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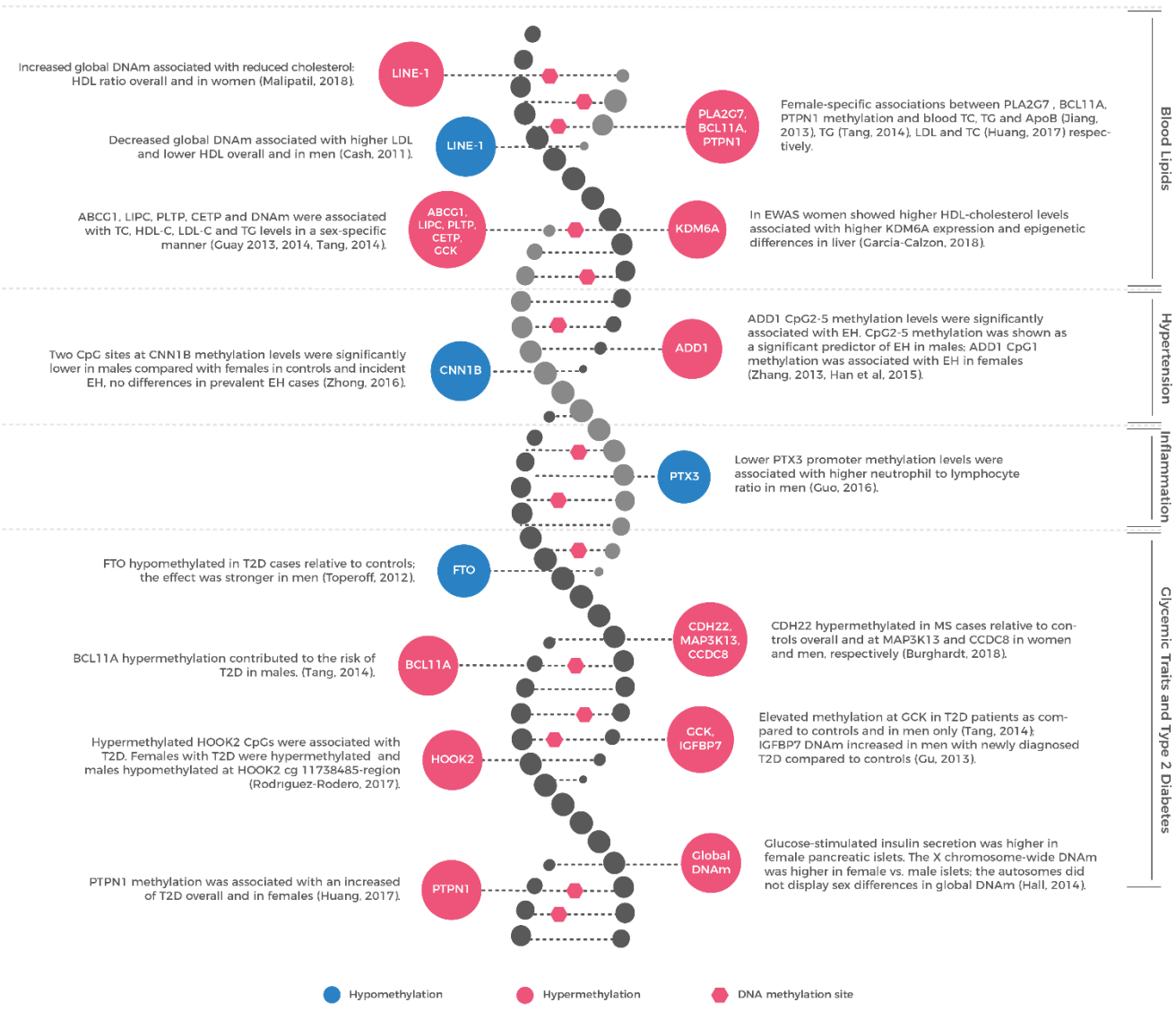
