- and Aγ-globin genes).	Milder expression of the disease (inferred from the study's	Non-coding promoter mutations) associated with a milder expression

			objective) and Hematological data (average values) for SS patients grouped by βs haplotype.	of the disease. By providing Hb data by haplotype, it directly correlates the presence of the haplotypic non-coding variants with a measure of severity/disease outcome.
1698102	Observations on the levels of Hb A2 in patients with different β-thalassemia mutations and a delta chain variant... The −88 C→T promoter mutation is linked to increased Hb A2 and Hb B2 levels.	Promoter mutation (−88 C→T β-globin gene promoter mutation).	Increased Hb A2 and Hb B2 levels (by 200% and 80% respectively) in the presence of a delta chain variant (Hb B2).	Direct link between a promoter mutation (non-coding variant) and a significant quantitative change in the levels of Hb A2 and its variant.
1709779	Gγ and Aγ globin genes are identical from −471 of the promoter midway through γIVSII... Three new mutations were found in γ IVSII.	Intronic mutations found in γ IVSII.	Elevated Fetal Hemoglobin (Hb F) (≥12%) in Sickle Cell Disease (SS) patients.	Direct link between multiple intronic mutations (non-coding variants) in the γ-globin gene and the elevated Hb F levels, which is a measure of reduced phenotypic severity in SCD.
1725229	Molecular basis of β-thalassemia intermedia in a southern Italian region... The C→T substitution at position −158 5′ of the Gγ-globin gene is linked to attenuated forms.	Promoter mutation (C→T at −158 5′ of Gγ gene).	Attenuated β-thalassemia (transfusion-independent thalassemia inte rmedia or late-presenting thalassemia maj or).	Direct link between a γ-globin gene promoter mutation (a non-coding variant) and reduced disease severity (transfusion independence), specifically noting its role as a modifier in patients with homozygous β0-thalassemia.
8438884	Mild type of Hb S−β+-thalassemia... −92 C→T of the β promoter.	β promoter mutation (−92 C→T).	Mild type of Hb S−β+-thalassemia (clinical severity).	Direct link between a promoter mutation (−92 C→T) and milder disease severity.
8571932	Two mutations in the LCR HS-2 of haplotype 19 βs chromosomes alter binding of trans-acting	Locus Control Region (LCR) SNP (A→G at 8598 in 5’ HS-2); Locus Control Region (LCR) SNP (A→T at 9114 in	SNP (A→G at 8598 in 5’ HS-2) Increased binding of Sp1 which is linked	SNP (A→G at 8598 in 5’ HS-2) has link between a non-coding LCR variant (enhancer element)

	factors	5’ HS-2)	to the Benin haplotype's low HbF level (1-10%); low HbF is a measure of increased SCD severity. SNP (A→T at 9114 in 5’ HS-2) sharply decreased binding of an unknown trans-acting factor which is linked to the Benin haplotype's low HbF level (1-10%); low HbF is a measure of increased SCD severity.	and altered transcription factor binding, proposing a molecular mechanism for the observed differences in HbF (a key severity measure) among SCD patients with the same βS mutation.; SNP (A→T at 9114 in 5’ HS-2) has link between a non-coding LCR variant and altered transcription factor binding, proposing a molecular mechanism for the observed differences in HbF (a key severity measure) among SCD patients with the same βS mutation.
8916973	Activation of δ-globin gene expression... for gene therapy of Sickle Cell Disease	Defective Promoter Element (CACCC box at -90 in δ-globin promoter)	Low HbA2 levels (a measure of δ-globin expression) which fails to inhibit HbS polymerization, thereby exacerbating Sickle Cell Disease severity.	Directly links a defective non-coding promoter element to low expression of a globin chain (δ-globin), which acts as a known anti-sickling agent. This demonstrates how a non-coding variant modulates the molecular basis of SCD severity.
8943885	An IVS1-116 (A→G) acceptor splice site mutation in the α2 globin gene causing α+ thalassaemia	Intronic Splice Site Mutation (IVS1-116 A→G, Acceptor site)	Causes the α+ thalassaemia phenotype in carriers, resulting from the absence of functional mRNA (a measure of gene function/anemia severity).	Direct link between a non-coding intronic splice site mutation and the resulting thalassemia phenotype. This falls under the objective of characterizing studies linking non-coding variations to the clinical severity

				of α-Thalassemia.
9056561	Molecular basis of asymptomatic β-thalassemia major (describes modification of severe β-thalassemia)	HBB Promoter Mutation (-29); Polymorphism (Xmn I SNP) upstream of the Gγ-globin gene	HBB Promoter Mutation (-29) contributes to the β-thalassemia phenotype but, in combination, results in an asymptomatic/extremely mild β-thalassemia phenotype (reduction in severity/avoidance of transfusion dependence). Xmn I SNP associated with elevated Hemoglobin F (HbF) level of 83%; HbF elevation confers an extremely mild/asymptomatic phenotype.	Direct link between a promoter mutation (-29) (non-coding) and the overall clinical severity of β-thalassemia major. Link between a non-coding upstream Xmn I SNP (modifier) and the primary mechanism of amelioration (high HbF), explaining the missing heritability in a severe genotype.
9140720	A significant β-thalassemia heterogeneity in the United Arab Emirates	α-Globin Gene Deletion (-α 3.7 kb deletion)	Ameliorating effect on the phenotype of β-thalassemia (reduction in severity/improved clinical outcome).	This study directly links a modifier variant (α-thalassemia deletion), which is a non-β-globin coding change, to the phenotypic severity of β-thalassemia. This demonstrates the modification of a primary mutation's severity by a secondary genomic variant.
9143928	Scanning method... of δ-globin gene (detection of novel promoter substitutions)	Promoter mutation (e.g., -65 A→G)	Responsible for δ-thalassemia, linked to altered δ-globin gene expression and slightly increased HbA2 levels (a key hematological	Direct finding of a novel non-coding promoter mutation that alters globin gene expression and is responsible for a thalassemia phenotype.

