

1 Mendelian randomization studies of biomarkers and type 2 diabetes

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22

23 **Abstract**

24 **CONTEXT:** Many biomarkers are associated with type 2 diabetes (T2D) risk
25 in epidemiological observations. The aim of this study was to identify and summarize current
26 evidence for causal effects of biomarkers on T2D.

27 **DESIGN AND METHODS:** A systematic literature search in PubMed and EMBASE (until
28 April 2015) was done to identify Mendelian randomization studies that examined potential
29 causal effects of biomarkers on T2D. To replicate the findings of identified studies, data from
30 two large-scale genome-wide association studies (GWAS) were used: 1) DIABetes Genetics
31 Replication And Meta-analysis (DIAGRAMv3) for T2D, and 2) the Meta-Analyses of
32 Glucose and Insulin-related traits Consortium (MAGIC) for glycaemic traits. GWAS
33 summary statistics were extracted for the same genetic variants (or proxy of variants) which
34 were used in the original Mendelian randomization studies.

35 **RESULTS:** Ten out of 21 biomarkers (from 28 studies) have been reported to be causally
36 associated with T2D in Mendelian randomization. Most biomarkers were investigated in a
37 single cohort study or population. Of the 10 biomarkers that were identified, nominally
38 significant associations with T2D or glycaemic traits were reached for those genetic variants
39 related to bilirubin, pro-B-type natriuretic peptide, Delta-6 desaturase and dimethylglycine
40 based on the summary data from DIAGRAMv3 or MAGIC.

41 **CONCLUSIONS:** Several Mendelian randomization studies investigated the nature of
42 associations of biomarkers with T2D. However, there were only few biomarkers that may
43 have causal effects on T2D. Further research is needed to broadly evaluate the causal effects
44 of multiple biomarkers on T2D and glycaemic traits using data from large-scale cohorts or
45 GWAS including many different genetic variants.

46

47 **Keywords:** Biomarkers, Epidemiology, Mendelian randomization, Genome-wide association
48 study, Type 2 diabetes
49

50 **Abbreviations:** BNP= B-type natriuretic peptide; D6D= Delta-6-desaturase; DIAGRAM=
51 DIAbetes Genetics Replication And Meta-analysis; GWAS=Genome-wide association
52 studies; MAGIC= Meta-Analyses of Glucose and Insulin-related traits Consortium; MIF=
53 macrophage migration inhibitory factor; SHBG= sex hormone binding protein

54 **Introduction**

55 Over the past decade, much interest in studying biological markers (biomarkers) for type 2
56 diabetes (T2D) has been attracted. This happened because multiple pathobiological processes
57 may contribute to the disease progression, which provides an opportunity to introduce
58 preventive and therapeutic interventions for T2D¹. In clinical practice, such biomarkers (e.g.,
59 glucose and glycated haemoglobin tests) are widely used for diagnosis of diabetes or for
60 monitoring of therapeutic intervention^{2,3}. Targeted intervention at biomarker level would be
61 useful where there is evidence for a causal relationship between an exposure (like a
62 biomarker) and T2D⁴.

63 Traditional epidemiological studies lack sufficient information to fill the evidence gap due
64 to unmeasured confounding or reverse causality⁴⁻⁷. It has been successfully shown that a
65 complementary analysis of genetic data, termed “Mendelian randomization”, has additive
66 value to infer a causal association⁴⁻⁸. The main assumption for Mendelian randomization is
67 that the genetic variants do not change over time and are inherited randomly (based on
68 Mendel’s laws). In other words, the genetic variants as proxy measures for exposures (e.g.,
69 biomarkers) are essentially considered free from confounding and reverse causation.
70 Therefore, the analysis of integrated observational-genetic data is considered similar to that of
71 the randomized trials^{9,10}. In Mendelian randomization, if there is a causal association between
72 a biomarker and T2D, the genetic variant(s) influencing biomarker and the outcome of
73 interest should be associated^{5,6,8}. In the current study, evidence for causal associations
74 between biomarkers and the risk of T2D was updated via a systematic literature search to
75 identify Mendelian randomization studies. Next, summary data from two largest genome-
76 wide association studies (GWAS) for T2D or glycaemic traits^{10,11} were used to examine the
77 effect estimates for each genetic variants compared with that of the identified studies.

78

79 **Methods**

80 *Search strategy for candidate biomarkers*

81 PubMed and EMBASE were searched to identify Mendelian randomization studies
82 examining the associations between biomarkers and T2D until April 2015. The overview of
83 this systematic literature search was conducted in accordance with the Preferred Reporting
84 Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, when applicable¹². A
85 manual search was also done for the references of included articles to identify other relevant
86 studies. Because a review of published original studies was performed, the Declaration of
87 Helsinki items related to “approval of medical ethics committee” and “permission
88 acquisition” are not applicable to the current study.

