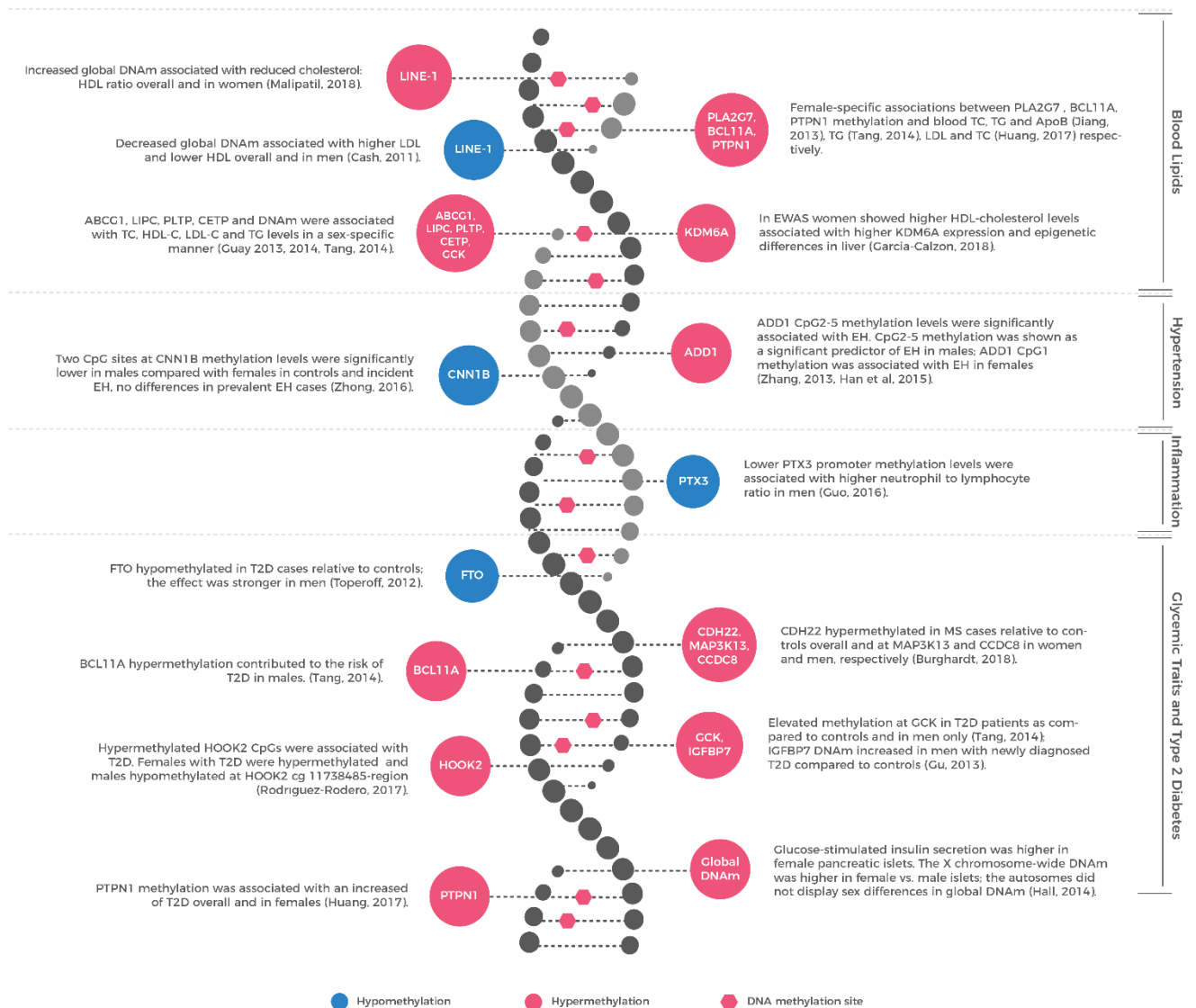


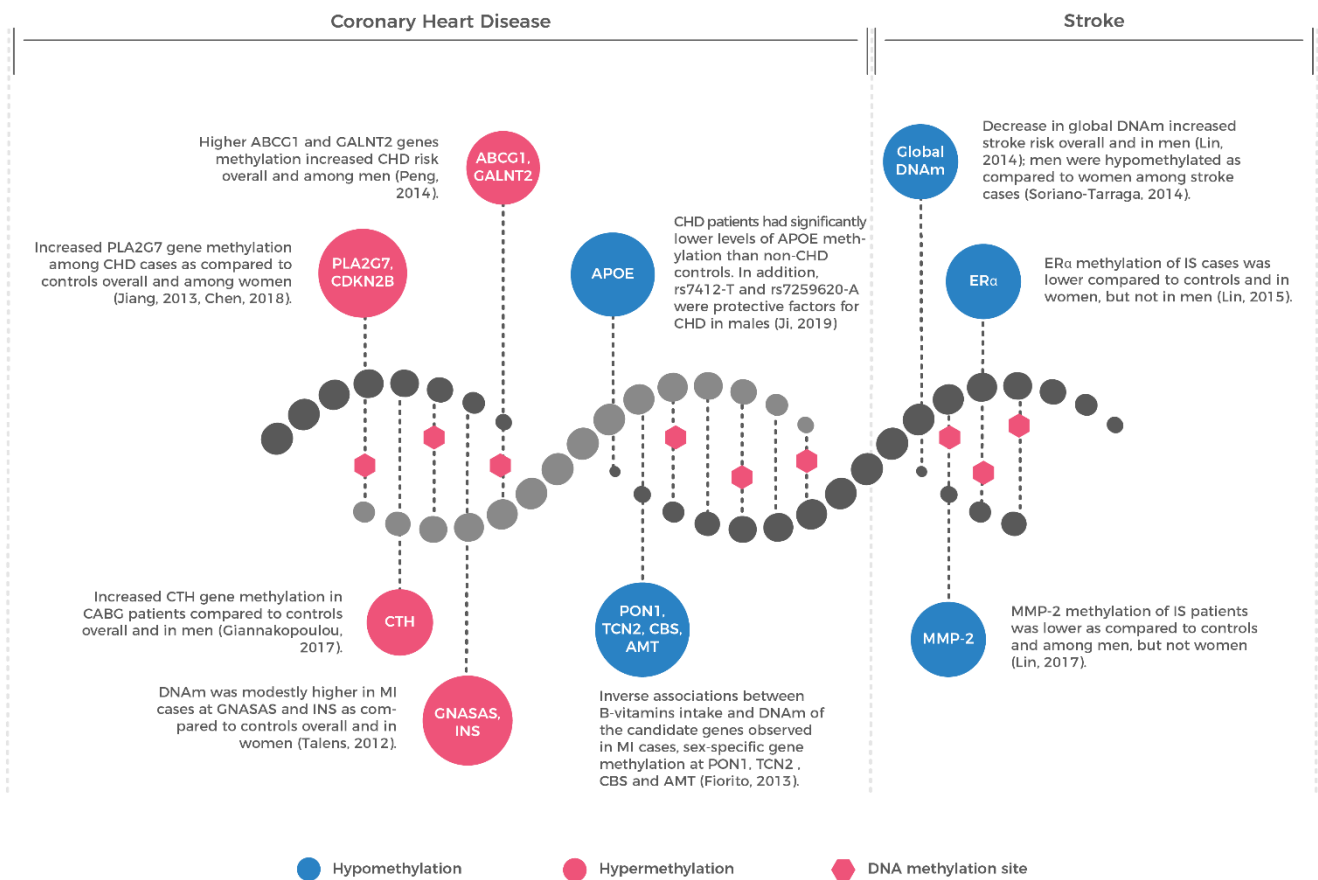
## Supplementary material

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



This figure is a graphic illustration of the genes found to be differentially methylated in outcomes such as lipids, hypertension, inflammation, glycemc 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 patterns can be found in Supplemental table 3.