			measure in thalassemias).	
9158662	Relative levels of α-, β-, and γ-mRNA... β-thalassemia major (links α/β-mRNA ratio differences to variable severity)	Hypothesized Promoter, Enhancer, and/or Locus Control Region (LCR) mutations	Explains variability in phenotypic severity (Thalassemia Intermedia vs. Transfusion-Dependent Severe Conditions) for patients with otherwise identical primary β-thalassemia mutations.	Mutations in promoter, enhancer, and/or locus control region sequences are likely responsible for the differences in disease severity observed for patients with the same primary β-globin gene mutation.
9234571	Silent thalassemias: genotypes and phenotypes (analysis of mild α- and β-thalassemia)	Promoter mutation (-101 C→T). Intronic mutation (IVS II 844 C→G)	Promoter mutation (-101 C→T) linked normal hematological picture with slightly raised Hb A2; classified as silent β+ thalassemia. Intronic mutation (IVS II 844 C→G) linked phenotype is even closer to normal; classified as silent β+ thalassemia.	Direct link between a promoter mutation (non-coding -101 C→T) and a measure of mild/silent phenotype. Direct link between an intronic mutation (non-coding IVS II 844 C→G) and a measure of very mild/silent phenotype.
12093744	An embryonic/fetal β-type globin gene repressor contains a nuclear receptor TR2/TR4 heterodimer.	Promoter Mutation (DR1 site mutation in γ-globin promoter)	Elevated γ-globin transcription (HPFH phenotype/high HbF) which ameliorates SCD.	References a natural non-coding DR1 site mutation in the γ-globin promoter that causes HPFH (high HbF), a powerful modifier of disease severity.
12176917	Homozygosity for nondeletion delta-β0 thalassemia resulting in a silent clinical phenotype. (Case of severe β-thalassemia	Aγ-globin Promoter mutation (-196C>T)	Silent clinical phenotype; High Hb F output (99.8%Hb F)	Direct link between a γ-globin promoter SNP and a severe β-thalassemia genotype resulting in a

	genotype resulting in a symptomless phenotype due to very high HbF)			symptomless/mild clinical phenotype due to very high HbF levels.
12210807	Spectrum of β-thalassemia mutations and their association with allelic sequence polymorphisms at the β-globin gene cluster in an Eastern Indian population. (Study investigating polymorphisms in cis-acting regulatory regions to understand genotype-phenotype correlations)	β-globin Locus Control Region (LCR HSs), γ-globin Promoter region, 3′ flanking region (Allelic Sequence Polymorphisms/Haplotypes)	Varying disease severity in β-thalassemia (genotype-phenotype relationship)	Explicitly studies the association of polymorphisms in cis-acting regulatory regions (LCR HSs, promoter regions, 3′ flanking) with the genotype-phenotype relationship and varying disease severity in β-thalassemia.
12393616	Variants in the VCAM1 gene and risk for symptomatic stroke in sickle cell disease. (Study analyzing non-coding SNPs in VCAM1 as genetic risk factors for a major clinical outcome in SCD)	Promoter SNPs and intronic regions (VCAM1 gene)	Risk for symptomatic stroke (a measure of phenotypic severity in SCD)	Investigated promoter SNPs and intronic regions of the VCAM1 gene for association with a major phenotypic severity measure in SCD: symptomatic stroke.
12614224	De novo deletion within the telomeric region flanking the human α globin locus as a cause of α thalassaemia. (Identification of a large deletion removing key regulatory elements, causing α-thalassemia)	Regulatory Element Deletion (HS-40 and HS-33/Enhancers)	Severely downregulated α-globin expression (causing α-thalassemia)	Direct link between a major non-coding deletion removing regulatory elements (enhancers HS-40, HS-33) and the resulting severe downregulation of α-globin expression, causing α-thalassemia.
12677174	UGT1A promoter polymorphisms influence bilirubin response to hydroxyurea therapy in sickle cell anemia. (UGT1A promoter variants affect bilirubin levels, a marker of hemolysis/severity, in SCA)	UGT1A Promoter polymorphism (e.g., 6/7 or 7/7 genotypes)	Serum Bilirubin levels (and influence on cholelithiasis/gallstone formation)	Direct link between a promoter polymorphism (UGT1A promoter) and a measure of clinical severity in SCA: serum bilirubin levels and the risk of gallstone formation.
12779270	Analysis of β-thalassemia mutations	β-globin Promoter mutations (-31 A>G and	β-thal major phenotype (a	Reports β-globin promoter mutations