89

90 *Selection criteria*

91 Studies were included if: 1) they formally quantified a causal association between one or
92 more biomarkers (as main exposures) and T2D (as the main outcome); 2) used data on
93 biomarker-associated genetic variants; 3) and classified/defined the exposure as a biomarker
94 that has been objectively measured in serum, plasma or urine. The following MeSH key
95 words or related terms were used: “Diabetes mellitus, Type 2□[Mesh]”, Type 2
96 Diabetes[tiab], Diabetes[ti]; and “Mendelian randomization”, “Mendelian randomisation”,
97 “instrumental variable”, “genetic risk score” or “causal association”.

98

99 *Data extraction and quality assessment*

100 A primary plan was made to extract necessary data from the full text of the original studies
101 or to contact the corresponding author(s) when appropriate. Figure 1 depicts the work-flow of
102 the literature search. T2D was determined as the main outcome if one or more of the
103 following conditions were fulfilled: 1) a physician diagnosed T2D as indicated by self-report

104 or in primary-care database; 2) fasting plasma glucose ≥ 7.0 mmol/l, a random sample plasma
105 glucose ≥ 11.1 mmol/l; or 3) initiation of glucose-lowering medication as retrieved from a
106 pharmacy registry or hospital records¹¹.

107

108 *Statistical analysis*

109 All genetic variants that affect identified biomarkers were obtained from the original
110 Mendelian randomization studies. To replicate the nature of relationship between each
111 biomarker and the outcome (i.e., T2D or glycaemic traits), a genetic approach using outcome-
112 association data for the biomarker-related genetic variants was applied^{5, 6, 8}. In brief, to
113 determine whether the same genetic variants (or a suitable proxy variant) were associated with
114 T2D (or glycaemic traits), the corresponding summary association statistics from GWAS for
115 T2D (DIABetes Genetics Replication And Meta-analysis [DIAGRAMv3])¹³ and glycaemic
116 traits (Meta-Analyses of Glucose and Insulin-related traits Consortium [MAGIC])¹⁴ were
117 extracted. DIAGRAMv3 is a meta-analysis of multiple GWAS with a total number of 12,171
118 diabetes cases and 56,862 controls of European descent¹³. Previously, details regarding the
119 use of GWAS data for Mendelian randomization were described^{5, 6, 10, 11}. These selected
120 single-test association analyses in the GWAS data are equivalent to that of individual-level
121 data analysis^{5, 6, 11}.

122 Extracted data were tabulated on Excel spreadsheets. All statistical analyses were
123 conducted using Excel or Stata/SE version 13.1 for Windows (<http://cran.r-project.org/>). A
124 two-sided *P* value < 0.05 was considered nominally significant.

125

126 **Results**

127 *Literature search and study characteristics*

128 After scanning 812 titles and selected abstracts, 33 articles were selected for full text review
129 ^{11, 15-46}. The literature search process is shown in Figure 1. Five studies were excluded as they
130 did not measure a specific biomarker (n=1) or investigated a measure of insulin resistance as
131 the main exposure (n=4)^{15, 38-40, 43}. The characteristics of the 28 studies are summarized in
132 Table 1. The studies were performed in different populations; most were cohort studies
133 included middle-aged adults in the US or Europe and were published between 2008-2015.
134 Four studies were conducted only in Asian populations including Chinese or Taiwanese. In 12
135 studies, data from multiple GWAS were combined to examine the associations between
136 genotypes and T2D. Six of these studies used data from DIAGRAMv2 (n=3)⁴⁷ or
137 DIAGRAMv3 (n=3)¹³, and the other six used at least two cohorts with genome-wide
138 genotyping. DIAGRAMv2 was a meta-analysis of eight GWAS comprising 8,130 individuals
139 with T2D and 38,987 controls of European descent⁴⁷. All Mendelian randomization studies
140 investigated only one biomarker as an exposure in relation to T2D. Some studies also
141 examined the causal associations of a single biomarker with several other outcomes such as
142 cardiovascular disease^{18, 24}, rheumatoid arthritis¹⁸ or osteoporosis²⁴. In the final sample,
143 studies included up to 28144/76344 T2D cases/controls or total participants.

