SUPPLEMENTARY DATA

Supplement to:

Pigeyre M, Sjaarda J, Chong M, Hess S, Bosch J, Yusuf S, Gerstein H, Paré G. Angiotensin-converting enzyme and type 2 diabetes risk: a Mendelian randomization study

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Part 1 - Additional materials

Supplementary Material 1. Genotyping, imputation procedures, and quality control steps

ORIGIN cohort

Individuals were genotyped on the HumanCore Exome chip (Illumina). Quality control steps were performed using PLINK (1) and GCTA (Genome-wide Complex Trait Analysis) (2). Imputation was performed using IMPUTE2 software (3) with 1000 Genomes Project data (4) as the reference panel. SNPs imputed with low certainty were removed (INFOscore < 0.6).

UK Biobank cohort

Individuals were genotyped using either the UK Biobank Array or the UK BiLEVE array. Phasing and imputation were performed using SHAPEIT3 (5) and IMPUTE2 (3), respectively, against a combined haplotype reference panel including UK10K (6) and 1000 Genomes Phase 3 (4). In addition to excluding samples belonging to the standard UK Biobank genomic analysis exclusion list, further quality control of samples was performed. Related samples, samples with low call rates (< 99%), inconsistent reported sex versus genetic sex, non-British ancestry, or quality control failure in the UK BiLEVE array were removed. Variants with low call rates (< 95%), low imputation quality (INFOscore < 0.6), low minor allele frequency (MAF < 0.01), or suggestive evidence for poor genotype calling (Hardy Weinberg Equilibrium $P < 10^{-6}$) were also removed.

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Supplementary Material 2. Design of meta-analysis of ACE inhibitors vs. placebo RCTs

Methods

Eligibility criteria

Studies were considered for inclusion if they met the following criteria:

1) type of study design was randomized, doubled-blind, controlled trials (RCTs);

2) compared an ACEI (i.e. benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril) with placebo. There were no restrictions based on the frequency, dosage, length or duration of the ACE inhibitor intervention;

3) reporting the incidence of new-onset diabetes;

4) conducted on adult participants aged ≥ 18 years;

5) published in English.

Information sources and search

We searched PubMed using the MeSH terms: (antihypertensive agents [MeSH Terms] OR angiotensin-converting enzyme inhibitors[MeSH Terms]) AND diabetes mellitus[MeSH Terms] AND (randomized controlled trial[MeSH Terms] OR meta-analysis[MeSH Terms]). This search was applied to PubMed on May 9, 2019.

Study selection, data collection process and data items

Based on the results of the search strategy, titles and abstracts for each reference were examined independently by two reviewers (MP and GP). Relevant studies obtained from the full-text screening phase were reviewed for methodological quality and disagreements were resolved through discussion between reviewers. The following information was extracted from each included trial: (1) characteristics of the study participants (i.e. age, sex, body mass index, ethnicity or country of origin); (2) characteristics of the study (i.e., study design, sample size, median follow-up period); (3) characteristics of the intervention (i.e. ACE inhibitor name, dose and frequency of the intervention, blood pressure-lowering effect); and (4) characteristics of the outcome measures (ie, criteria for defining diabetes, number of new-onset diabetes during follow-up).

Summary measures

The treatment effect on diabetes incidence was expressed as an odds ratio (OR) with the 95% CI and p-value.

Summary results

Random effects model was used for statistical analysis due to wide clinical and methodological variability across the trials. Heterogeneity was tested using restricted maximum-likelihood estimation (REML) as recommended for meta-analysis with a small number of included studies (7), and inconsistency (I^2) was measured by assessing the percentage of total variation of the effects of ACE inhibitors across studies due to heterogeneity. A low p-value ($p<0.10$) or I^2 of > 30% provided evidence of heterogeneity of intervention effects.

Results

Study characteristics

A total of 6 studies were identified for inclusion in this review. The structured literature search of PubMed databases derived a total of 541 citations and 18 additional citations revealed by scrutinizing the reference lists of identified studies. Of these, 510 studies were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet our inclusion criteria. The full-text of the remaining 49 citations were examined in more detail. It appeared that 41 articles did not meet the inclusion criteria. Of the included articles, there were six RCTs (8)(9)(10)(11)(12)(13) enrolling a total of 31,200 participants. (see below the flow diagram of the study selection process).