	in northern Thailand using an automated fluorescence DNA sequencing technique. (Reports the identification of novel β-globin promoter mutations)	-87 C>A)	measure of anemia severity/transfusion dependence)	(-31 A>G and -87 C>A) that, when compound heterozygous with a β0-thal mutation, result in the β-thal major phenotype (a measure of severity).
12850481	Analysis of the A(TA)nTAA configuration in the promoter region of the UGT1A1 gene in Greek patients with thalassemia intermedia and sickle cell disease. (Analysis of a promoter polymorphism known to affect bilirubin in both patient groups)	UGT1A1 Promoter polymorphism (A(TA)n TAA repeat)	Thalassemia intermedia and Sickle Cell Disease (analyzing a modifier variant in these patient groups)	Analyzes the A(TA)nTAA repeat polymorphism (a non-coding variant) in the UGT1A1 promoter in patients with β-thalassemia intermedia and SCD, directly linking a non-coding variant to a known severity modifier locus.
16829478	[β0/β0 thalassemia with a mild phenotype]. (A severe β-thalassemia major patient has a mild course due to an XmnI promoter polymorphism)	Gγ gene Promoter polymorphism (XmnI -158, C>T)	Mild/intermediate phenotype (alleviated severity); High level of synthesis of foetal hemoglobin (HbF)	Direct link between the homozygous XmnI -158 C>T promoter polymorphism and the amelioration of a severe β-thalassemia major phenotype to a milder form, due to high HbF levels.
17178667	Molecular pathogenesis and clinical variability of homozygous β0-thalassemia in populations of Jammu region of $\text{J}& \text{K}$ state (India).	γ-globin gene non-coding SNP (XmnI polymorphism)	Lesser severity of β0-thalassemia (transfusion dependence vs. non-dependence/intermedia phenotype)	Direct link between a known non-coding SNP modifier (XmnI) and clinical severity/transfusion dependency in β-thalassemia
17516066	A novel mutation of −73(A→T) in the CCAAT box of the β-globin gene identified in a patient with the mild β-thalassemia intermedia.	β-globin gene promoter mutation (novel −73(A→T) in CCAAT box)	Mild β-thalassemia intermedia phenotype, transfusion independent	Direct link between a novel β-globin promoter mutation (non-coding) and a reduced-severity clinical phenotype
17593033	The linear effects of α-thalassaemia, the UGT1A1 and HMOX1 polymorphisms on	UGT1A1 gene promoter polymorphism ([TA]n repeat)	Increased risk of SCD complication: cholelithiasis (gallstones) and	Direct link between a non-globin promoter polymorphism and a major SCD

	cholelithiasis in sickle cell disease.		elevated serum bilirubin levels	complication
17600229	Confirmation of an association between the TNF(−308) promoter polymorphism and stroke risk in children with sickle cell anemia.	TNF−α gene promoter polymorphism (TNF(−308)G/A)	Increased risk of large vessel stroke (major SCD complication)	Direct link between a non-globin promoter polymorphism and a critical measure of SCD phenotypic severity
17894837	β-globin gene cluster polymorphisms are strongly associated with severity of HbE/β-thalassaemia.	XmnI polymorphism located 158-bp upstream to the G gamma gene	Modulation of HbF levels and HbE/β-thalassaemia severity	Explicit association of non-coding SNPs (polymorphisms) in XmnI 158-bp upstream to the G gamma gene to clinical disease severity and HbF levels
17916081	The β+IVS−I−6T→C mutation is the most frequent cause for the atypical β-thalassemia carrier phenotype in Portugal.	β-globin gene intronic splice site mutation (β+IVS−I−6T→C)+C94	Atypical β-thalassemia carrier phenotype	Direct link between an intronic (non-coding) mutation and an atypical, milder presentation of β-thalassemia
18697826	The HBS1L−MYB intergenic region on chromosome 6q23 is a quantitative trait locus controlling fetal haemoglobin level in carriers of β-thalassaemia.	HBS1L−MYB intergenic region QTL (non-coding SNPs)	Control of fetal haemoglobin (HbF) level (a severity modifier)	Direct link between a well-known non-coding QTL (defined by SNPs) in an intergenic region and the HbF modifier in β-thalassemia
20172753	Association of variant alleles of MBL2 gene with vasoocclusive crisis in children with sickle cell anemia.	MBL2 gene promoter -221 (alleles Y/X) and exon polymorphisms	Modification of SCA phenotype related to vasoocclusive crisis (VOC)	Direct link between non-coding MBL2 promoter polymorphisms and a major measure of SCD severity (VOC)
20351105	Placenta growth factor (PlGF), a novel inducer of plasminogen activator inhibitor-1 (PAI−1) in sickle cell disease (SCD).	PAI−1 gene promoter (HRE−1,HRE−2, and AP−1 sites).	SCD phenotype link: Increased PAI−1 (a prothrombotic state) due to non-coding PAI−1 promoter sites.	Although indirect, it links a major SCD complication (prothrombotic state) to the activity of a non-coding promoter region in a non-globin gene.
20472475	The XmnI (G)γ polymorphism influences hemoglobin F synthesis contrary to BCL11A and	Gγ-globin gene promoter SNP (XmnI) and intergenic/intronic SNPs (BCL11A and HBS1L−MYB QTLs).	HbF level (a major severity modifier) in β-thalassemia intermedia.	Direct comparison and finding a strong correlation between the non-coding XmnI SNP and a key severity