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

| Blood Lipids  |
|---|
| <p><b>Embase.com</b><br/> (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 (acetyl* 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)</p> <p><b>Medline ovid</b><br/> (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR long interspersed) ADJ3 (acetyl* 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.</p> <p><b>Cochrane</b><br/> ((((histone* OR dna OR 'long interspersed') NEAR/3 (acetyl* 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)</p> <p><b>Web-of-science</b><br/> TS=(((histone* OR dna OR "long interspersed") NEAR/2 (acetyl* 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)</p> <p><b>Google scholar</b><br/> "histone dna methylation modification" epigenetics "lipid cholesterol triacylglycerol triglyceride level levels blood serum plasma concentration"  "blood plasma lipids cholesterol"  hypercholesterolemia hypercholesterolaemia</p> |
| Blood pressure  |
| <p><b>embase.com</b><br/> (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 (acetyl* 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)</p> <p><b>Medline (Ovid)</b><br/> (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR long interspersed) ADJ3 (acetyl* 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.</p> <p><b>Cochrane</b><br/> ((((histone* OR dna OR 'long interspersed') NEAR/3 (acetyl* 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)</p> <p><b>Web-of-science</b><br/> TS=(((histone* OR dna OR "long interspersed") NEAR/2 (acetyl* 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)</p> <p><b>Google scholar</b><br/> "histone dna methylation modification" epigenetics hypertension hypotension "blood pressure"</p>  |
| Inflammation  |
| <p><b>Embase.com</b><br/> (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 (acetyl* 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)</p> <p><b>Medline ovid</b><br/> (Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone* OR dna OR "long interspersed") ADJ3 (acetyl* 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.</p> <p><b>Cochrane central</b></p>   |

((((histone\* OR dna OR 'long interspersed') NEAR/3 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*):ab,ti) AND (((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)) OR atherosclero\* OR ((intima-media OR intimamedia ) NEAR/3 thickness\*) OR (coronar\* NEAR/3 calcif\*)):ab,ti)

**Web of science**

TS=(((histone\* OR dna OR "long interspersed") NEAR/2 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*)) AND (((inflammat\* NEAR/2 (chronic\* OR marker\* OR biomarker\* OR interleukin\* OR crp OR "c reactive" OR cytokine\* OR fibrinolys\* OR fibrinogenlys\* OR "tumor necrosis factor" OR tnf)) OR atherosclero\* OR ((intima-media OR intimamedia ) NEAR/2 thickness\*) OR (coronar\* NEAR/2 calcif\*))) AND DT=(article)

**Google scholar**

"histone|dna methylation|modification"|epigenetics "chronic inflammation"| "inflammation marker|markers"

**Atherosclerosis**

**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 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*):ab,ti) AND (atherosclerosis/de OR 'atherosclerotic plaque'/de OR 'carotid atherosclerosis'/exp OR 'coronary artery atherosclerosis'/de OR 'arterial wall thickness'/de OR 'coronary artery calcification'/de OR (atherosclero\* OR ((intima-media OR intimamedia ) NEAR/3 thickness\*) OR (coronar\* NEAR/3 calcif\*)):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 (acetyl\* OR demethyl\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*).ab,ti.) AND (atherosclerosis/ OR Plaque, Atherosclerotic/ OR Carotid Artery Diseases/ OR "Coronary Artery Disease"/ OR "Carotid Intima-Media Thickness"/ OR (atherosclero\* OR ((intima-media OR intimamedia ) ADJ3 thickness\*) OR (coronar\* ADJ3 calcif\*)):ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt.

**Cochrane central**

((((histone\* OR dna OR 'long interspersed') NEAR/3 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*):ab,ti) AND ((atherosclero\* OR ((intima-media OR intimamedia ) NEAR/3 thickness\*) OR (coronar\* NEAR/3 calcif\*)):ab,ti)

**Web of science**

TS=(((histone\* OR dna OR "long interspersed") NEAR/2 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*)) AND ((atherosclero\* OR ((intima-media OR intimamedia ) NEAR/2 thickness\*) OR (coronar\* NEAR/2 calcif\*))) AND DT=(article)