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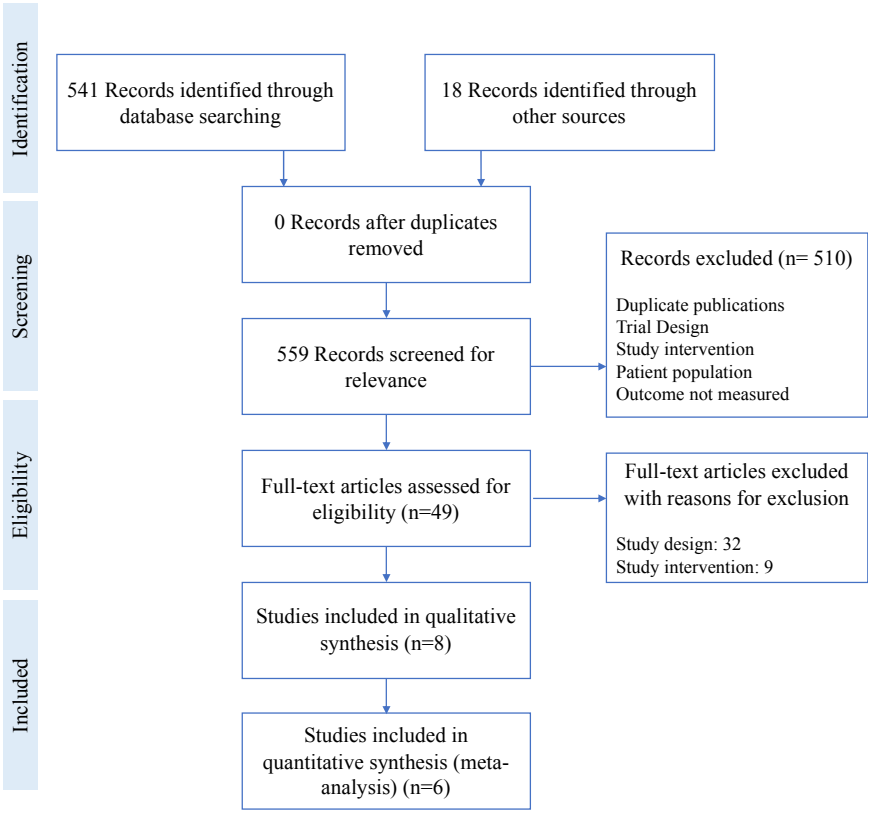

Study flow diagram for the meta-analysis of ACE inhibitors vs. placebo

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Supplementary Material 3. Standardization of the *ACE GRS* for mean arterial blood pressure change

The ACE GRS was standardized to be given in genetically determined ACE concentration equivalent to a 2.4 mmHg lower MAP. We estimated the relationship between MAP and *ACE GRS* in the UK Biobank participants lacking type 2 diabetes (N=326,508), using a linear regression model, in which MAP (measured in mmHg) was the dependent variable and ACE GRS was the independent variable of interest. We next used the regression coefficient (β) obtained from this linear model to rescale the *ACE GRS* such that $ACE\ GRS_{standardized}$ was equal to the product of *ACE GRS**β*2.4, such that 1 higher score unit corresponded to a genetically ACE concentration change associated with a 2.4 mmHg lower MAP. Then, we performed a logistic regression to estimate the association between type 2 diabetes prevalence (dependent variable) and $ACE\ GRS_{standardized}$ (independent variable) in the UK Biobank participants. This model was adjusted for age, sex, ACE inhibitor usage at baseline, and the first ten principal components.

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Part 2 - Additional tables

Supplementary Table 1. Studies including in DIAGRAM consortium

Study name	Study design	Ethnicity	Total sample size (*N* [cases / controls])
ARIC	population-based	White European	755/7009
BioMe^ (Affy)	population-based	White European	132/455
BioMe^ (Illumina)	population-based	White European	255/1647
deCODE	population-based	White European	7339/83049
DGDG	Case-control	White European	679/697
DGI	T2D Case-Control	White European	1023/1074
EGCUT-370	population-based	White European	80/1768
EGCUT-OMNI	population-based	White European	389/6013
EPIC-InterAct	case-control nested into population-based	White European	4624/4668
FHS	family-based	White European Americans	673/7660
FUSION	Case-control	White European	1161/1174
GoDARTS	Case-Control	White European	3298/2643
HPFS	population-based	White European	1124/1298
KORAgen	population-based	White European	347/1550
NHS	population-based	White European	1467/1754
PIVUS	population-based	White European	111/838
RS-I	population-based	White European	654/5219
ULSAM	population-based	White European	166/953
WTCCC	population-based	White European	1924/2938

Adapted from Scott et al. (14)

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Supplementary Table 2. List of biomarkers

	Biomarker	Gene	Inter-Run CV at Intermediate Concentrations
1	6Ckine	*CCL21*	13%
2	Adiponectin	*ADIPOQ*	4%
3	Adrenomedullin	*ADM*	7%
4	Agouti-Related Protein	*AGRP*	7%
5	Aldose Reductase	*AKR1B1*	11%
6	Alpha-1-acid glycoprotein 1	*ORM1*	15%
7	Alpha-1-Antichymotrypsin	*SERPINA3*	6%
8	Alpha-1-Antitrypsin	*SERPINA1*	14%
9	Alpha-1-Microglobulin	*AMBP*	5%
10	Alpha-2-Macroglobulin	*A2M*	6%
11	Angiogenin	*ANG*	10%
12	Angiopoietin-2	*ANGPT2*	6%
13	Angiopoietin-related protein 3	*ANGPTL3*	8%
14	Angiotensin-Converting Enzyme	*ACE*	12%
15	Angiotensinogen	*AGT*	6%
16	Antithrombin-III	*SERPINC1*	6%
17	Apolipoprotein A-I	*APOA1*	10%
18	Apolipoprotein A-II	*APOA2*	8%
19	Apolipoprotein A-IV	*APOA4*	9%
20	Apolipoprotein B	*APOB*	9%
21	Apolipoprotein C-I	*APOC1*	9%
22	Apolipoprotein C-III	*APOC3*	20%
23	Apolipoprotein D	*APOD*	18%
24	Apolipoprotein E	*APOE*	20%
25	Apolipoprotein H	*APOH*	12%
26	Apolipoprotein(a)	*LPA*	16%
27	AXL Receptor Tyrosine Kinase	*AXL*	10%
28	B cell-activating factor	*TNFSF13B*	9%
29	B Lymphocyte Chemoattractant	*CXCL13*	10%
30	Beta Amyloid 1-40	*APP*	13%
31	Beta-2-Microglobulin	*B2M*	13%
32	Brain-Derived Neurotrophic Factor	*BDNF*	5%
33	C-Peptide	*INS*	4%
34	C-Reactive Protein	*CRP*	13%
35	Cathepsin D	*CTSD*	9%
36	CD 40 antigen	*CD40*	8%
37	CD163	*CD163*	11%
38	CD40 Ligand	*CD40LG*	9%
39	CD5 Antigen-like	*CD5L*	14%
40	Cellular Fibronectin	*FN1*	17%
41	Chemerin	*RARRES2*	4%
42	Chemokine CC-4	*CCR4*	7%
43	Chromogranin-A	*CHGA*	7%
44	Clusterin	*CLU*	10%