144

145 *Biomarkers and Mendelian randomization*

146 From 28 studies, data were retrieved on causal associations of biomarkers with T2D. In
147 these studies, 21 unique biomarkers that were investigated at least once (16 biomarkers),
148 twice (three biomarkers) and three times (two biomarkers) were identified (Table 1). Nineteen
149 biomarkers were completely investigated in independent studies. However, the two
150 biomarkers with three Mendelian randomization studies were investigated in combined

151 studies where the same sample , e.g. DIAGRAMv2 for adiponectin^{19, 43}, or a part of whole
152 cohort, e.g. EPIC-Potsdam for vitamin D^{17, 45}, were used to make total cases/controls. Eleven
153 studies used one genetic variant as a single instrumental variable in Mendelian randomization.
154 Eight studies used at least two independent genetic variants in the same locus as instrumental
155 variables. The rest of nine studies used multiple genetic variants in different loci or created a
156 multi-locus genetic risk score for each biomarker.

157 In main or sensitivity analyses, four studies^{11, 26, 44, 45} examined causal associations of
158 bilirubin, Lipoprotein(a), vitamin D, interleukin 1 receptor antagonist (with corresponding
159 biomarker-associated genotypes) with type 2 diabetes using the DIAGRAMv3 summary data.
160 In Table 1, the value for each causal estimate can be interpreted as odds ratio (OR), hazard
161 ratio (HR) or log OR (β coefficient) for diabetes per one unit change in genetically
162 determined biomarkers or biomarker-associated genotypes. Evidence of causal association
163 was reported for adiponectin, bilirubin, N-terminal pro B-type natriuretic peptide (NT
164 proBNP), Delta-6 desaturase (D6D), dimethylglycine, ferritin (Transmembrane protease
165 serine 6), homocysteine, macrophage migration inhibitory factor (MIF), sex hormone binding
166 protein (SHBG) and resistin (Table 1). For adiponectin, causal estimates were calculated as an
167 OR of 0.86 per allele³⁵ or a β coefficient of 0.3 for adiponectin multi-locus genotypic risk
168 score¹⁹. Causal estimate for bilirubin was reported as an OR of 0.58 per 1-SD genetically
169 increased log-transformed bilirubin¹¹. For NT proBNP³⁷, D6D³⁰, dimethylglycine³², ferritin²²,
170 MIF²³ and resistin¹⁸, the expected ORs for T2D were 0.96, 0.64, 1.1, 0.79, 1.74 and 1.38 per
171 each copy of risk alleles or genotypes, respectively. For homocysteine, causal estimates were
172 reported as an OR of 1.29 per 5 μ mol/L genetically increased homocysteine²⁴, or ORs of 1.93
173 and 1.52 for CC and CC/TT genotypes²⁵, respectively. For SHBG, the expected ORs for T2D
174 were 0.92 per each copy of the SHBG lowering allele³⁴ or 0.3 per 1-SD genetically increased
175 natural log-transformed in SHBG²¹.

176 Using the GWAS data from DIAGRAMv3 or MAGIC^{13, 14}, associations of the genetic
177 variants influencing these biomarkers with T2D and glycaemic traits were tested. A nominally
178 significance ($P < 0.05$) was reached for the genetic variants that affect bilirubin ($P = 0.03$ for
179 glucose and HOMA-IR), NT proBNP ($P = 0.03$ for T2D), D6D activity ($P = 0.003$ for T2D;
180 $P = 2.7 \times 10^{-8}$ for glucose) and dimethylglycine ($P = 0.004$ for glucose) in relation to T2D or
181 glycaemic traits (Table 2). For adiponectin, a nominally significant association with T2D or
182 glycaemic traits was observed for seven out of 19 genetic variants. All these seven variants,
183 except rs12637534, were non-*ADIPOQ* adiponectin genetic variants. In line with previous
184 Mendelian randomization studies, the overall effect of non-*ADIPOQ* variants on T2D or
185 glycaemic traits together with null association of *ADIPOQ* variants is compatible with
186 pleiotropic effects of adiponectin on T2D⁴².

187

188 **Discussion**

189 This literature search of Mendelian randomization studies shows here that 10 out of 21
190 identified biomarkers were reported to be causally associated with T2D. In particular, the
191 presence of potential causal associations (defined as nominally significant) between the
192 biomarker-related variants and T2D and/or glycaemic traits can be confirmed for four
193 biomarkers using the publically-available GWAS data. The inconsistency between the
194 identified studies and the summary data from DIAGRAMv3 or MAGIC can be to some extent
195 explained by different design and populations applying across studies, the possibility of false
196 positive associations, the heterogeneity in T2D, the use of varied sources to ascertain T2D
197 cases, and differences in data quality control and pre-analysis preparations^{6, 11}.