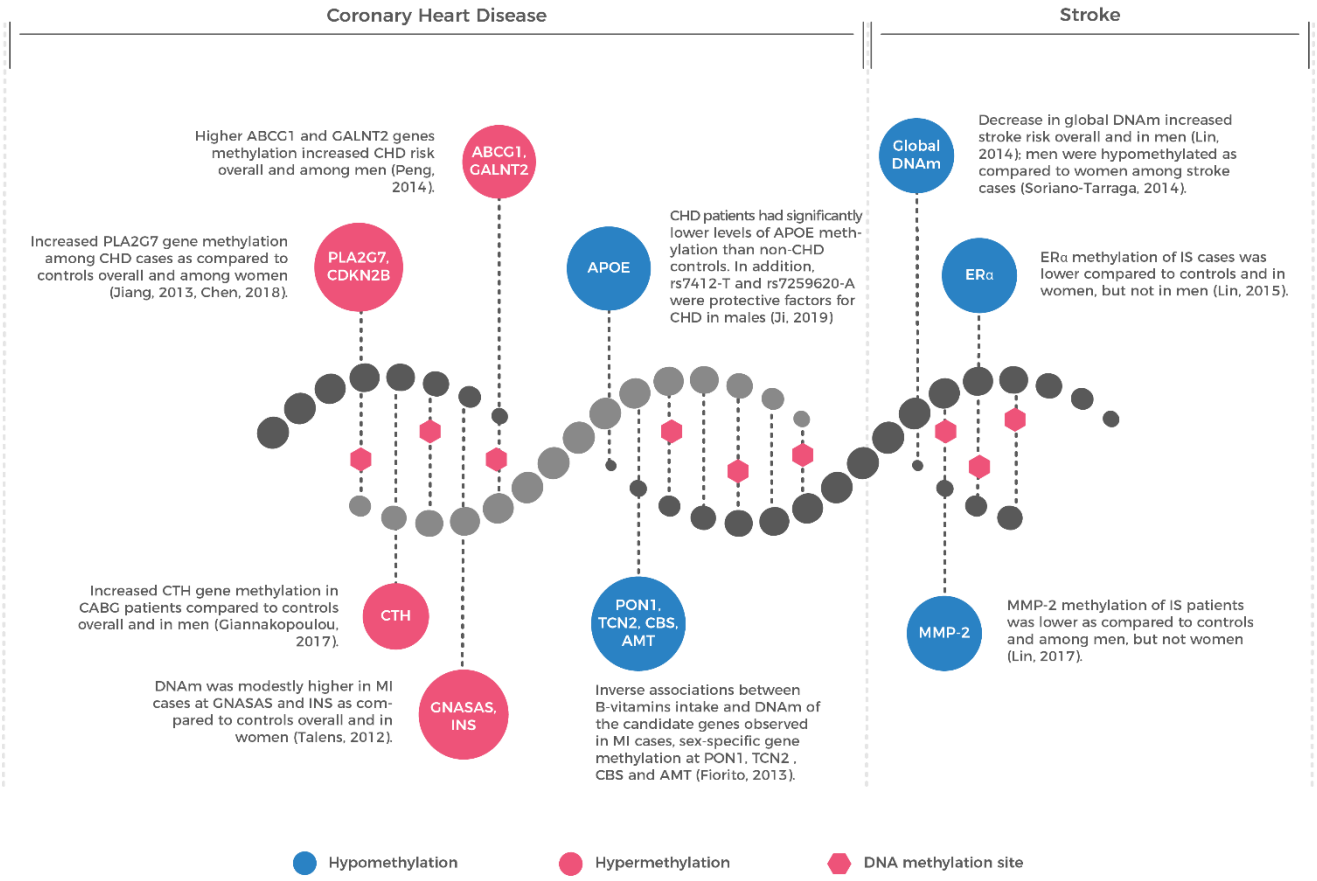
Supplementary material