	HBS1L−MYB SNPs in a cohort of 57 β-thalassemia intermedia patients.			measure (HbF).
20709051	The effect of UGT1A1 promoter polymorphism on bilirubin response to hydroxyurea therapy in hemoglobinopathies.	UGT1A1 gene promoter polymorphism.	Bilirubin levels (a measure of hemolysis severity) and response to therapy.	Direct link between a non-globin promoter polymorphism and a measurable clinical severity factor (bilirubin/hemolysis) in hemoglobinopathy patients.
21144779	Xmn I polymorphism associated with concomitant activation of Gγ and Aγ globin gene transcription on a β0-thalassemia chromosome.	Gγ-globin gene promoter polymorphism (Xmn I C→T).	Moderately severe β0-thalassemia phenotype (despite total HbA absence).	Direct link between the non-coding XmnI SNP and the overall clinical severity (moderately severe phenotype).
21250885	β+-Thalassemia trait due to a novel mutation in the β-globin gene promoter: −26 (A>C) [HBB c.−76A>C].	β-globin gene promoter mutation (novel −26 (A>C)).	β+-Thalassemia trait (mild phenotype).	Direct link between a novel non-coding promoter mutation and the resultant, relatively mild β-thalassemia phenotype.
21757944	A 13-bp deletion in the 3′ untranslated region of the β-globin gene causes β-thalassemia major in compound heterozygosity with IVSII−1 mutation.	β-globin gene 3′ untranslated region (UTR) deletion (13-bp deletion).	β-Thalassemia major (severe phenotype).	Direct link between a UTR (non-coding) variant and the most severe clinical classification (β-thalassemia major).
21801233	The β-globin promoter −71 C>T mutation is a β+ thalassemic allele.	β-globin gene promoter mutation (novel −71 C>T).	β+ thalassemic allele (a classification of β-thalassemia severity/function).	Direct link between a non-coding promoter mutation and its effect on gene expression/severity classification.
22217218	Identification of a novel mutation in the β-globin gene 3′ untranslated region [+1,506 (A>C)] in a Japanese male with a heterozygous β-thalassemia phenotype.	β-globin gene 3′ untranslated region (UTR) mutation (novel +1,506 (A>C)).	Heterozygous β-thalassemia phenotype (severity classification).	Direct link between a novel UTR mutation (non-coding) and the resulting clinical phenotype.

22576309	Protein Z polymorphisms associated with vaso-occlusive crisis in young sickle cell disease patients.	Protein Z promoter SNPs (rs3024718,rs3024719,rs3024731) and intron SNP (rs3024735).	SCD complication: Vaso-occlusive crisis (VOC) (major severity measure).	Direct link between non-globin, non-coding SNPs (promoter and intronic) and a key measure of SCD phenotypic severity (VOC frequency).
22862814	Two novel mutations in the 3′ untranslated region of the β-globin gene that are associated with the mild phenotype of β-thalassemia.	β-globin gene 3′ untranslated region (UTR) mutations (HBB:c.∗+108A>G and HBB:c.∗+132C>T).	β-Thalassemia mild phenotype.	Direct link between novel non-coding UTR mutations and a specific, less severe clinical outcome.
22966170	Heme oxygenase-1 gene promoter polymorphism is associated with reduced incidence of acute chest syndrome among children with sickle cell disease.	Heme oxygenase−1 (HMOX1) gene promoter polymorphism (GT repeat SNP).	SCD complication: Acute chest syndrome (ACS) (a major severity measure).	Direct link between a non-globin promoter SNP (non-coding) and a critical, major measure of SCD phenotypic severity (ACS incidence).
23425204	Association in cis of the mutations +20 (C>T) in the 5′ untranslated region and IVS−II−745 (C>G) on the β-globin gene.	β-globin gene 5′ untranslated region (UTR) mutation (+20 (C>T)).	Association with mild β-thalassemia (severity classification).	Direct link between a UTR mutation (non-coding) and the resulting milder clinical phenotype.
23541515	The influence of the BCL11A polymorphism on the phenotype of patients with β-thalassemia could be affected by the β-globin LCR...	Intronic SNPs (in BCL11A); Locus Control Region (LCR) polymorphism.	Phenotype (Severity) and HbF variation in β-thalassemia.	Directly links BCL11A intronic SNPs and an LCR polymorphism to β-thalassemia phenotype and HbF levels, which modifies disease severity.
23556445	Genomic variation in the MAP3K5 gene is associated with β-thalassemia disease severity and hydroxyurea treatment efficacy.	Promoter short tandem repeat in MAP3K5; Intronic variants in MAP3K5.	Low HbF levels and a severe disease phenotype in β-hemoglobinopathy.	Directly links non-coding variants (promoter/intronic) in a modifier gene to HbF levels and disease severity.
23606168	Genetic modifiers of sickle cell anemia in the BABY HUG cohort: influence on laboratory and clinical phenotypes.	Intronic SNPs (BCL11A, HBS1L-MYB, XmnI); UGT1A1 promoter polymorphisms; α-thalassemia deletion.	Baseline HbF, serum bilirubin, and pain phenotype in SCD.	Links multiple classic non-coding variants (intronic, promoter, gene deletion) to HbF, bilirubin, and clinical phenotype (pain) in SCD.