45	Collagen IV	*COL4A1,COL4A2,COL4A3,COL4A4,COL4A5,COL4A6*	14%
46	Complement C3	*C3*	10%
47	Complement Factor H Related Protein 1	*CFHR1*	9%
48	Cortisol	*NA*	8%
49	Creatine Kinase-MB	*CKM,CKB*	12%
50	Cystatin-C	*CST3*	8%
51	E-Selectin	*SELE*	5%
52	EN-RAGE	*S100A12*	4%
53	Endoglin	*ENG*	8%
54	Endostatin	*COL18A1*	10%
55	Eotaxin-1	*CCL11*	11%
56	Eotaxin-2	*CCL24*	9%
57	Eotaxin-3	*CCL26*	16%
58	Epithelial-Derived Neutrophil-Activating Protein 78	*CXCL5*	12%
59	Erythropoietin	*EPO*	10%
60	Ezrin	*EZR*	10%
61	Factor VII	*F7*	4%
62	Fas Ligand	*FASLG*	8%
63	FASLG Receptor	*TNFRSF6B*	2%
64	Fatty Acid-Binding Protein adipocyte	*FABP4*	6%
65	Fatty Acid-Binding Protein liver	*FABP1*	12%
66	Ferritin	*FTL,FTH1*	6%
67	Fetuin-A	*AHSG*	17%
68	Fibroblast Growth Factor 21	*FGF21*	12%
69	Fibroblast growth factor 23	*FGF23*	9%
70	Fibulin-1C	*FBLN1*	9%
71	Ficolin-3	*FCN3*	7%
72	Follicle-Stimulating Hormone	*FSHB,CGA*	16%
73	Galectin-3	*LGALS3*	8%
74	Gastric inhibitory polypeptide	*GIP*	12%
75	Gelsolin	*GSN*	12%
76	Glucagon-like Peptide 1 total	*GCG*	7%
77	Glucose-6-phosphate Isomerase	*GPI*	7%
78	Glutathione S-Transferase alpha	*GSTA1,GSTA2,GSTA3,GSTA4,GSTA5*	11%
79	Glycogen phosphorylase isoenzyme BB	*PYGB*	6%
80	Granulocyte Colony-Stimulating Factor	*CSF3*	6%
81	Growth differentiation factor 15	*GDF15*	10%
82	Growth Hormone	*GH1,GH2*	9%
83	Growth-Regulated alpha protein	*CXCL1*	5%
84	Haptoglobin	*HP*	8%
85	Heat-Shock protein 70	*HSPA1A,HSPA1B,HSPA1L,HSPA2,HSPA4,HSPA4L,HSPA5,HSPA6,HSPA8,HSPA9,HSPA12A,HSPA12B,HSPA13,HSPA14*	8%
86	Hemopexin	*HPX*	9%

87	Hepatocyte Growth Factor	*HGF*	18%
88	Hepatocyte Growth Factor receptor	*MET*	13%
89	Hepsin	*HPN*	4%
90	Human Epidermal Growth Factor Receptor 2	*ERBB2*	2%
91	Immunoglobulin A	*IGH*	11%
92	Immunoglobulin E	*IGH*	4%
93	Immunoglobulin M	*IGH*	19%
94	Insulin	*INS*	7%
95	Insulin-like Growth Factor Binding Protein 4	*IGFBP4*	6%
96	Insulin-like Growth Factor Binding Protein 5	*IGFBP5*	8%
97	Insulin-like Growth Factor Binding Protein 6	*IGFBP6*	17%
98	Insulin-like Growth Factor I	*IGF1*	8%
99	Insulin-like Growth Factor-Binding Protein 1	*IGFBP1*	8%
100	Insulin-like Growth Factor-Binding Protein 2	*IGFBP2*	7%
101	Insulin-like Growth Factor-Binding Protein 3	*IGFBP3*	9%
102	Intercellular Adhesion Molecule 1	*ICAM1*	7%
103	Interferon gamma	*IFNG*	11%
104	Interferon gamma Induced Protein 10	*CXCL10*	8%
105	Interferon-inducible T-cell alpha chemoattractant	*CXCL11*	16%
106	Interleukin-1 beta	*IL1B*	10%
107	Interleukin-1 receptor antagonist	*IL1RN*	6%
108	Interleukin-10	*IL10*	8%
109	Interleukin-12 Subunit p40	*IL12B*	7%
110	Interleukin-16	*IL16*	5%
111	Interleukin-17	*IL17A*	6%
112	Interleukin-18	*IL18*	9%
113	Interleukin-2	*IL2*	8%
114	Interleukin-2 receptor alpha	*IL2RA*	2%
115	Interleukin-23	*IL23A,IL12B*	9%
116	Interleukin-6	*IL6*	6%
117	Interleukin-6 receptor	*IL6R*	6%
118	Interleukin-6 receptor subunit beta	*IL6ST*	9%
119	Interleukin-7	*IL7*	6%
120	Interleukin-8	*CXCL8*	8%
121	Kallikrein 5	*KLK5*	14%
122	Kidney Injury Molecule-1	*HAVCR1*	9%
123	Lactoferrin	*LTF*	9%
124	Lactoylglutathione lyase	*GLO1*	6%
125	Latency-Associated Peptide of Transforming Growth Factor beta 1	*LTBP1*	7%
126	Lectin-Like Oxidized LDL Receptor 1	*OLR1*	4%