**Google scholar**

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

**Glucose and Type 2 Diabetes**

**Embase.com**

(epigenetics/exp OR 'genetic epigenesis'/exp OR 'DNA methylation'/exp OR 'histone modification'/exp OR 's adenosylmethionine'/exp OR 'CpG island'/exp OR 'histone deacetylase inhibitor'/exp OR 'histone acetyltransferase'/exp OR (((histone\* OR dna OR 'long interspersed') NEAR/3 (acetyl\* OR demethyl\* OR deacetyla\* OR acetyltransferase\* OR methyl\* OR demethyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenom\* OR neuroepigenetic\* OR neuroepigenomic\* OR (HDAC NEAR/3 inhibitor\*) OR (genet\* NEAR/3 epigenes\*)):ab,ti) AND ('diabetes mellitus'/exp OR 'insulin response'/exp OR 'glucose blood level'/exp OR 'insulin blood level'/exp OR hyperinsulinism/exp OR (((glucose OR sugar OR insulin\*) NEAR/3 (level\* OR blood OR serum OR plasma\* OR concentration\*)) OR glucosaem\* OR glucosem\* OR glycaem\* OR glycem\* OR hyperinsulin\* OR hypoinsulin\* OR insulinaem\* OR insulinem\* OR (insulin NEAR/3 (response OR dependen\* OR resistan\* OR sensitiv\*)):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 "Epigenesis, Genetic"/ OR "DNA methylation"/ OR "Histone Code"/ OR "S-Adenosylmethionine"/ OR "CpG Islands"/ OR exp "Histone Deacetylase Inhibitors"/ OR exp "Histone Acetyltransferases"/ OR (((histone\* OR dna OR "long interspersed") ADJ3 (acetyla\* OR demethyl\* OR deacetyla\* OR acetyltransferase\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenom\* OR (HDAC ADJ3 inhibitor\*) OR (genet\* ADJ3 epigenes\*)):ab,ti.) AND (exp diabetes mellitus/ OR Insulin Resistance/ OR glucose/bl OR insulin/bl OR hyperinsulinism/ OR ((glucose OR sugar OR insulin\*) ADJ3 (level\* OR blood OR serum OR plasma\* OR concentration\*)) OR glucosaem\* OR glucosem\* OR glycaem\* OR glycem\* OR hyperinsulin\* OR hypoinsulin\* OR insulinaem\* OR insulinem\* OR (insulin ADJ3 (response OR dependen\* OR resistan\* OR sensitiv\*)):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 (acetyla\* OR demethyl\* OR deacetyla\* OR acetyltransferase\* OR methyl\* OR demethyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenom\* OR neuroepigenetic\* OR neuroepigenomic\* OR (HDAC NEAR/3 inhibitor\*) OR (genet\* NEAR/3 epigenes\*)):ab,ti) AND (((glucose OR sugar OR insulin\*) NEAR/3 (level\* OR blood OR serum OR plasma\* OR concentration\*)) OR glucosaem\* OR glucosem\* OR glycaem\* OR glycem\* OR hyperinsulin\* OR hypoinsulin\* OR insulinaem\* OR insulinem\* OR (insulin NEAR/3 (response OR dependen\* OR resistan\* OR sensitiv\*)):ab,ti)

**Web -of-science**

TS=(((histone\* OR dna OR "long interspersed") NEAR/2 (acetyla\* OR demethyl\* OR deacetyla\* OR acetyltransferase\* OR methyl\* OR demethyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenom\* OR neuroepigenetic\* OR neuroepigenomic\* OR (HDAC NEAR/2 inhibitor\*) OR (genet\* NEAR/2 epigenes\*)) AND (((glucose OR sugar OR insulin\*) NEAR/2 (level\* OR blood OR serum OR plasma\* OR concentration\*)) OR glucosaem\* OR glucosem\* OR glycaem\* OR glycem\* OR hyperinsulin\* OR hypoinsulin\* OR insulinaem\* OR insulinem\* OR (insulin NEAR/2 (response OR dependen\* OR resistan\* OR sensitiv\*))) AND DT=(article)

**Google scholar**

"histone|dna methylation|modification"|epigenetics diabetes| "glucose|insulin blood"| "insulinemia"| "insulin response|dependence|resistance|sensitivity"

**Cardiovascular diseases**

**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 (acetyl\* OR demethyl\* OR methyl\* OR phosphorylat\* OR ubiquitin\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR

epigenetic\* OR epigenomic\*):ab,ti) AND ('cardiovascular disease'/de OR 'heart failure'/de OR 'congestive heart failure'/de OR 'heart disease'/de OR 'coronary artery disease'/de OR 'ischemic heart disease'/exp OR 'cerebrovascular accident'/de OR 'atherosclerotic cardiovascular disease'/de OR 'brain ischemia'/exp OR ( ((cardiovascular OR coronar\*) NEAR/3 (disease\* OR event\*)) OR cvd OR cvds OR ((ischemi\* OR ischaemi\* OR fail\* OR insufficien\*) NEAR/3 (heart OR cardia\*)) OR (cerebrovascular\* NEAR/3 accident\*) OR cva OR stroke\* OR ((brain OR cerebral) NEAR/3 (ischemi\* OR ischaemi\*))) :ab,ti) NOT (([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim))