23619273	Early complication in Sickle Cell Anemia children due to A(TA)nTAA polymorphism at the promoter of UGT1A1 gene.	Promoter polymorphism (A(TA)nTAA repeat) in UGT1A1.	Hyperbilirubinemia and gallstones formation (cholelithiasis) in SCD.	Directly links a promoter polymorphism to a measure of severity/complication (gallstones/hyperbilirubinemia) in SCD.
24060717	UGT1A1 promoter polymorphism associated with serum bilirubin level in Saudi patients with sickle cell disease.	Promoter polymorphism (A(TA)n repeat) in UGT1A1.	Serum bilirubin level and gallstones (cholelithiasis) in SCD.	Directly links a promoter polymorphism to hemolysis biomarkers (bilirubin) and cholelithiasis in SCD.
24065537	Association between clinical expression and molecular heterogeneity in β-thalassemia Tunisian patients.	Intronic SNP (XmnI polymorphism at-158 of the Gγ gene	Clinical expression (β-thalassemia major vs. intermedia).	Directly links the XmnI intronic polymorphism (a known HbF modifier) to the key phenotypic severity measure (β-thalassemia major vs. intermedia).
24168396	Genetic variation in CD36, HBA, NOS3 and VCAM1 is associated with chronic haemolysis level in sickle cell anaemia: a longitudinal study.	VCAM1 promoter haplotype; α-globin gene deletion (non-coding modifier).	Haemolysis biomarkers (LDH, total bilirubin, reticulocyte count).	Links non-coding variants (promoter haplotype, α-thalassemia deletion) to chronic hemolysis (a measure of severity) in SCD.
24204915	The effect of UGT1A1 promoter polymorphism in the development of hyperbilirubinemia and cholelithiasis in hemoglobinopathy patients.	Promoter polymorphism ((TA)n repeat) in UGT1A1.	Hyperbilirubinemia and cholelithiasis development in SCD and β-thalassemia.	Confirms the direct link between a promoter polymorphism and severity (complication/bilirubin) in both β-thalassemia and SCD.
24401016	Identification of three new nucleotide substitutions in the β-globin gene: laboratoristic approach and impact on genetic counselling for beta-thalassaemia.	Promoter/CAP site (HBB: c.-35 A>G); Intron 2 (HBB: c.316-373); 3' UTR (HBB: c.*+182 G>A).	Phenotypic expression in β-thalassemia.	Reports new non-coding variants (Promoter, Intronic, 3' UTR) in the β-globin gene and discusses their correlation with phenotypic expression/severity.
24614105	HBS1L-MYB intergenic variants modulate fetal	Intergenic variant rs66650371in Enhancer elements in HBS1L-	Elevated fetal hemoglobin (HbF) levels	Directly links intergenic/enhancer non-coding variants

	hemoglobin via long-range MYB enhancers.	MYB region.	and ameliorate sickle cell and β-thalassemia disease severity.	to HbF levels, a major modifier of severity in β-thalassemia and SCD.
24620945	Role of co-inherited Gilbert syndrome on hyperbilirubinemia in Indian beta thalassemia patients.	Promoter region (TA)n motifs of the bilirubin UGT1A1 gene.	Serum bilirubin levels in β-thalassemia (transfusion-dependent and intermedia).	Directly links a promoter polymorphism to a measure of severity (hyperbilirubinemia) in β-thalassemia.
25069958	Erythroid Krüppel-like factor-1, an iron-sensing protein, is a critical regulator of placenta growth factor, which is implicated in the vasculopathy of sickle cell disease.	PlGF promoter region (via EKLF binding). rs9376090, rs66650371, rs9399137, rs35786788, rs4895441, rs9389269, rs9402686, rs9494142, rs9494145 and rs948378 are associated with High-HbF.	Early mortality and iron overload markers in SCD.	Links gene regulation through its promoter region (a non-coding element) to a clinical severity measure (early mortality).
25657036	A novel promoter mutation (HBB: c.-75G>T) was identified as a cause of β(+)-thalassemia.	Promoter mutation (HBB: c.-75G>T).	β-thalassemia intermedia (β-TI) phenotype.	Directly links a novel promoter mutation (non-coding) to the overall phenotypic severity classification (β-TI).
25876995	Erythropoietin-mediated expression of placenta growth factor is regulated via activation of hypoxia-inducible factor-1α and post-transcriptionally by miR-214 in sickle cell disease.	Intronic microRNA (miR-214); PlGF promoter HREs.	Pulmonary hypertension (PHT) (SCD complication/severity).	Links a non-coding RNA (miR-214, located in an intron) and promoter HREs to a gene product (PlGF) and a major severity outcome (PHT) in SCD.
25928412	Genetic association of fetal-hemoglobin levels in individuals with sickle cell disease in Tanzania maps to conserved regulatory elements within the HBS1L-MYB intergenic region.	Intergenic/Enhancer regulatory elements within the HBS1L-MYB region.	Fetal-hemoglobin (HbF) levels in SCD.	Directly links non-coding regulatory elements in the intergenic region to HbF levels, a key measure of disease severity.
26291972	First Description of a β-Thalassemia Mutation, -86 (C>G) (HBB: c.-136C>G), in a Chinese Family.	Promoter mutation (HBB: c.-136C>G, in the CACCC box).	β(+)-thalassemia phenotype (a measure of severity).	Directly links a mutation in the promoter (CACCC box) of the β-globin gene to a resulting thalassemic