Supplemental figure 1. Summary of the sex-specific findings on DNAm and lipids, hypertension, inflammation, glycemic traits and T2D



This figure is a graphic illustration of the genes found to be differentially methylated in outcomes such as lipids, hypertension, inflammation, glycemic traits and T2D. The position of the genes is random and is shown for descriptive purposes only and it doesn't represent their real position in the genome. Functional annotation of genes with sex-specific DNA methylation patters can be found in Supplemental table 2.

Supplemental figure 2. Summary of the sex-specific findings on DNAm and coronary heart disease and stroke



This figure is a graphic illustration of the genes found to be differentially methylated in men and women in CHD and stroke. The position of the genes is random and only for descriptive purposes and it doesn't represent their real position in the genome. Functional annotation of genes with sex-specific DNA methylation patters can be found in Supplemental table 3.

Supplemental table 1. Search strategy used in the current systematic review

Blood Lipids
Embase.com (epigenetics/exp OR 'DNA methylation'/exp OR 'histone modification'/exp OR 's adenosylmethionine'/exp OR 'CpG island'/exp OR (((histone* OR dna OR 'long interspersed') NEAR/3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR 's adenosylmethionine' OR cpg OR epigenetic* OR epigenomic*):ab,ti) AND ('lipid blood level'/exp OR (((lipid* OR cholester* OR triacylglycerol* OR triglyceride* OR HDL* OR LDL* OR VLDL* OR VHDL*) NEAR/6 (level* OR blood OR serum OR plasma* OR concentration*)) OR hypercholesterol*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) Medline ovid (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR long interspersed) ADJ3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR s adenosylmethionine OR cpg OR epigenetic*).ab,ti.) AND (exp lipids/bl OR (((lipid* OR cholester* OR triacylglycerol* OR triglyceride* OR HDL* OR LDL* OR VLDL* OR VHDL*) ADJ6 (level* OR blood OR serum OR plasma* OR concentration*)) OR hypercholesterol*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. Cochrane ((((histone* OR dna OR 'long interspersed') NEAR/3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR 's adenosylmethionine' OR cpg OR epigenetic* OR epigenomic*):ab,ti) AND ((((lipid* OR cholester* OR triacylglycerol* OR triglyceride* OR HDL* OR LDL* OR VLDL* OR VHDL*) NEAR/6 (level* OR blood OR serum OR plasma* OR concentration*)) OR hypercholesterol*):ab,ti) Web-of-science TS=(((((histone* OR dna OR "long interspersed") NEAR/2 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR "s adenosylmethionine" OR cpg OR epigenetic* OR epigenomic*)) AND ((((lipid* OR cholester* OR triacylglycerol* OR triglyceride* OR HDL* OR LDL* OR VLDL* OR VHDL*) NEAR/5 (level* OR blood OR serum OR plasma* OR concentration*)) OR hypercholesterol*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine) NOT human*)) AND dt=(article) Google scholar "histone|dna methylation|modification"|epigenetics "lipid|cholesterol|triacylglycerol|triglyceride level|levels|blood|serum|plasma|concentration"|"blood|plasma lipids|cholesterol"|hypercholesterolemia|hypercholesterolaemia
Blood pressure
embase.com (epigenetics/exp OR 'DNA methylation'/exp OR 'histone modification'/exp OR 's adenosylmethionine'/exp OR 'CpG island'/exp OR (((histone* OR dna OR 'long interspersed') NEAR/3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR 's adenosylmethionine' OR cpg OR epigenetic* OR epigenomic*):ab,ti) AND ('abnormal blood pressure'/exp OR 'blood pressure'/exp OR (hypertensi* OR hypotensi* OR 'blood pressure*'):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) Medline (Ovid) (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR long interspersed) ADJ3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR s adenosylmethionine OR cpg OR epigenetic* OR epigenomic*).ab,ti.) AND (exp Hypertension/ OR exp Hypotension/ OR exp blood pressure/ OR (hypertensi* OR hypotensi* OR blood pressure*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. Cochrane ((((histone* OR dna OR 'long interspersed') NEAR/3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR 's adenosylmethionine' OR cpg OR epigenetic* OR epigenomic*):ab,ti) AND ((hypertensi* OR hypotensi* OR 'blood pressure*'):ab,ti) Web-of-science TS=(((((histone* OR dna OR "long interspersed") NEAR/2 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR "s adenosylmethionine" OR cpg OR epigenetic* OR epigenomic*)) AND ((hypertensi* OR hypotensi* OR "blood pressure*")) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline) NOT (human* OR patient* OR man OR men OR woman OR women))) AND DT=(Article) Google scholar "histone|dna methylation|modification"|epigenetics hypertension|hypotension|"blood pressure"
Inflammation
Embase.com (epigenetics/exp OR 'DNA methylation'/exp OR 'histone modification'/exp OR 's adenosylmethionine'/exp OR 'CpG island'/exp OR (((histone* OR dna OR 'long interspersed') NEAR/3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR 's adenosylmethionine' OR cpg OR epigenetic* OR epigenomic*):ab,ti) AND ((inflammation/de AND (marker/de OR 'C reactive protein'/exp OR cytokine/de OR fibrinolysis/exp OR 'tumor necrosis factor alpha'/exp)) OR 'chronic inflammation'/exp OR ((inflammat* NEAR/3 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR 'c reactive' OR cytokine* OR fibrinolys* OR fibrinogenlys* OR 'tumor necrosis factor' OR tnf)):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) **Medline ovid** (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR "long interspersed") ADJ3 (acetylat* OR demethylat* OR methylat* OR phosphorylat* OR ubiquitinat* OR modif*)) OR "s adenosylmethionine" OR cpg OR epigenetic* OR epigenomic*).ab,ti.) AND ((inflammation/ AND (exp Biological Markers/ OR C-Reactive Protein/ OR cytokine/ OR fibrinolysis/ OR Tumor Necrosis Factor-alpha/)) OR ((inflammat* ADJ3 (chronic* OR marker* OR biomarker* OR interleukin* OR crp OR "c reactive" OR cytokine* OR fibrinolys* OR fibrinogenlys* OR "tumor necrosis factor" OR tnf)).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. **Cochrane central**