198 Taken together, these findings support that the oxidative stress system (bilirubin or
199 metabolites of bilirubin), the BNP hormone system, D6D activity, and dimethylglycine may
200 contribute to the development of diabetes or insulin resistance through secondary effects (i.e.,
201 pleiotropy) or direct mechanisms^{11, 37, 42}. Bilirubin that is the major end-product of heme
202 catabolism has antioxidant properties and may compensate the oxidative stress^{11, 48}. Oxidative
203 stress has been shown as an important factor in the pathophysiology of diabetes¹¹. At the
204 cellular level, bilirubin can be oxidized to its precursor, biliverdin, to detoxify excess of
205 oxidants. Biliverdin is rapidly recycled to bilirubin via the action of biliverdin reductase,
206 generating a physiologic cytoprotective cycle in several tissues⁴⁹. The underlying mechanism
207 of a protective role of BNP in the aetiology of T2D is unknown in humans³⁷. In mice, over-
208 expressed BNP signalling cascade can protect against diet-induced insulin resistance and
209 obesity through promoting muscle mitochondrial biogenesis and fat oxidation^{37, 50}. The
210 biological mechanisms of the relationship between D6D activity T2D are not well
211 understood³⁰. Although data of human experimental studies are scarce, observational studies
212 have shown that D6D activity or lifestyle-induced changes in D6D activity was associated

213 with insulin resistance^{30, 51, 52}. Since D6D catalyses the synthesis of fatty acids, one can
214 speculate that the link between D6D activity and T2D is likely to be mediated by changes in
215 fatty acid composition, which in turn may affect insulin signalling and receptor binding
216 affinities³⁰. Dimethylglycine is metabolized to glycine by dimethylglycine dehydrogenase
217 (DMGDH) in mammals³². Accordingly, a recent GWAS identified that the *DMGDH* genetic
218 variants were strongly associated with blood-based dimethylglycine⁵³. Epidemiological
219 studies have observed an inverse association between the precursor of dimethylglycine –
220 betaine – and metabolic risk factors⁵⁴, but a positive association of elevated glycine with
221 increased insulin sensitivity³². In humans, cardiometabolic effects of inhibition of DMGDH or
222 supplementation of dimethylglycine have not been investigated³². However, experimental
223 animal studies have suggested a protective role of dimethylglycine in glucose metabolism
224 through reduction in DMGDH function^{32, 55, 56}.

225 In the post-omics era, epidemiological studies basically suggest that the levels of a
226 given biomarker differ between patients with T2D (or the individuals at high risk for
227 developing diabetes) and individuals without diabetes^{2, 57}. If the biomarker is not causally
228 related to the disease outcome, the process of developing diabetes may cause the increase or
229 decrease in the levels of biomarker, as one of the T2D consequences, called reverse causality^{4,}
230 ^{26, 37}. Unmeasured confounding or measured confounding factors with errors (for example,
231 physical activity by self-report) is another explanation for the observed associations between
232 most biomarkers and T2D. In this context, the use of genetic data (like in Mendelian
233 randomization) can enhance the likelihood that association between a biomarker and T2D is
234 causal or not, where biomarkers are subject to the evaluation of causal inference^{4, 36, 37}. It
235 remains to be further confirmed for the potential role of biomarkers in the development of
236 T2D and the trajectories of glycaemic traits using longitudinal analysis^{6, 11}. The latter
237 analytical approach can provide insight into potential value of biomarkers which indicate

238 pathobiological signals of metabolic changes in the aetiology of T2D. T2D is influenced by
239 interactions of multiple genes or a gene may have been mapped to multiple biomarkers other
240 than the biomarker of interest^{4, 13, 14}. Thus, an extensive knowledge of gene function,
241 biological processes and that the genome interacts with environmental factors is needed to
242 better understand how genetic variations in the human genome contributes to lifelong risk of
243 T2D^{4, 11, 13, 14, 57}.

244 In this review, most studies only investigated a single biomarker-diabetes association
245 and statistically significant associations are reported more often. Here publication bias should
246 be considered. Other limitations include lack of complementary analyses in the genetic
247 associations for glycaemic traits, and that set of genetic variants or large-scale GWAS for
248 biomarkers were scarce. Similarly, the Mendelian randomization approach using GWAS
249 summary statistics can be extended as a secondary analysis of several datasets that have data
250 on the biomarker-associated variants (or their proxies) for several diseases or traits. This
251 multi-disciplinary research requires that a large group of consortia are contacted to obtain
252 summary association statistics from GWAS consortia for outcomes of interest. Moreover, for
253 the biomarkers linked to T2D, underlying biological mechanisms remain unknown. To
254 uncover the underlying mechanisms, one needs to perform a complementary strand of
255 experimental research. Before that, an *in-silico* functional gene network (pathway) analysis
256 can be used to speculate on the possible biological mechanisms of biomarker-disease
257 associations^{58, 59}. Finally, Mendelian randomization cannot completely control for the
258 possibility of developmental compensation, called canalization, confounding and pleiotropic
259 effects^{5, 6, 8, 11, 37}.