				phenotype/severity.
28871148	Editing an α-globin enhancer in primary human hematopoietic stem cells as a treatment for β-thalassemia.	Enhancer deletion (MCS-R2 α-globin enhancer).	Ameliorating the clinical severity (β-thalassemia corrected globin chain imbalance).	Although a gene-editing study, it directly establishes the functional link between deleting a non-coding element (enhancer) and correcting the pathology/severity of β-thalassemia.
28879539	Synergistic effect of two β globin gene cluster mutations leading to the hereditary persistence of fetal hemoglobin (HPFH) phenotype.	Promoter mutation (Novel Gγ promoter 5bp deletion)	Hereditary Persistence of Fetal Hemoglobin (HPFH) phenotype (High HbF levels)	Directly links a promoter deletion (non-coding) to significantly elevated HbF levels, which ameliorates β-thalassemia severity.
29227829	A long noncoding RNA from the HBS1L-MYB intergenic region on chr6q23 regulates human fetal hemoglobin expression.	Intergenic/Enhancer lncRNA (HMI-LNCRNA); Intergenic 3-bp deletion polymorphism (rs66650371).	Fetal hemoglobin (HbF) expression (A key modifier of disease severity).	Links a non-coding RNA transcribed from the HBS1L−MYB enhancer region to the regulation of HBG expression/HbF levels, directly impacting β-thalassemia and SCD severity.
29590102	Common α-globin variants modify hematologic and other clinical phenotypes in sickle cell trait and disease.	Enhancer SNP (rs11865131 in MCS-R2 α-globin enhancer); α-thalassemia deletion (-α3.7 deletion).	Stroke risk (major SCD complication/severity); Anemia; Chronic Kidney Disease (CKD).	Links a regulatory variant (SNP) in the α-globin enhancer and the α-thalassemia deletion (non-coding modifier) to major SCD clinical complications and anemia severity.
31688634	New Deletion at Promoter of HBG1 Gene in Sickle Cell Disease Patients With High HbF Level.	Promoter deletion (GCAG deletion at -273 in HBG1 promoter).	High HbF Level (a key modifier of SCD severity).	Directly links a novel promoter deletion (non-coding variant) to elevated HbF levels, which naturally ameliorates SCD severity.
31788855	HbS/β+ thalassemia: Really a mild disease? A National survey	Promoter mutation (A class of β+ mutations including promoter	Clinical Severity (SCD-related events	Links the β+ promoter mutation class to a milder

	from the AIEOP Sickle Cell Disease Study Group with genotype-phenotype correlation.	types).	like VOC, ACS, Stroke); Correlates with lower severity vs. IVS-I-110 group.	clinical phenotype (fewer severe events) compared to the IVS-I-110 splicing mutation.
32142096	Three Mexican Families with β thalassemia intermedia with different molecular basis.	3' UTR mutation (HBB: c.*132C>A).	β-thalassemia intermedia (β-TI) phenotype.	Directly links a novel 3' UTR mutation (non-coding variant) with the mutation c.118C > T (p.Gln39*) and a new duplication of the alpha globin gene cluster to the β-TI phenotype, a measure of reduced severity/transfusion independence.
34999313	VCAM1, HMOX1 and NOS3 differential endothelial expression may impact sickle cell anemia vasculopathy.	Promoter Haplotypes (VCAM1 promoter haplotypes).	Cerebral vasculopathy and severe hemolysis (major complication/severity measures) in SCA.	Directly links promoter haplotypes (non-coding variants) in a modifier gene (VCAM1) to the risk of a major SCD complication (vasculopathy) and severe hemolysis.
35095995	Whole Blood Transcriptome Analysis in Children with Sickle Cell Anemia.	Non-coding RNA SNPs (in RYR2 gene); Non-coding RNA (JHDM1D-AS1).	Fetal hemoglobin (HbF) regulation (key severity modifier).	Identifies SNPs in a novel non-coding RNA (RYR2) and links another non-coding RNA (JHDM1D-AS1) to the regulation of HBG mRNA levels/HbF expression, which influences SCD severity.
37857886	Iron overload induces dysplastic erythropoiesis and features of myelodysplasia in Nrf2-deficient mice.	Promoter SNP (NRF2 promoter SNP rs35652124).	Erythroid dysplasia (indicated by increased MCV); Iron overload (severity measure) in Hemochromatosis patients.	Links a promoter SNP in a modifier gene (NRF2) to clinical/anemia severity measures (MCV) in a related hemoglobinopathy patient group (HFE-Hemochromatosis) that shares pathophysiology (ineffective erythropoiesis/IOL)

				with β-thalassemia.
38293057	Structural Insights into the DNA-Binding Mechanism of BCL11A: The Integral Role of ZnF6.	Promoter mutations (γ-globin gene promoter mutations).	Increased HbF in adults (HPFH phenotype).	Directly mentions that rare γ-globin promoter mutations (non-coding variants) naturally perturb BCL11A binding, leading to increased HbF and the Hereditary Persistence of Fetal Hemoglobin (HPFH) phenotype, which ameliorates β-thalassemia/SCD severity.
38674403	Genetic Modifiers of Sickle Cell Anemia Phenotype in a Cohort of Angolan Children.	Intronic SNPs (Two SNPs in the intronic region of BCL11A on 2q16.1).	Decreasing HbF levels and Vaso-Occlusive Crises (VOC) (key severity measures).	Directly links intronic SNPs in the major modifier gene BCL11A to the major clinical severity outcome, VOC, and the primary biomarker, HbF, in a patient cohort.
40089598	In vivo deletion of a GWAS-identified Myb distal enhancer acts on Myb expression, globin switching, and clinical erythroid parameters in β-thalassemia.	Enhancer deletion (Myb distal enhancer, -84kb enhancer in human / -81kb in mouse).	Globin switching and clinical erythroid parameters in β-thalassemia (Severity model).	Directly establishes the in vivo function of a GWAS-identified non-coding enhancer in regulating a modifier gene (MYB), confirming its role in β-thalassemia severity (phenotype). This provides strong functional validation for natural enhancer variants.
40159794	Unusual Causes of β Thalassemia Trait: Discovery of another Three Novel SUPT5H Variants.	Intronic variant (c.307+1G>A in SUPT5H).	β thalassemia trait phenotype (hypochromic microcytic indices, increased HbA2 without globin gene mutation).	Directly links a novel intronic variant that alters splicing in the non-globin gene SUPT5H to the β-thalassemia phenotype/severity, which is outside the globin cluster.
20602015	Promoter region sequence differences	γ-globin gene Promoter SNPs (HBG2: -396_-	HbF levels.	Direct link between cis-acting promoter