127	Leptin	*LEP*	6%
128	Leptin Receptor	*LEPR*	11%
129	Leucine-rich alpha-2-glycoprotein	*LRG1*	4%
130	Luteinizing Hormone	*LHB,CGA*	6%
131	Macrophage Colony-Stimulating Factor 1	*CSF1*	5%
132	Macrophage inflammatory protein 3 beta	*CCL19*	10%
133	Macrophage Inflammatory Protein-1 alpha	*CCL3*	7%
134	Macrophage Inflammatory Protein-1 beta	*CCL4*	6%
135	Macrophage Inflammatory Protein-3 alpha	*CCL20*	4%
136	Macrophage Migration Inhibitory Factor	*MIF*	6%
137	Macrophage-Derived Chemokine	*CCL22*	9%
138	Macrophage-Stimulating Protein	*MST1*	6%
139	Matrix Metalloproteinase-1	*MMP1*	12%
140	Matrix Metalloproteinase-10	*MMP10*	11%
141	Matrix Metalloproteinase-3	*MMP3*	9%
142	Matrix Metalloproteinase-7	*MMP7*	12%
143	Matrix Metalloproteinase-9	*MMP9*	6%
144	Matrix Metalloproteinase-9 total	*MMP9*	14%
145	Mesothelin	*MSLN*	10%
146	Methylglyoxal	*NA*	9%
147	MHC class I chain-related protein A	*MICA*	5%
148	Monocyte Chemotactic Protein 1	*CCL2*	5%
149	Monocyte Chemotactic Protein 2	*CCL8*	6%
150	Monocyte Chemotactic Protein 3	*CCL7*	7%
151	Monocyte Chemotactic Protein 4	*CCL13*	7%
152	Monokine Induced by Gamma Interferon	*CXCL9*	10%
153	Myeloid Progenitor Inhibitory Factor 1	*CCL23*	4%
154	Myeloperoxidase	*MPO*	16%
155	Myoglobin	*MB*	6%
156	N-terminal prohormone of brain natriuretic peptide	*NPPB*	5%
157	Neuronal Cell Adhesion Molecule	*NRCAM*	5%
158	Neuropilin-1	*NRP1*	11%
159	Neutrophil Activating Peptide 2	*PPBP*	7%
160	Neutrophil Gelatinase-Associated Lipocalin	*LCN2*	12%
161	Omentin	*ITLN1*	11%
162	Osteocalcin	*BGLAP*	9%
163	Osteopontin	*SPP1*	9%
164	Osteoprotegerin	*TNFRSF11B*	9%
165	P-Selectin	*SELP*	6%
166	Pancreatic Polypeptide	*PPY*	13%
167	Paraoxanase-1	*PON1*	16%

168	Pentraxin-3	*PTX3*	12%
169	Pepsinogen I	*NA*	6%
170	Peptide YY	*PYY*	7%
171	Periostin	*POSTN*	11%
172	Peroxiredoxin-4	*PRDX4*	8%
173	Phosphoserine Aminotransferase	*PSAT1*	7%
174	Pigment Epithelium Derived Factor	*SERPINF1*	7%
175	Plasminogen Activator Inhibitor 1	*SERPINE1*	8%
176	Platelet-Derived Growth Factor BB	*PDGFB*	6%
177	Progesterone	*NA*	8%
178	Progranulin	*GRN*	6%
179	Proinsulin Intact	*INS*	5%
180	Proinsulin Total	*INS*	6%
181	Prolactin	*PRL*	15%
182	Prostasin	*PRSS8*	6%
183	Prostatic Acid Phosphatase	*ACPP*	11%
184	Protein S100-A4	*S100A4*	7%
185	Protein S100-A6	*S100A6*	8%
186	Pulmonary and Activation-Regulated Chemokine	*CCL18*	10%
187	Receptor for advanced glycosylation end products	*AGER*	5%
188	Receptor tyrosine-protein kinase erbB-3	*ERBB3*	10%
189	Resistin	*RETN*	8%
190	Retinol-binding protein 4	*RBP4*	13%
191	Secreted frizzled-related protein 4	*SFRP4*	12%
192	Selenoprotein P	*SEPP1*	6%
193	Serotransferrin	*TF*	8%
194	Serum Amyloid A Protein	*SAA1,SAA2,SAA4,SAA3P*	11%
195	Serum Amyloid P-Component	*APCS*	10%
196	Serum Glutamic Oxaloacetic Transaminase	*GOT1,GOT2*	12%
197	Sex Hormone-Binding Globulin	*SHBG*	14%
198	Sortilin	*SORT1*	5%
199	ST2	*IL1RL1*	11%
200	Stem Cell Factor	*KITLG*	6%
201	Stromal cell-derived factor-1	*CXCL12*	10%
202	Superoxide Dismutase 1 soluble	*SOD1*	7%
203	T Lymphocyte-Secreted Protein I-309	*CCL1*	11%
204	T-Cell-Specific Protein RANTES	*CCL5*	16%
205	Tamm-Horsfall Urinary Glycoprotein	*UMOD*	17%
206	Tenascin-C	*TNC*	4%
207	Testosterone Total	*NA*	7%
208	Tetranectin	*CLEC3B*	15%
209	Thrombin-activable fibrinolysis inhibitor	*CPB2*	5%