260 In conclusion, this is the first study that updates evidence for causal associations between
261 biomarkers and T2D to date. Several Mendelian randomization studies investigated the nature
262 of associations of biomarkers with T2D. Most biomarkers were investigated in a single cohort

263 study or population. However, there are only few biomarkers that may have causal effects on
264 T2D. Further research is warranted to broadly evaluate the causal effects of multiple
265 biomarkers on T2D and glycaemic traits using data from large-scale cohorts or combined
266 GWAS including many different genetic variants. This genetic approach may advance our
267 understanding of the causes of T2D, and potentially enable us to explore novel targets for the
268 prevention and treatment of diabetes.

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Table 1: Mendelian randomization studies for biomarkers and type 2 diabetes

| Biomarkers | No. of Study | Study | Country/year | Cases/ total or controls | Genetic variant(s)/locus | Causal estimate | Type of associations |
|--------------------|-------------------------|---|---------------------------|--------------------------|--|-----------------|--|
| Adiponectin | 3 ^{19, 35, 42} | DIAGRAMv2, ARIC, FUSION, WTCCC, EPIC-InterAct | US, Europe/2013 | 15960/64731 | rs17300539,rs1736653,rs3774261,rs3821799/ <i>ADIPOQ</i> | Null | |
| | | BHS, CUDAS, FDS | Australia/2013 | 967/2355 | rs12637534, rs16861209, rs17366568/ <i>ADIPOQ</i> | OR, 0.86 | per allele |
| | | DIAGRAMv2 | US/Europe/2012 | -/22044 | rs3001032/ <i>LYPLAL1</i> , rs1108842/ <i>GNL3</i> , rs1597466/ <i>TSC22D2</i> , rs6810075/ <i>ADIPOQ</i> , rs998584/ <i>VEGFA</i> , rs2980879/ <i>TRIB1</i> , rs7955516/ <i>PDE3A</i> , rs601339/ <i>GPR109A</i> , rs7133378/ <i>DNAH10</i> , rs2925979/ <i>CMIP</i> , rs12922394/ <i>CDH13</i> , rs731839/ <i>PEPD</i> | β , -0.30 | average additive effect of adiponectin-raising alleles |
| Beta-carotene | 1 ³³ | WTCCC, DGI, FUSION | US, Europe/2009 | 4549/5579 | rs6564851/ <i>BCMO1</i> | Null | |
| Bilirubin | 1 ¹¹ | PREVEND | Netherlands/ 2015 | 210/3381 | rs6742078/ <i>UGT1A1</i> | OR, 0.58 | 1-sd |
| B-type proBNP | 1 ³⁷ | DIAGRAMv2, Norfolk Diabetes, Cambridgeshire, ADDITION-Ely, French, Swiss 1, Swiss 2, Austrian, MONICA, INCA, UK | US, Europe/2011 | 23382/57898 | rs198389/ <i>NPPB</i> | OR, 0.96 | C allele |
| C-reactive protein | 1 ¹⁶ | Whitehall II | UK/2008 | 354/ 5274 | rs1130864, rs1205, rs3093077/ <i>CRP</i> | Null | |
| Delta-6 desaturase | 1 ³⁰ | EPIC-Potsdam | Germany/2011 | 673/2724 | rs174546/ <i>FADS1</i> | RR, 0.64 | <i>TT</i> genotype |
| Dimethylglycine | 1 ³² | MDC-CC, MDC, MPP | Sweden/2015 | 4201/33898 | rs2431332/ <i>DMGDH</i> | OR, 1.1 | A allele |
| Ferritin/TMPRSS6 | 1 ²² | Beijing | China/2012 | 272/1574 | rs855791, rs4820268/ <i>TMPRSS6</i> | OR, 0.79 | <i>AG</i> haplotype |
| Fetuin-a | 1 ²⁷ | CHS | US/2013 | 259/3093 | rs4917, rs2248690/ <i>AHSG</i> | Null | |
| Homocysteine | 2 ^{24, 25} | Hangzhou | China/2014 | 774/500 | rs1801131/ <i>MTHFR</i> , rs4646356/ <i>PEMT</i> | OR, 1.93, 1.52 | <i>CC, CT+TT</i> |
| | | - | Europe, Asia, Africa/2013 | 4011/ 4303 | rs12134663, rs1801133/ <i>MTHFR</i> | OR, 1.29 | 5 μ mol/L |
| IL-1Ra | 1 ²⁶ | DIAGRAMv3 and EPIC-InterAct | US, Europe/2015 | 18715/61692 | rs6743376, rs1542176/ <i>IL1RN</i> | Null | |

