SUPPLEMENTARY MATERIAL:

TRANSCEND Consortium Group Members

(TRansomics ANalysis of Complications and ENdpoints in Diabetes)

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Cohort descriptions

The Hong Kong Diabetes Register (HKDR) Study

The HKDR baseline study ran from 1995 to 2014 and consists of >10,000 patients with diabetes (1; 2). It was established as a quality improvement program and the study of outcomes for Chinese patients with diabetes at the Prince of Wales Hospital in Hong Kong, serving a population of over 1.2 million. These patients were referred from hospital-based specialty clinics, community clinics, and general practitioners. The Register consecutively enrolled patients with diabetes who were referred to the Diabetes Mellitus and Endocrine Centre for comprehensive assessment of diabetic complications and metabolic control. Type 2 Diabetes (T2D) was diagnosed according to the 1998 World Health Organization (WHO) criteria. Type 1 diabetic patients with acute ketotic presentation, or patients with non-Chinese or unknown nationality, or missing data on the type of diabetes, or continuous requirement of insulin within one year of diagnosis were excluded. In addition to detailed collection of clinical information and comprehensive assessment of diabetes complications at baseline according to the EURODIAB protocol, participants attended regular repeat diabetes complication assessment. Additional information on hospitalization, new diagnoses, prescription, and biochemical investigations are also available and captured. All participants provided written informed consent at the time of enrolment. Ethical approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

The Hong Kong Diabetes Biobank (HKDB) Phase 1 and 2 Studies

The HKDB is a multicenter prospective cohort study coordinated by the Prince of Wales Hospital, initiated in 2014 (3). It was established as a multicentre diabetes registry and biobank for identification of novel biomarkers of diabetes and related complications. The HKDB recruited participants through 11 diabetes centres and three renal units at major public

hospitals across Hong Kong. Participants attending a scheduled and standardized diabetes complication assessment based on the modified European DIABCARE protocol (4) were invited to take part in the study. Similar enrolment and assessment methods were used as in HKDR, incorporating comprehensive and structured assessment of clinical and biochemical risk factors, as well as diabetes complications (2). When enrolled, the participant is followed until death. More than 20,000 Chinese patients with T2D were enrolled consecutively from 2014 to 2019. DNA samples of 7,335 (phase 1 study) and 6,715 (phase 2 study) patients from the HKDB study were genotyped in two different phases using different genotyping platforms. Participants from the HKDB study overlapped in the HKDR study were excluded from the analysis. Written informed consent was obtained on collection of clinical data and biological samples for research at the time of enrolment. Approvals were obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee and the clinical research ethics committee of each participating hospital.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study

The FIELD Study is a long-term, double-blind, placebo-controlled trial of fibrate therapy in diabetes conducted in 63 clinical centres in Australia, Finland and New Zealand (5). Patients with T2D and aged 50 - 75 years were randomly allocated between February, 1998, and November, 2000, to once-daily micronised fenofibrate 200 mg (Laboratoires Fournier, Dijon, France) or matching placebo capsules to assess benefits of treatment on the occurrence of coronary and other vascular events. Patients were recruited from hospital clinics and community-based sources. Those who had total-cholesterol (TC) concentration 3.0 – 6.5 mmol/L, plus either a TC/HDL-cholesterol ratio ≥ 4·0 or a triglyceride (TG) concentration 1.0 – 5.0 mmol/L, with no clear indication for, or treatment with, lipid-modifying therapy at study entry, were eligible. Exclusion criteria included renal impairment (blood creatinine >130

μmol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within the 3 months before recruitment. Among 5,040 patients with T2D included in the *in-silico* replication study, a total of 764 patients (15.2%) progressed to CHD during the study period. All patients provided written informed consent. The study protocol was approved by local and national ethics committees and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

The Biobank Japan (BBJ) Study reported by Ishigaki et al. (6) and Koyama et al. (7)

The BBJ Project is one of the largest non-European single-descent biobanks with detailed phenotypes (8). Details of the study design of the BBJ Project have been previously described (8). Briefly, this project is a multi-institutional hospital-based registry that collected DNA, serum, and clinical information of approximately 200,000 patients from 66 hospitals affiliated with 12 medical institutes between fiscal years 2003 and 2007. All study participants had been diagnosed with one or more of the 47 target diseases by physicians at the cooperating hospitals as described in the previous reports (8).