	in the A and G γ globin genes of Brazilian sickle cell anemia patients.	391 del, -369 SNP; HBG1: -271 SNP).		variants (SNPs and a deletion) and the primary severity modifier (HbF) in SCD.
20808897	Disease-associated mutations that alter the RNA structural ensemble.	C33G SNP in the 5′ UTR of HBB	β-Thalassemia disease phenotype.	Identifies SNPs in UTRs that alter mRNA structure, suggesting a mechanism for phenotypic outcome in β-Thalassemia.
21264913	Severe sickle cell anemia is associated with increased plasma levels of TNF−R1 and VCAM−1.	SNPs (GWAS-identified) in VCAM1 (rs1041163) and ARFGEF2 (rs2273102).	SCA severity (mild vs. severe). VCAM1 (rs1041163) significantly associated with SCA severity (Bayes Factor = 3.5). ARFGEF2 (rs2273102)involved in endothelial release of TNF-R1 into circulation (Bayes Factor = 70	GWAS association linking SNPs in non-globin genes to the overall clinical severity of SCD.
26372199	Hereditary Persistence of Fetal Hemoglobin Caused by Single Nucleotide Promoter Mutations in Sickle Cell Trait and Hb SC Disease.	γ-globin gene Promoter Point Mutation.	High HbF levels (e.g., 38.0%).	Direct evidence of a naturally occurring γ-globin promoter mutation leading to HPFH and high HbF, a major ameliorating factor for SCD severity.
26977272	Impact of Mannose-Binding Protein Gene Polymorphisms in Omani Sickle Cell Disease Patients.	MBL2 Promoter SNPs and Exonic Haplotype.	VOC episodes (Vaso-occlusive crises).	Links non-globin gene promoter variants to a core clinical severity measure (VOCs) in SCD.
32447424	Functional polymorphisms of BCL11A and HBS1L−MYB genes affect both HbF level and clinical outcomes in a cohort of children with sickle cell anemia.	Noncoding SNPs independently associated with HbF levels: rs4671393 in BCL11A, rs9399137 in HMIP-2A, and rs4895441 in HMIP-2B	HbF level and clinical outcomes (severity).	Comprehensive association study directly linking established non-coding genetic modifier SNPs to HbF and overall clinical severity in SCD.

15710570	Association of UGT1A1 polymorphism with prevalence and age at onset of cholelithiasis in sickle cell anemia.	UGT1A1 promoter polymorphism ((TA)n repeats)	Major genetic risk factor modifying the frequency and age-at-onset of cholelithiasis (a major complication/severity measure) in SCA patients.	Non-globin non-coding variant modifying the complication-related severity of SCD.
15813858	Co-inheritance of Hb Sun Prairie mutation with a point mutation at 5'-UTR in the eastern Indian population.	5'-UTR point mutation (C→T)	Depression of translation due to conserved base in the 5'-UTR might explain the clinical severity	Direct link between a non-coding 5′−UTR mutation and clinical severity in α-globinopathy.
16044458	Nucleotide -88 (C→T) promoter mutation is a common β-thalassemia mutation in India	Promoter mutation (-88 C→T) and Polymorphism (XmnI Gγ)	Homozygotes are clinically mild with high Hb F (38.1-68.6%). Milder compound heterozygote phenotype associated with XmnI Gγ polymorphism.	Confirms the ameliorating role of a β-globin promoter mutation and the XmnI SNP on β-thalassemia severity.
16628735	UGT1A1 polymorphism outweighs the modest effect of deletional (-3.7 kb) α-thalassemia on cholelithogenesis in SCA.	UGT1A1 promoter polymorphism coinherited wiith α-Globin Gene Deletion (-3.7 kb)	α-thalassemia is associated with modest reduction in hemolysis (SCD severity measure).	Directly links the non-coding α-thalassemia deletion (modifier) to a reduction in SCD severity (hemolysis).
16704446	α-haemoglobin stabilising protein is a quantitative trait gene that modifies the phenotype of β-thalassaemia.	Promoter homopolymer variant (Tn) in the AHSP gene	Alters AHSP expression, a "relevant contributory factor in the haematological phenotype" of β-thalassaemia.	Non-globin non-coding variant modifying β-thalassemia severity (phenotype). Addresses "missing heritability".
19050890	The Hellenic type of nondeletional hereditary persistence of fetal hemoglobin results from a novel mutation (g.−109G→T) in the HBG2 gene promoter.	Promoter mutation HBG2:g.-109G>T	Results in elevated Hb F in adults (a measure that ameliorates β-thalassemia/SCD severity).	Direct link between a γ-globin promoter mutation and the severity-ameliorating factor HbF.