| | | | | | | | |
|---|-----------------------|---|-----------------|-------------|--|----------|----------|
| Leukocytr telomere length | 1 ⁴⁶ | WHI-OS | US/2012 | 1675/2382 | rs34368910/ <i>TRF1</i> , rs4888444/ <i>TRF2</i> , rs4975605/ <i>TERT</i> , rs938886, rs2228041,rs12880583/ <i>TPP1</i> | Null | |
| Lipoprotein(a) | 2 ^{29,44} | Danish general population | Denmark/2014 | 2157/28567 | rs10455872/ <i>LPA</i> | Null | |
| | | DIAGRAMv3,EPIC-Norfolk | US, Europe/2014 | 10088/68346 | rs10455872/ <i>LPA</i> | Null | |
| Macrophage migration inhibitory factor miRNAs | 1 ²³ | MONICA/KORA Augsburg | Germany/2008 | 502/1632 | rs1007888/ <i>MIF</i> | HR, 1.74 | C allele |
| | 1 ⁴¹ | Harbin | China/2015 | 995/967 | rs895819/miR-27a, rs531564/miR-124a, rs2910164/miR-146a | Null | |
| Resistin | 1 ¹⁸ | CVDFACTS | Taiwan/2014 | 230/3400 | rs3745367,rs1423096/ <i>RETN</i> | OR, 1.38 | GG |
| Sex hormone binding globulin | 2 ^{21,34} | WTCCC, Dundee, EFS-Y2D, Danish, DGI, MCC, FUSION 1-2, KORA, Cambridgeshire, ADDITION-Ely, NDCCS, DeCODE, METSIM, DIAGEN | | 27657/58481 | rs1799941/ <i>SHBG</i> | OR, 0.92 | G allele |
| | | WHS | US/2009 | 359/359 | rs6259/ <i>SHBG</i> | OR, 0.3 | 1-sd |
| Triglycerides | 1 ²⁰ | Go-DARTS | UK/2011 | 5637/ 6860 | rs2954029/ <i>TRIB1</i> , rs714052/ <i>MLXIPL</i> , rs7557067/ <i>APOB</i> , rs17216525/ <i>NCAN</i> , rs10889353/ <i>ANGPTL3</i> , rs7679/ <i>PLTP</i> , rs7819412/ <i>XKR6-AMACIL2</i> , rs328/ <i>LPL</i> , rs3135506/ <i>APOA5</i> , rs662799/ <i>APOA5</i> | Null | |
| Uric acid | 1 ³⁶ | Cambridgeshire, ADDITION-Ely, Norfolk Diabetes | UK/2011 | 7504/ 8560 | rs12129861/ <i>PDZK1</i> , rs742132/ <i>LRRC16A</i> , rs505802/ <i>SLC22A12</i> , rs12356193/ <i>SLC16A9</i> , rs17300741/ <i>SLC22A11</i> , rs1165151/ <i>SLC17A1</i> , rs2231142/ <i>ABCG2</i> , rs734553/ <i>SLC2A9</i> | Null | |
| Vitamin D | 3 ^{17,28,45} | DIAGRAMv3, ADDITION-Ely, Norfolk Diabetes, Cambridgeshire, EPIC-InterAct | US, Europe/2015 | 28144/76344 | rs12785878/ <i>DHCR7</i> ,rs10741657/ <i>CYP2R1</i> ,rs4588/ <i>DBP</i> ,rs17217119/ <i>CYP24A1</i> | Null | |
| | | EPIC-Potsdam | Germany/2013 | 1572/2121 | rs2282679,rs1155563,rs12785878,rs3829251,rs10741657,rs6013897,rs6599638, rs10877012/ <i>DBP GC</i> , <i>DHCR7</i> , <i>CYP2R1</i> , <i>CYP24A1</i> ,Ch10orf88, <i>CYP27B1</i> | Null | |

| | | | | | | | |
|---------------------------|-----------------|--------|-------------|-----------|---|------|--|
| | | Tromsø | Norway/2012 | 1092/9528 | rs2298850/ <i>DBP GC</i> , rs10741657/ <i>CYP2R1</i> , rs3794060/ <i>NADSYN1</i> , rs6013897/ <i>CYP24A1</i> | Null | |
| Vitamin D binding protein | 1 ³¹ | CaMos | Canada/2014 | 201/2254 | rs2282679/ <i>DBP GC</i> | Null | |

695 OR, odds ratio; RR, relative risk; HR, hazard ratio; BNP, brain natriuretic peptide, interleukin 1 receptor antagonist (IL1-Ra)