The Japanese GWAS reported by Matsunaga et al.

This study performed a meta-analysis of two Japanese genome-wide association studies (GWASs) using independent case-control cohorts (9). All samples were from patients of Japanese ancestry. In the first GWAS, the cases of MI were selected from BBJ (8) and the controls were obtained from Tohoku Medical Megabank Organization (ToMMo), Iwate Tohoku Medical Megabank Organization (IMM) (10), the Japan Public Health Center-based Prospective (JPHC) Study (11), and the Japan Multi-Institutional Collaborative Cohort (JMICC) Study (12). In the second GWAS, the cases were selected from the Osaka Acute Coronary Insufficiency Study (OACIS) (13), and the controls were obtained from BBJ, for

those with MI, unstable angina pectoris, stable angina pectoris, cerebral infarction, or peripheral arterial disease were excluded from the analysis (8). Informed consent was obtained from all participants by following the protocols approved by their institutional ethical committees before enrollment, and the Institutional Review Board (IRB) approved this study.

The meta-analysis of CARDIoGRAMplusC4D and UK Biobank data reported by van der Harst et al. (14)

The CARDIoGRAMplusC4D consortium represents a collaborative effort to combine data from multiple large-scale genetic studies to identify risk loci for coronary artery disease and myocardial infarction. The detailed methods have been described elsewhere (15).

The UK Biobank enrolled the individuals aged 40-69 years and registered with a general practitioner of the UK National Health Service (NHS). A total of 503,325 individuals were included between 2006–2010. All study participants provided informed consent and the approval was obtained by the North West Multicentre Research Ethics Committee. Detailed methods used by UK Biobank have been described elsewhere (16).

The FinnGEN Project

The FinnGEN Project launched in 2017, is a study that combines genome information with digital health care data, based on a public-private partnership between Finnish universities, biobanks, hospital districts, and several international pharmaceutical companies (17). It aims to collect biological samples from 500,000 participants in Finland over six years with the aim of improving human health through genetic research, and ultimately identify new therapeutic targets and diagnostics for treating numerous diseases. The collected samples consist of two entities: 1) legacy samples (prospected number ~200,000), mainly collected by the THL

(National Institute for Health and Welfare); and 2) ~300 000 prospective samples which will mainly be collected by hospital biobanks.

The Joint T2D-CHD GWAS reported by Zhao et al.

The Joint T2D-CHD GWAS is a genome-wide, multi-ancestry study of genetic variation for both T2D and CHD in up to 265,678 subjects for T2D and 260,365 subjects for CHD (18). A meta-analysis was performed on data from eight different studies with 48,437 individuals (13,525 T2D cases and 34,912 controls); four studies (PROMIS, RACE, BRAVE, and EPIDREAM) included participants of South Asian origin (n = 28,139; 9,654 T2D cases and 18,485 controls) and four studies (FINRISK, MedStar, MDC, and PennCATH) included subjects of European origin (n = 20,298; 3,871 T2D cases and 16,427 controls). This study further used published data from the DIAGRAM Consortium and conducted combined discovery analysis on 198,258 participants (48,365 T2D cases and 149,893 controls).

The MEGASTROKE Consortium

This consortium performed a multi-ancestry GWAS of 520,000 subjects and identified 32 loci associated with stroke and stroke subtypes. The descriptions for individual cohorts are available in previous reports (19).

The SUMMIT Consortium

This consortium conducted a meta-analysis of multiple GWASs for diabetic kidney disease in up to 40,340 subjects with diabetes. Meta-analyses were performed separated in subjects with T1D and T2D, and were then combined yielding 38 meta-analyses in total. The individual cohorts have been described elsewhere (20; 21).

The CKDGen Consortium

The CKDGen Consortium is an international collaborative effort dedicated to the investigation of the genetic underpinnings of kidney function in health and disease (22). This consortium includes studies with individuals of European, East and South Asian, African American, and Hispanic ancestry. Recently, it has expanded to study not only DNA sequence variations but also epigenetic modifications that integrate the influence of genetics and environment, through epigenome-wide association studies. The detailed methods used by the CKDGen Consortium have been previously described (22).