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Web of science
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Google scholar
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Atherosclerosis

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Google scholar
"histone|dna methylation|modification"|epigenetics atherosclerosis|"intima media thickness"|"coronary*calcification"

Glucose and Type 2 Diabetes

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Web –of-science
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Cardiovascular diseases

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Cochrane
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Web-of-science
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Google scholar
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ischemia|ischaemia|ischemic|ischaemic|failure|infarct|attack|infarction|disease|diseases"|cva|stroke

Supplemental table 2. Functional annotation of genes with sex-specific DNA methylation patters

Gene	Gene Name	Gene Function
ABCG1	ATP Binding Cassette Subfamily G Member 1	nucleotide binding, ATP binding, phospholipid binding, phospholipid transporter activity, cholesterol binding
ADD1	Adducin 1	RNA binding, actin binding, structural molecule activity, protein binding, calmodulin binding
AMT	Aminomethyltransferase;	glycine cleavage system
APOE	Apolipoprotein E	The protein encoded by this gene is a major apoprotein of the chylomicron. It binds to a specific liver and peripheral cell receptor, and is essential for the normal catabolism of triglyceride-rich lipoprotein constituents
BCL11A	B Cell CLL/Lymphoma 11	RNA polymerase II proximal promoter sequence-specific DNA binding, RNA polymerase II transcription factor activity, sequence-specific DNA binding, transcriptional repressor activity, RNA polymerase II proximal promoter sequence-specific DNA binding, nucleic acid binding, DNA binding transcription factor activity
CBS	Cystathionine-beta-synthase	catalyse the conversion of homocysteine to cystathionine
CCDC8	Coiled-Coil Domain Containing 8	protein binding
CETP	Cholesteryl Ester Transfer Protein	lipid transporter activity, phospholipid transporter activity, lipid binding, cholesterol binding, cholesterol transporter activity
CNN1	Calponin 1	protein binding, microtubule binding , identical protein binding, dynein light intermediate chain binding
CTH	Cystathionine c-lyase	**c**atalyses the last step in the trans-sulfuration pathway from methionine to cysteine; mediate sulfhydration of target proteins: GAPDH, PTPN1 and NF-kappa-B subunit RELA
CDKN2B	cyclin dependent kinase inhibitor 2B	Encodes a cyclin-dependent kinase inhibitor, which forms a complex with CDK4 or CDK6, and prevents the activation of the CDK kinases, thus the encoded protein functions as a cell growth regulator that controls cell cycle G1 progression. The expression of this gene was found to be dramatically induced by TGF beta, which suggested its role in the TGF beta induced growth inhibition.
ER-α	Estrogen receptor appha	encodes an oestrogen receptor, a ligand-activated transcription factor important for hormone binding, DNA binding, and activation of transcription
FTO	Alpha-Ketoglutarate Dependent Dioxygenase	ferrous iron binding, oxidoreductase activity, oxidative RNA demethylase activity, oxidative DNA demethylase activity, DNA-N1-methyladenine dioxygenase activity
GCK	Glucokinase	Hexokinases phosphorylate glucose to produce glucose-6-phosphate, the first step in most glucose metabolism pathways. In contrast to other forms of hexokinase, this enzyme is not inhibited by its product glucose-6-phosphate but remains active while glucose is abundant
GALNT2	Polypeptide N-Acetylgalactosaminyltransferase 2	polypeptide N-acetylgalactosaminyltransferase activity, protein binding, transferase activity, transferase activity, transferring glycosyl groups, manganese ion binding