#### Medline (OvidSP)

(Epigenomics/ OR DNA methylation/ OR S-Adenosylmethionine/ OR CpG Islands/ OR (((histone\* OR dna OR long interspersed) ADJ3 (acetyl\* OR demethylat\* OR methylat\* OR phosphorylat\* OR ubiquitinat\* OR modif\*)) OR s adenosylmethionine OR cpg OR epigenetic\*).ab,ti.) AND (cardiovascular diseases/ OR exp heart failure/ OR heart diseases/ OR Coronary Artery Disease/ OR Myocardial Ischemia/ OR stroke/ OR Atherosclerosis/ OR exp brain ischemia/ OR (((cardiovascular OR coronar\*) ADJ3 (disease\* OR event\*)) OR cvd OR cvds OR ((ischemi\* OR ischaemi\* OR fail\* OR insufficien\*) ADJ3 (heart OR cardia\*)) OR (cerebrovascular\* ADJ3 accident\*) OR cva OR stroke\* OR ((brain OR cerebral) ADJ3 (ischemi\* OR ischaemi\*))).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 (acetyl\* OR demethylat\* OR methylat\* OR phosphorylat\* OR ubiquitinat\* OR modif\*)) OR 's adenosylmethionine' OR cpg OR epigenetic\* OR epigenomic\*):ab,ti) AND (((cardiovascular OR coronar\*) NEAR/3 (disease\* OR event\*)) OR cvd OR cvds OR ((ischemi\* OR ischaemi\* OR fail\* OR insufficien\*) NEAR/3 (heart OR cardia\*)) OR (cerebrovascular\* NEAR/3 accident\*) OR cva OR stroke\* OR ((brain OR cerebral) NEAR/3 (ischemi\* OR ischaemi\*))) :ab,ti)

#### Web-of-science

TS=(((histone\* OR dna OR "long interspersed") NEAR/3 (acetyl\* OR demethylat\* OR methylat\* OR phosphorylat\* OR ubiquitinat\* OR modif\*)) OR "s adenosylmethionine" OR cpg OR epigenetic\* OR epigenomic\*) AND (((cardiovascular OR coronar\*) NEAR/3 (disease\* OR event\*)) OR cvd OR cvds OR ((ischemi\* OR ischaemi\* OR fail\* OR insufficien\*) NEAR/3 (heart OR cardia\*)) OR (cerebrovascular\* NEAR/3 accident\*) OR cva OR stroke\* OR ((brain OR cerebral) NEAR/3 (ischemi\* OR ischaemi\*)))) NOT ((animal\*) NOT (human\* OR patient\* OR man OR men OR woman OR women))) AND DT=(Article)

#### Google scholar

"histone | dna methylation | modification" | epigenetics | epigenetic | epigenomic  
"heart | cardiac | cardial | myocardial | cardiovascular | cerebrovascular | cerebral | brain  
ischemia | ischaemia | ischemic | ischaemic | failure | infarct | attack | infarction | disease | diseases" | cva | stroke

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

| 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                             | catalyses 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 Metalloproteinase 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 phosphotyrosine residues of insulin receptor kinase. |
| <b>PTX3</b> | Pentraxin 3       | complement component C1q binding, (1->3)-beta-D-glucan binding, protein binding, identical protein binding, virion binding   |
| <b>TCN2</b> | Transcobalamin II | binds cobalamin and mediates the transport of cobalamin into cell  |

**Supplemental table 3.** PRISMA checklist

| Section/topic                      | #  | Checklist item  | Reported on page # |
|------------------------------------|----|---|--------------------|
| <b>TITLE</b>                       |    |   |                    |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | 1                  |
| <b>ABSTRACT</b>                    |    |   |                    |
| 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                  |
| <b>INTRODUCTION</b>                |    |   |                    |
| 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                |
| <b>METHODS</b>                     |    |   |                    |
| 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                 |
| <b>RESULTS</b>                     |    |   |                    |
| 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    |
| <b>DISCUSSION</b>             |    |  |       |
| 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 |
| <b>FUNDING</b>                |    |  |       |
| 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    |