Supplementary Data 1: List of articles screened in the study. [1–527]

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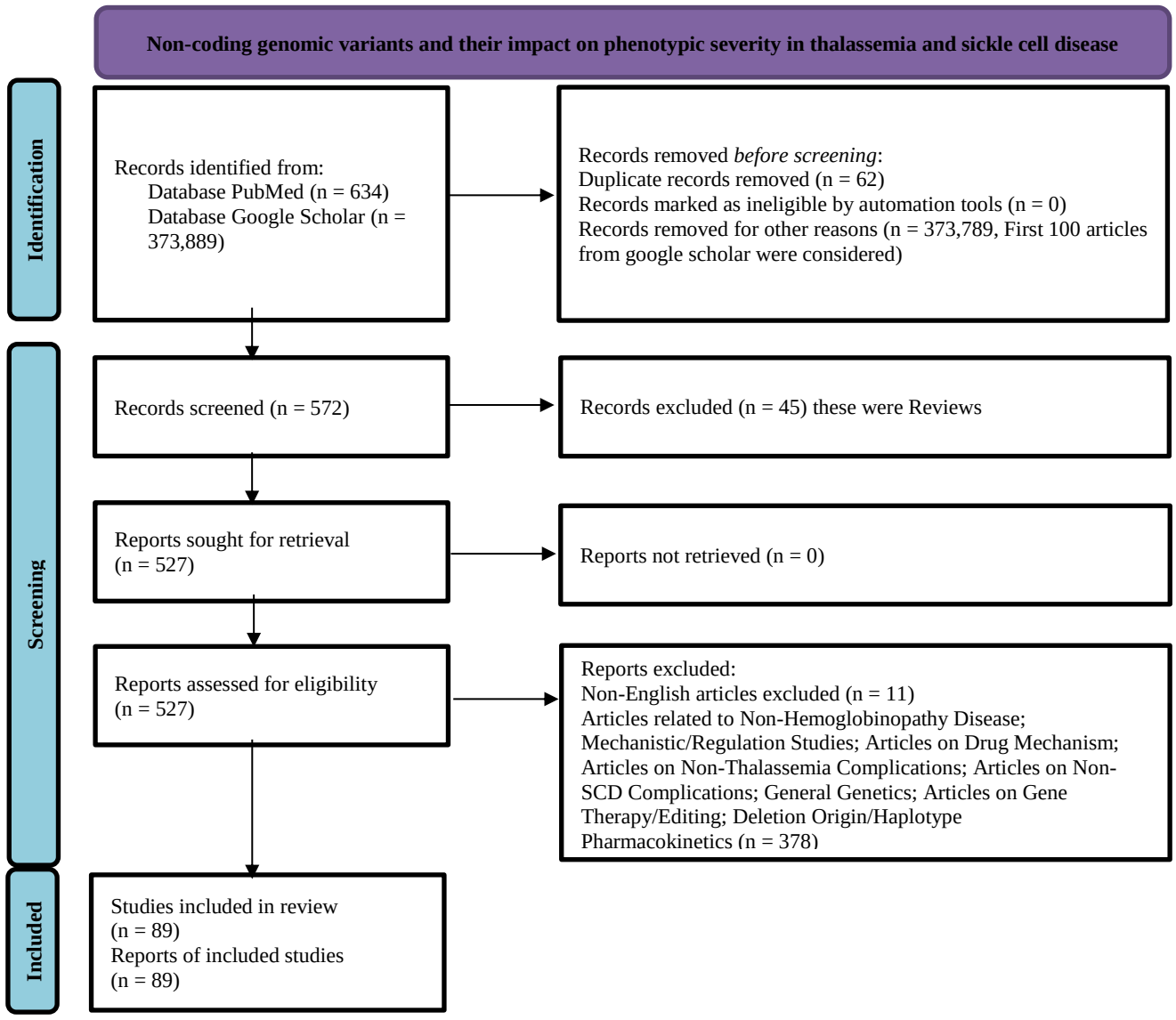
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Supplementary Figure S1: PRISMA 2020 flow diagram for studies on non-coding genomic variants in thalassemia and SCD.



Supplementary Data S2: PRISMA 2020 Checklist and PRISMA 2020 for Abstracts Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Yes
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Yes
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Yes
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Yes
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Yes
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Confirmed by both investigators. No automation tools used
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Yes
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Limitation added
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Limitation added
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Yes
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Limitation added
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Yes Included in Table S1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Limitation added
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Limitation

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			added
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Limitation added
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Yes Included in Table S1
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Yes
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Yes
Study characteristics	17	Cite each included study and present its characteristics.	Yes
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Limitation added
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Limitation added
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Limitation added
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Limitation added
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Yes
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Yes
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Limitation added
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Limitation added
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Yes
	23b	Discuss any limitations of the evidence included in the review.	Yes
	23c	Discuss any limitations of the review processes used.	Yes
	23d	Discuss implications of the results for practice, policy, and future research.	Yes
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Yes
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Yes

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Yes
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Yes
Competing interests	26	Declare any competing interests of review authors.	Yes
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Limitation added
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/