GNASAS	GNAS Antisense RNA	Related to 49 phenotypes in humans, most relevant: Elevated circulating parathyroid hormone level, Hyperphosphatemia, Hyperphosphatemia, Obesity, etc
HOOK2	Hook Microtubule Tethering Protein 2	actin binding, protein binding, calmodulin binding
IFNG	Interferon Gamma	cytokine activity, interferon-gamma receptor binding, protein binding
IGFBP7	Insulin like growth factor binding protein 7	encodes a member of the insulin-like growth factor (IGF)-binding protein (IGFBP) family. IGFBPs bind IGFs with high affinity, and regulate IGF availability in body fluids and tissues and modulate IGF binding to its receptors. This protein binds IGF-I and IGF-II with relatively low affinity, and belongs to a subfamily of low-affinity IGFBPs. It also stimulates prostacyclin production and cell adhesion. Alternatively spliced transcript variants encoding different isoforms have been described for this gene, and one variant has been associated with retinal arterial macroaneurysm
INS	Insulin	protease binding, insulin receptor binding, insulin-like growth factor receptor binding, hormone activity, protein binding
KDM6A	Lysine Demethylase 6A	RNA polymerase II proximal promoter sequence-specific DNA binding, transcriptional activator, RNA polymerase II transcription factor binding, chromatin binding, protein binding, oxidoreductase activity
LIPC	Lipase C, Hepatic Type	phospholipase activity, triglyceride lipase activity, protein binding, heparin binding, lipase activity
MAP3K13	Mitogen-Activated Protein Kinase Kinase Kinase 13	protein kinase activity, protein serine/threonine kinase activity, MAP kinase activity, protein binding, ATP binding
MMP-2	Matrix Metallopeptidase 2; MMP14.	Vasculature remodelling, angiogenesis, tissue repair, tumor invasion, inflammation, and atherosclerotic plaque rupture. As well as degrading extracellular matrix proteins, can also act on several nonmatrix proteins such as big endothelial 1 and beta-type CGRP promoting vasoconstriction. Also cleaves KISS at a Gly- -Leu bond. Appears to have a role in myocardial cell death pathways. Contributes to myocardial oxidative stress by regulating the activity of GSK3beta. Cleaves GSK3beta in vitro. Involved in the formation of the fibrovascular tissues in association with
PLA2G7	Phospholipase A2 Group VII	1-alkyl-2-acetylglycerophosphocholine esterase activity, phospholipid binding, hydrolase activity, hydrolase activity, acting on ester bonds, calcium-independent phospholipase A2 activity
PLTP	Phospholipid Transfer Protein	lipid transporter activity, phospholipid transporter activity, lipid binding, phosphatidylethanolamine binding, phosphatidylcholine transporter activity
PON1	Paraoxonase 1	hydrolyses thiolactones and xenobiotics
PTPN1	Protein tyrosine phosphatase non-receptor type 1	Catalyse the hydrolysis of the phosphate monoesters specifically on tyrosine residues. Members of the PTP family share a highly conserved catalytic motif,

		which is essential for the catalytic activity. PTPs are known to be signalling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. This PTP has been shown to act as a negative regulator of insulin signalling by dephosphorylating the phosphotryosine residues of insulin receptor kinase.
PTX3	Pentraxin 3	complement component C1q binding, (1->3)-beta-D-glucan binding, protein binding, identical protein binding, virion binding
TCN2	Transcobalamin II	binds cobalamin and mediates the transport of cobalamin into cell

Supplemental table 3. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6,42
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5,43
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5,42
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,43
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5,6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6,31

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6,31
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	31
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	31
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22