210	Thrombomodulin	*THBD*	7%
211	Thrombospondin-1	*THBS1*	14%
212	Thyroid-Stimulating Hormone	*TSHB,CGA*	8%
213	Thyroxine-Binding Globulin	*SERPINA7*	15%
214	Tissue Inhibitor of Metalloproteinases 1	*TIMP1*	7%
215	Tissue type Plasminogen activator	*PLAT*	5%
216	TNF-Related Apoptosis-Inducing Ligand Receptor 3	*TNFRSF10C*	7%
217	Transthyretin	*TTR*	8%
218	Trefoil Factor 3	*TFF3*	7%
219	Troponin		4%
220	Tumor Necrosis Factor alpha	*TNF*	5%
221	Tumor necrosis factor receptor 2	*TNFRSF1B*	7%
222	Tumor Necrosis Factor Receptor I	*TNFRSF1A*	8%
223	Tyrosine kinase with Ig and EGF homology domains 2	*TIE1*	7%
224	Urokinase-type Plasminogen Activator	*PLAU*	9%
225	Urokinase-type plasminogen activator receptor	*PLAUR*	8%
226	Vascular Cell Adhesion Molecule-1	*VCAM1*	8%
227	Vascular Endothelial Growth Factor	*VEGFA*	7%
228	Vascular Endothelial Growth Factor C	*VEGFC*	10%
229	Vascular endothelial growth factor D	*FIGF*	7%
230	Vascular Endothelial Growth Factor Receptor 2	*FLT1*	6%
231	Vascular endothelial growth factor receptor 3	*FLT4*	7%
232	Visceral adipose tissue derived serpin A12	*SERPINA12*	7%
233	Visfatin	*NAMPT*	15%
234	Vitamin D-Binding Protein	*GC*	11%
235	Vitamin K-Dependent Protein S	*PROS1*	9%
236	Vitronectin	*VTN*	18%
237	von Willebrand Factor	*VWF*	12%
238	YKL-40	*CHI3L1*	8%

The respective CVs are from the customized validation report provided by Myriad RBM Inc. for the biomarkers assayed for this study (15); the company's White Paper on Quality systems was accessed at https://myriadrbm.com/scientific-media/quality-control-systems-white-paper/.

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Supplementary Table 3. Characteristics of ORIGIN participants

Variables	Proteomic study participants (n=8197)	Genetic study participants (n=4147)
Age (years)	63.72 (7.94)	63.45 (7.98)
Sex (% male)	66.11	64.14
Ethnicity - Europeans (%)	55.41	46.56
- Latin Americans (%)	34.28	53.44
- South Asian (%)	5.49	-
- Black (%)	4.36	-
- South East Asian (%)	0.46	-
Smoking (%, ever)	60.10	60.16
Body mass index (kg/m^2)	30.04 (5.27)	30.45 (5.33)
Prior type 2 diabetes (%)	81.66	87.56
Fasting plasma glucose (mmol/L)	7.33 (2.02)	7.58 (2.17)
HbA_1c (%)	6.5 (0.95)	6.6 (0.98)
(mmol/mol)	48.0 (10.4)	49.0 (10.7)
Prior hypertension (%, yes)	78.91	82.9
LDL (mmol/L)	2.89 (1.03)	3.07 (1.05)
HDL (mmol/L)	1.18 (0.32)	1.17 (0.32)
Triglycerides (mmol/L)	1.89 (1.24)	1.93 (1.17)
Prior cardio-vascular event (%, yes)	59.57	53.29
ACE inhibitor usage at baseline (%, yes)	57.59	63.25

Data are presented as mean (SD) unless stated otherwise.

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Supplementary Table 4. Single nucleotide polymorphisms associated with ACE serum levels and included in the Mendelian randomization analysis of type 2 diabetes risk