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697 DIAGRAM, DIAbetes Genetics Replication And Meta-analysis; EPIC-InterAct, European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct; ARIC,

698 Atherosclerosis Risk in Communities; WTCCC, Wellcome Trust Case Control Cohort; FUSION, Finland-US Investigation of NIDDM genetics

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700 BHS, Busselton Population Health Survey; CUDAS, Carotid Ultrasound Disease Assessment Study; FDS, Fremantle Diabetes Study

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702 PREVEND, Prevention of Renal and Vascular End-stage Disease;

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704 iNCA, iNsuffisance CADiaque; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease

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706 MDC, Malmö Diet and Cancer Study; MDC-CC, Malmö Diet and Cancer Cardiovascular Cohort; MPP, Malmö Preventive Project;

709 CVDFACTS , CardioVascular Disease risk FACTors Two-township Study

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712 KORA, kooperative gesundheitsforschung in der region Augsburg; EFS-Y2D; DGI, Diabetes Genetics Initiative; Norfolk Diabetes Case Control Study, NDCCS; METSIM,

713 Metabolic Syndrome in Men; DIAGEN, DIAbetes GENetic Study

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715 CHS, Cardiovascular Health Study

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717 WHI-OS, Women's Health Initiative Observational Study Cohort

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719 ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care

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721 MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease

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723 Genetics of Diabetes Audit and Research in Tayside Scotland, Go-DARTS

724 CaMos, Canadian Multicentre Osteoporosis Study

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Table 2: Nominally significance for each biomarker-associated genetic variants with glucose, HOMA-IR and the risk of type 2 diabetes

| Biomarkers | Genetic variants | P value* | | | Nominally significance |
|------------------|------------------|--------------------|-----------------------|-----------------------|------------------------|
| | | T2DM ¹³ | Glucose ¹⁴ | HOMA-IR ¹⁴ | |
| Adiponectin | rs1736653 | - | - | - | NA |
| | rs2980879 | 0.96 | 0.9613 | 0.9276 | Null |
| | rs16861209 | 0.89 | 0.846 | 0.505 | Null |
| | rs601339 | 0.89 | 0.8344 | 0.02762 | Yes |
| | rs17300539 | 0.87 | 0.8116 | 0.1489 | Null |
| | rs7955516 | 0.86 | 0.8366 | 0.8286 | Null |
| | rs12922394 | 0.54 | 0.07314 | 0.1932 | Null |
| | rs3821799 | 0.51 | 0.1882 | 0.7989 | Null |
| | rs731839 | 0.41 | 0.3386 | 0.01373 | Yes |
| | rs3774261 | 0.32 | 0.4418 | 0.7559 | Null |
| | rs17366568 | 0.31 | 0.9738 | 0.3994 | Null |
| | rs7133378 | 0.16 | 0.2134 | 0.3286 | Null |
| | rs12637534 | 0.15 | 0.379 | 0.0006 | Yes |
| | rs6810075 | 0.1 | 0.7728 | 0.5248 | Null |
| | rs998584 | 0.06 | 0.808 | 0.6827 | Null |
| | rs1108842 | 0.032 | 0.4706 | 0.05447 | Yes |
| | rs3001032 | 0.029 | 0.2725 | 0.0001 | Yes |
| | rs1597466 | 0.0087 | 0.06167 | 0.4695 | Yes |
| rs2925979 | 0.0023 | 0.05063 | 0.1782 | Yes | |
| Beta-carotene | rs6564851 | 0.22 | 0.3938 | 0.2702 | Null |
| Bilirubin | rs6742078 | 0.1 | 0.0239 | 0.03327 | Yes |
| B-type proBNP | rs198389 | 0.034 | 0.3651 | 0.3891 | Yes |
| CRP | rs1205 | 0.66 | 0.6836 | 0.6402 | Null |
| | rs3093077 | 0.048 | 0.9494 | 0.393 | Yes |
| | rs1130864 | - | 0.1199 | 0.7696 | Null |
| D6-desaturase | rs174546 | 0.0032 | 2.7×10 ⁻⁸ | 0.8911 | Yes |
| Dimethylglycine | rs2431332 | 0.51 | 0.00421 | 0.2899 | Yes |
| Ferritin/TMPRSS6 | rs855791 | 1 | 0.09508 | 0.2457 | Null |
| | rs4820268 | 0.73 | 0.1492 | 0.1271 | Null |
| Fetuin-a | rs4917 | 0.082 | 0.1046 | 0.6666 | Null |
| | rs2248690 | 0.055 | 0.9571 | 0.7713 | Null |
| Homocysteine | rs4646356 | 0.88 | 0.4332 | 0.3475 | Null |
| | rs12134663 | 0.78 | 0.6857 | 0.6192 | Null |
| | rs1801131 | 0.22 | 0.6088 | 0.2367 | Null |
| | rs1801133 | 0.096 | 0.459 | 0.4294 | Null |
| IL-1Ra | rs1542176 | 0.64 | 0.00802 | 0.7087 | Yes |
| | rs6743376 | - | 0.9109 | 0.4552 | Null |
| LTL | rs12880583 | - | - | - | NA |
| | rs2228041 | - | - | - | NA |
| | rs34368910 | - | - | - | NA |
| | rs938886 | 0.88 | 0.04159 | 0.7375 | Yes |
| | rs4975605 | 0.66 | 0.4506 | 0.6104 | Null |
| | rs4888444 | 0.086 | 0.9143 | 0.3436 | Null |
| Lp(a) | rs10455872 | 0.36 | 0.4242 | 0.3231 | Null |
| MIF | rs1007888 | 0.39 | 0.2167 | 0.9401 | Null |
| miRNAs | rs12610873 | 0.033 | 0.8022 | 0.7117 | Yes |
| | rs531564 | 0.66 | 0.5302 | 0.9714 | Null |
| | rs2910164 | 0.52 | 0.01256 | 0.3573 | Yes |
| Resistin | rs3745367 | 0.77 | 0.9917 | 0.5793 | Null |
| | rs1423096 | 0.72 | 0.8155 | 0.3391 | Null |
| SHBG | rs12150660 | 0.18 | 0.5165 | 0.2413 | Null |
| | rs6259 | 0.94 | 0.4235 | 0.3504 | Null |
| Triglycerides | rs12285095 | 0.41 | 0.9737 | 0.6178 | Null |
| | rs7557067 | 0.9 | 0.7824 | 0.1467 | Null |