Supplementary Methods

Genotyping, quality control (QC), and imputation

In the HKDR, HKDB Phase 1 and 2 Studies, DNA samples were genotyped using one of three arrays: 1) Illumina Omni2.5 + Exome Array, 2) Infinium® Global Screening Array, and 3) Infinium® Asian Screening Array. Samples from the FIELD Study underwent genotyping with the Affymetrix Axiom Array.

We applied the same standard quality control procedures on each genome-wide SNP array data. The per-individual QC of genotype data consists of four steps: 1) sex checking based on the genotype call from chromosomes X and Y; 2) detection of low-quality samples based on call rate and heterozygosity rate; 3) detection of possible familial relationship or duplicated individuals using estimates of identity-by-descent (IBD); 4) detection of population stratification by performing principal component (PC) analysis (Supplementary Figure S5). Only biallelic autosomal SNPs were included in the per-marker QC. SNPs were excluded from further analysis if: 1) Hardy–Weinberg equilibrium (HWE) p $<1\times10^{-4}$; 2) minor allele frequency (MAF) <1%; or 3) call rate <95%. In particular, SNPs with MAF ≥1% but ≤5% are excluded if their call rate is <99%.

Within each individual cohort, we imputed the genotype data to the 1000 Genomes Project phase III reference panel (October 2014) using the Michigan Imputation Server (23). SNPs with MAF <1%, or imputation quality score Rsq <0.5 were removed. Finally, ~6.6 million SNPs overlapped among the discovery cohorts (i.e. HKDR and HKDB Phase 1 Studies) were included in the meta-analysis of GWASs for CHD.

Outcome variables

In the HKDR, HKDB Phase 1 and 2 Studies, all clinical endpoints were defined based on the discharge principle diagnoses of hospital admissions and mortality until 31st December,

2019. We retrieved the data of hospital admissions from the Hong Kong Hospital Authority Central Computer System, which records the admissions to all public hospitals, deaths and causes of death. Hospital discharge principal diagnoses coded by the International Classification of Diseases, Ninth Revision (ICD-9) were used to identify the outcome event. Ascertainment of our primary endpoint CHD was based on a composite of acute myocardial infarction (MI), nonfatal ischemic heart disease, or angina pectoris. The secondary endpoints of this study were MI, stroke (defined as the occurrence of ischemic stroke except transient ischemic attack, hemorrhagic stroke, or acute but ill-defined cerebrovascular disease), peripheral vascular disease (PVD, defined as the occurrence of amputation, gangrene, or peripheral revascularization), cardiovascular disease (CVD, defined as the occurrence of CHD, stroke, or PVD), congestive heart failure (CHF, defined as the occurrence of new or worsening signs and/or symptoms, and initiation or up-titration of oral or intravenous diuretics with appropriate response), chronic kidney disease (CKD, defined as the requirement of chronic dialysis or kidney transplant, or having sustained eGFR <60 ml/min/1.73 m^2 in 90 days apart), and kidney failure (KF, defined as the requirement of chronic dialysis or kidney transplant, or having sustained eGFR ≤15 ml/min/1.73 m^2 in 90 days apart). In the FIELD study, CHD was defined based on a composite of non-fatal MI, coronary death and revascularization.

In the case-control analysis, patients with a particular endpoint occurred either at baseline or during follow-up were classified as cases for that endpoint. Patients were classified as controls if they had duration of diabetes ≥10 years, and were free from CVD (CKD) for the analysis of cardiovascular (renal) endpoints. In the prospective analysis, patients with a particular endpoint at enrolment were excluded from the analysis of that endpoint. Follow-up time was calculated as the period from enrolment to the first occurrence of endpoint, the date of death or 31st December 2019, whichever came first.

For individuals taking anti-hypertensive medications, 15 mmHg was added to systolic blood pressure (SBP) and 10 mmHg was added to diastolic blood pressure (DBP) in the replication analysis for BP, suggested by previous study (24). Hypertension was defined as BP ≥130/80 mmHg, or use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or use of other antihypertensive medications (25). According to the American Diabetes Association (ADA) guideline, ABC goals refer to 1) HbA_{1c} <7%; 2) BP <130/80 mmHg; 3) and low-density lipoprotein cholesterol (LDL-C) <2.6 mmol/l (26).