Biomarker	Gene	SNP	Genomic position	Effect/ Other allele	EAF Europeans (ORIGIN, n=1931)	EAF Latin Americans (ORIGIN, n=2216)	Regression coefficient (se) of ACE level per allele	*P*-value	Proportion of variance explained of ACE level	F-statistic	OR (95%CI) for type 2 diabetes per allele	*P*-value
ACE	*ACE*	rs4343	17:61566031	A/G	0.45	0.46	-0.63 (0.02)	$1.53x10^{-213}$	0.21	64.23	0.97 (0.94-0.99)	0.01
		rs1074637	17:61442830	T/C	0.90	0.91	-0.24 (0.04)	$4.40x10^{-9}$	0.01	2.03	1.00 (0.96-1.05)	0.86
		rs11650201	17:61544349	G/T	0.16	0.18	-0.28 (0.03)	$2.69x10^{-18}$	0.02	4.49	0.97 (0.94-1.02)	0.21
		rs117808108	17:61641531	T/C	0.89	0.94	-0.12 (0.04)	$1.13x10^{-3}$	0.00	0.62	1.04 (1.00-1.08)	0.068
		rs12452187	17:61648920	A/G	0.60	0.61	-0.23 (0.02)	$2.53x10^{-27}$	0.03	6.96	0.97 (0.94-0.99)	0.012
		rs12602457	17:61330017	G/T	0.85	0.89	-0.23 (0.03)	$2.64x10^{-14}$	0.01	3.41	0.99 (0.95-1.03)	0.59
		rs13342595	17:61488575	C/T	0.23	0.24	-0.14 (0.02)	$2.48x10^{-9}$	0.01	2.10	0.98 (0.95-1.01)	0.17
		rs1443431	17:61373314	A/G	0.03	0.04	-0.24 (0.05)	$4.20x10^{-6}$	0.01	1.24	1.02 (0.96-1.08)	0.58
		rs2137143	17:61805401	T/G	0.96	0.98	-0.35 (0.06)	$7.50x10^{-9}$	0.01	1.97	0.97 (0.92-1.02)	0.28
		rs4313	17:61561017	C/T	0.96	0.04	-0.24 (0.05)	$1.53x10^{-5}$	0.00	1.10	1.02 (0.97-1.09)	0.43
		rs4968780	17:61538867	C/A	0.05	0.06	-0.28 (0.05)	$1.86x10^{-8}$	0.01	1.86	0.96 (0.91-1.02)	0.23
		rs71377703	17:61765115	C/T	0.90	0.86	-0.18 (0.04)	$1.07x10^{-6}$	0.01	1.40	0.94 (0.88-1.00)	0.042
		rs72845888	17:61667008	T/C	0.05	0.03	-0.26 (0.05)	$1.50x10^{-7}$	0.01	1.62	0.90 (0.86-0.95)	$9.60x10^{-5}$
		rs72847305	17:61741113	A/G	0.10	0.09	-0.33 (0.04)	$4.52x10^{-17}$	0.02	4.17	0.95 (0.90-0.99)	0.025
		rs74251225	17:61365909	G/A	0.04	0.13	-0.26 (0.04)	$1.57x10^{-10}$	0.01	2.41	0.93 (0.84-1.03)	0.16
		rs75457471	17:61848360	A/G	0.38	0.40	-0.19 (0.02)	$8.10x10^{-15}$	0.01	3.55	0.98 (0.94-1.01)	0.22
		rs79480822	17:61654225	C/T	0.93	0.97	-0.55 (0.05)	$6.37x10^{-24}$	0.02	6.03	0.95 (0.89-1.01)	0.071

SNP: single nucleotide polymorphism, EAF: effect allele frequency, SE: standard error, OR: odd ratio, CI: confidence interval.

The proportion of variance explained for each SNPs was calculated as follows: $R^2 = (2\beta^2 EAF(1-EAF))/(2\beta^2 EAF(1-EAF) + (SE)^2 2N * EAF(1-EAF))$

The F-statistic for each SNP was calculated as follows: $F = \frac{N-k-1}{k} * \frac{R^2}{1-R^2}$

Where β was the regression coefficient, EAF the effect allele frequency, se the standard error, N the sample size, k the number of SNPs.

The total variance explained by the 17 SNPs was calculated by summing the variance explained by each SNP.

The total F-statistic was calculated from the total variance explained according to the aforementioned equation.

SUPPLEMENTARY DATA

Supplementary Table 5. Characteristics of UK Biobank participants

Variables	Participants (n= 341,872)
Age (years)	56.87 (8.00)
Sex (% male)	46.18
Body mass index (kg/m^2)	27.39 (4.75)
Type 2 diabetes (%)	4.77
Mean arterial blood pressure (mmHg)	101.55 (12.46)
Fasting plasma glucose (mmol/L)	5.12 (1.21)
HbA1c (mmol/mol)	35.93 (6.49)
ACE inhibitor usage at baseline (%)	10.07

Data are presented as mean (SD) unless stated otherwise.

SUPPLEMENTARY DATA

Supplementary Table 6. MR associations of ACE concentrations with body mass index and 15 glucose- and insulin-related traits available in the GIANT (16) and the MAGIC consortia (17)(18)(19)(20)