| | | | | | |
|--------------|------------|--------|---------|---------|------|
| | rs7679 | 0.88 | 0.9 | 0.2909 | Null |
| | rs2954029 | 0.72 | 0.6368 | 0.871 | Null |
| | rs662799 | 0.28 | 0.04162 | 0.5552 | Yes |
| | rs714052 | 0.28 | 0.807 | 0.8035 | Null |
| | rs10889353 | 0.19 | 0.4164 | 0.2106 | Null |
| | rs7819412 | 0.079 | 0.8028 | 0.00979 | Yes |
| | rs328 | 0.025 | 0.05081 | 0.03923 | Yes |
| | rs17216525 | 0.0035 | 0.9843 | 0.8103 | Yes |
| Uric acid | rs1165151 | 0.74 | 0.4165 | 0.8597 | Null |
| | rs2231142 | 0.73 | 0.8335 | 0.3608 | Null |
| | rs505802 | 0.62 | 0.6034 | 0.6212 | Null |
| | rs734553 | 0.57 | 0.1985 | 0.7163 | Null |
| | rs742132 | 0.25 | 0.5028 | 0.9073 | Null |
| | rs12356193 | 0.14 | 0.9486 | 0.4696 | Null |
| | rs12129861 | 0.083 | 0.9366 | 0.502 | Null |
| | rs17300741 | 0.026 | 0.3446 | 0.3608 | Yes |
| Vitamin-D | rs10877012 | - | - | - | NA |
| | rs3755967 | 0.74 | 0.8454 | 0.1899 | Null |
| | rs1155563 | 0.93 | 0.7691 | 0.06121 | Null |
| | rs2298850 | 0.66 | 0.8892 | 0.1472 | Null |
| | rs3829251 | 0.54 | 0.08705 | 0.2639 | Null |
| | rs3794060 | 0.34 | 0.2832 | 0.1035 | Null |
| | rs6599638 | 0.3 | 0.1749 | 0.4272 | Null |
| | rs10741657 | 0.23 | 0.3746 | 0.0788 | Null |
| | rs12785878 | 0.14 | 0.3232 | 0.1677 | Null |
| | rs17217119 | 0.061 | 0.3553 | 0.2098 | Null |
| | rs6013897 | 0.057 | 0.3293 | 0.1185 | Null |
| Vitamin D-BP | rs2282679 | 0.76 | 0.997 | 0.1191 | Null |

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*p values for each of the biomarker variants were extracted from publicly available meta-analyses of genome-wide association studies^{13,14}.

NA, not applicable; CRP, C-reactive protein; BNP, brain natriuretic peptide; interleukin 1 receptor antagonist (IL1-Ra); Lp(a)Lipoprotein(a); MIF, Macrophage migration inhibitory factor; LTL, Leukocyte telomere length; SHBG, Sex hormone binding globulin, Vitamin D-BP, Vitamin D binding protein