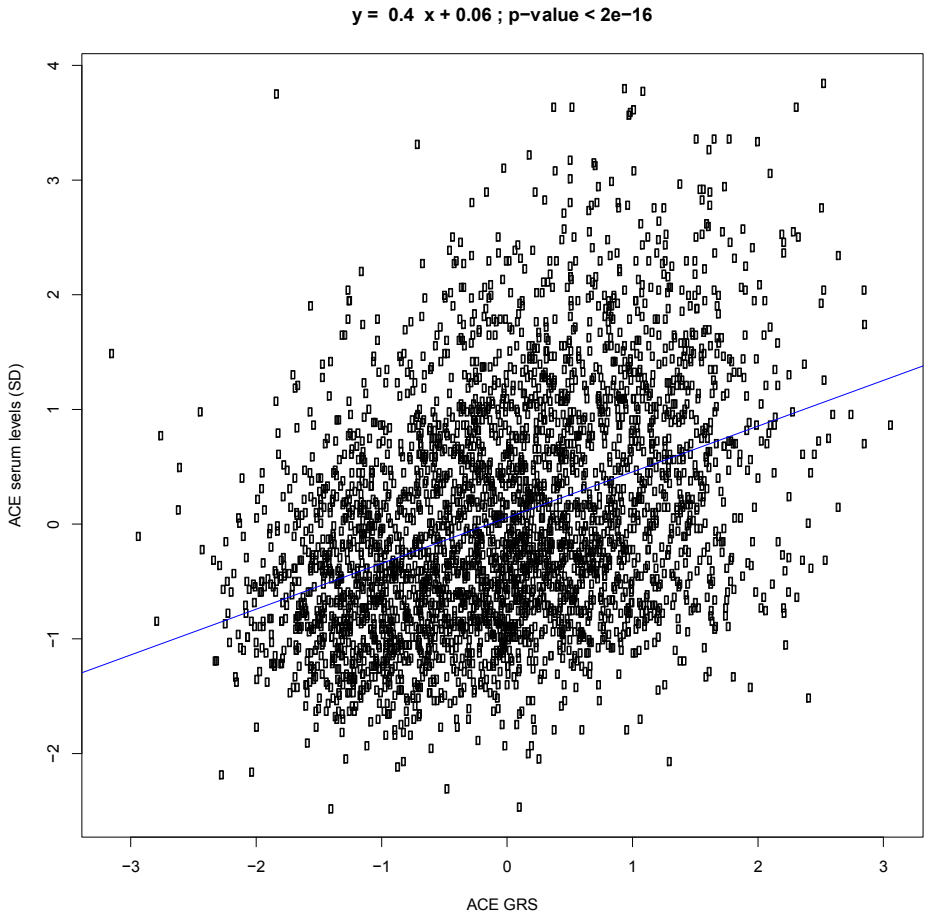
Trait	Sample size	Unit	Beta coefficient per 1 SD lower genetically determined ACE level	95% Lower CI	95% Upper CI	P-value	Number of *cis* ACE SNPs	Author	Minimum effect size detectable for a P-value < 0.05 and a power of 80%
Body mass index	339224	SD (kg/m2)	-0.0177	-0.028	-0.0074	7.42x10-4	6	Locke AE	0.002
Insulin at 30 minutes during oral glucose tolerance test	4483	SD	-0.0870	-0.1467	-0.0273	0.0043	7	Prokopenko I	0.016
Insulin sensitivity index (ISI)	4769	SD	0.0701	0.0108	0.1294	0.0206	7	Prokopenko I	0.016
Fasting proinsulin	10701	log pmol/L	-0.0244	-0.0495	0.0008	0.0573	8	Dupuis J	0.011
Insulin disposition index (IDI) during oral glucose tolerance test	5130	SD	0.0529	-0.0023	0.1081	0.0603	7	Prokopenko I	0.015
Glycated hemoglobin	46368	%	-0.0091	-0.024	0.0058	0.229	9	Soranzo N	0.005
Incremental insulin at 30 minutes adjusted for insulin sensitivty index	4789	SD	0.0324	-0.0265	0.0913	0.2812	7	Prokopenko I	0.016
Corrected insulin response during oral glucose tolerance test	4447	SD	-0.0355	-0.1066	0.0356	0.3277	8	Prokopenko I	0.016
Insulin secretion	4789	SD	0.0230	-0.0333	0.0792	0.4242	7	Prokopenko I	0.016
Fasting insulin	38238	log pmol/L	-0.0052	-0.0207	0.0103	0.5112	8	Dupuis J	0.006
Homeostatic model assessment for beta-cell function (HOMA-B)	46186	log HOMA	-0.0028	-0.0155	0.0099	0.6672	8	Dupuis J	0.005
Area under the curve of insulin levels during oral glucose tolerance test	4324	SD (mU*min/l)	-0.0115	-0.0851	0.0621	0.7591	8	Prokopenko I	0.017
Fasting glucose	46186	mmol/L	0.0013	-0.0114	0.0141	0.8397	8	Dupuis J	0.005
Ratio of the area under the curve for insulin and glucose levels	4213	SD	0.0038	-0.0704	0.078	0.9204	8	Prokopenko I	0.017
2 hour glucose adjusted for BMI	15234	mmol/L	0.0014	-0.0508	0.0537	0.9568	7	Saxena R	0.009
Homeostatic model assessment for insulin resistance (HOMA-IR)	46186	log HOMA	-0.0004	-0.0163	0.0156	0.9642	8	Dupuis J	0.005

SUPPLEMENTARY DATA

Part 3 - Additional figures

Supplementary Figure 1. Association of *ACE GRS* with ACE serum levels in ORIGIN participants

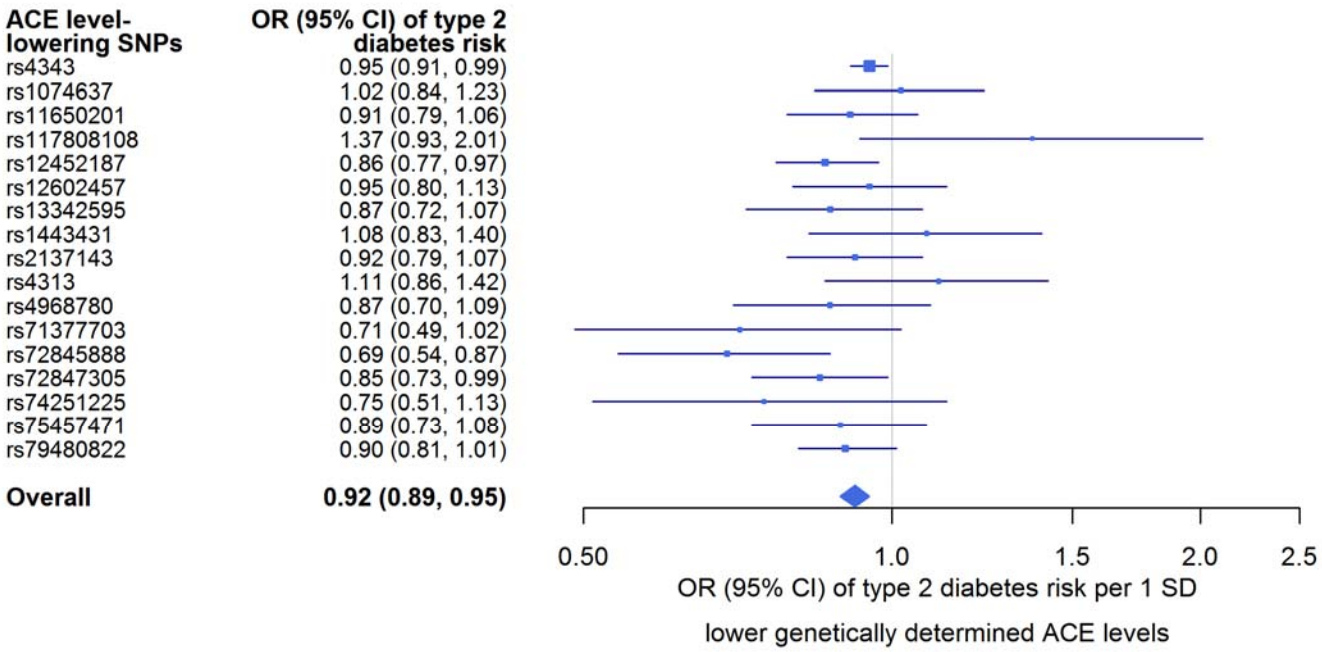
Scatter plot represents individual data point of ORIGIN participants, with *ACE GRS* plotted in x-axis and ACE serum levels plotted in Y-axis. The line represents the regression line of the association of *ACE GRS* with ACE serum levels. Equation of the regression line is shown on the top of the figure.



SUPPLEMENTARY DATA

Supplementary Figure 2. Association of ACE concentration change with risk of type 2 diabetes using a two-sample MR

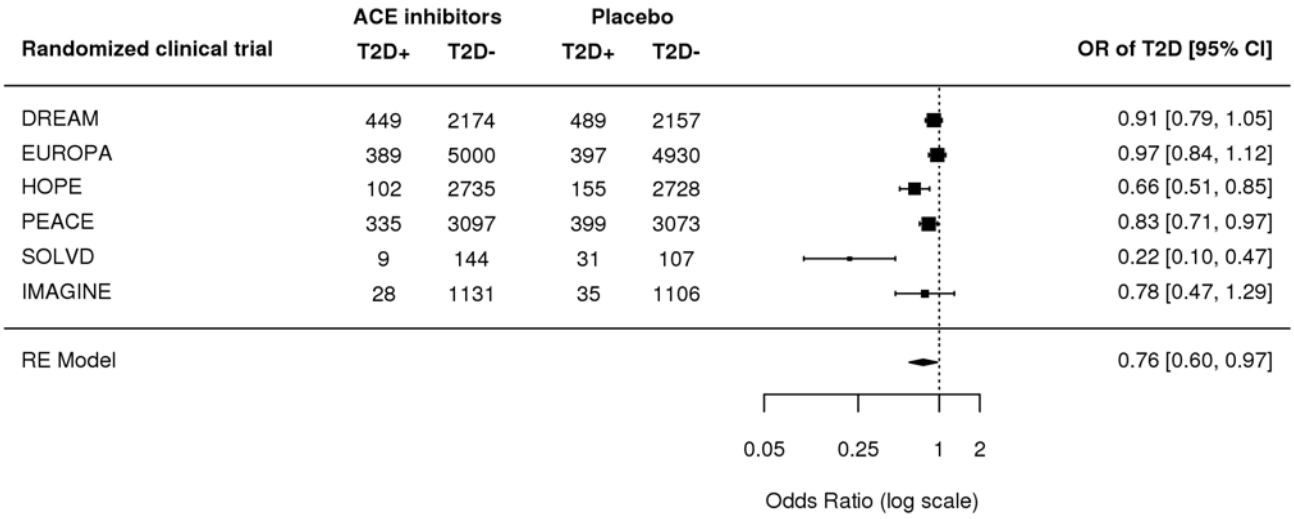
Forest plots depict a summary of the MR results for ACE. A single SNP MR was conducted for each independent SNP (pairwise $r^2 < 0.1$) using the same method as described for the multi-SNP MR. ORs were determined by the Wald method by regressing the effect estimates from the type 2 diabetes association (from DIAGRAM) on the ACE association (from ORIGIN). A two-tailed p-value was calculated using a Z-test from 100,000 random simulations.



SUPPLEMENTARY DATA

Supplementary Figure 3. Forest plot of the association of ACE inhibitors and new-onset type 2 diabetes (T2D) risk

Odds ratio was estimated using inverse variance weighted random effects model (RE model). Heterogeneity was assessed using restricted maximum likelihood estimation (REML).



tau^2 (estimated amount of total heterogeneity) : 0.0653 (se= 0.0554)
I^2 (total heterogeneity / total variability) : 85.61%
H^2 (total variability / sampling variability) : 6.95
Test for heterogeneity: Q= 19.6789, p-value= 0.0014

SUPPLEMENTARY DATA

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