Phenome-wide association study (PheWAS)

To understand the pathways by which the identified locus/loci might be related to cardiovascular diseases, we looked up associations of the sentinel variant(s) with a wide range of risk factors, molecular traits and clinical disorders from 11 data sources, including the available GWAS datasets and the web portals. For this analysis, phenotype associations were queried using the PheWAS database available at the T2D Knowledge Portal (https://t2d.hugeamp.org/), the PhenoScanner (27; 28), the GWAS Atlas (29), the GWAS Catalog (https://www.ebi.ac.uk/gwas/), the Open Targets Genetics Portal (30), the UKB PheWeb (https://pheweb.org/UKB-Neale/), and the FinnGEN PheWeb (https://r5.finngen.fi/about) (17). We additionally queried the published GWAS contributed by the BBJ Project (31; 32), the UKB and ICBP blood pressure GWAS (24), the Heart Rate and Hypertension GWAS (33), and the GIANT UK Biobank GWAS (34). We considered only the phenotypes that were associated with the identified variant(s) at $P \leq 5\times10^{-8}$, and further tested these associations in the HKDR Study, the HKDB Phase 1 and 2 Studies if the phenotype data were available.

Bioinformatic analyses

We carried out the cis-expression quantitative trait loci (eQTL) and multi-tissue transcriptome-wide association study (TWAS) analyses to examine underlying biological pathways linking variants to cardiovascular disease. In the eQTL analysis, we determined whether the identified variant(s) influence(s) levels of tissue-specific gene expression, using the data from the Genotype Tissue Expression version 8 (GTEx-v8) Portal (https://gtexportal.org/home/). Expression and genotype data of these samples were obtained using the RNA-seq (Illumina TruSeq; Illumina Inc) and whole-genome sequencing, respectively. Only variants with MAF ≥1% and within 1 MB window upstream and downstream of the transcription start site for each gene were included. For each gene and tissue, the effect of genotype on gene expression level was assessed by linear regression. A false discovery rate threshold of ≤0.05 was applied to identify a significant eQTL. To combine gene expression data across tissues, meta-analysis under a random effects model was implemented in Metasoft (35).

In the multi-tissue TWAS analysis, we tested whether the genetic variants exert effects on CHD risk through regulating tissue-specific expression of causal gene. We adopted a gene-based association approach to investigate the associations between genetically regulated gene expression and CHD risk at loci of interest. This analysis was implemented by the S-PrediXcan function from the MetaXcan toolset (version 0.7.5), leveraging on 1) the meta-analysis association statistics for CHD from our discovery cohorts (the HKDR and HKDB Phase 1 studies) and, 2) the MASHR models of GTEx-v8 release eQTL (36-38). We used the genotype covariance matrices based on the European populations in the 1000 Genomes Project to account for LD structure in the analysis. The tissue-specific associations obtained from S-PrediXcan were then meta-analyzed using MultiXcan. MultiXcan provided the evidence of multi-tissue association by integrating the information across all the tissue types under investigation while accounting for the correlation among them.

Statistical analysis

All analyses were performed using PLINK v1.9 and v2.0 (39), IBM SPSS Statistics 26, and R 3.4.4 (http://www.r-project.org/, 31st December, 2019) unless specified otherwise. Data are described with percentage (*n*), mean ± SD, or median (Q1-Q3). Meta-analysis was implemented by METAL software (40). FUMA was used to annotate, prioritize, and interpret the GWAS results (41). Regional plot around genome-wide locus were visualized using LocusZoom (http://csg.sph.umich.edu/locuszoom/). Differences between groups were tested with chi-squared test, Student's T-test, or Mann-Whitney test, as appropriate. *P*-values <0.05 and $<5.0\times10^{-8}$ were considered significant and genome-wide significant, respectively. To qualify as replication, an association was required to have $P \leq 0.05$ and a consistent direction of effect.

Within cohort, logistic regression and Cox proportional hazards regression were used to examine the associations between genetic variants under an additive genetic model and diabetes cardio-renal complications (e.g. CHD, MI, stroke, PVD, CVD, CHF, CKD and KF), with different covariate adjustments in the case-control and prospective analysis, respectively. Using a cross-sectional study design, associations of genetic variants with baseline binary (e.g. status of hypertension) and quantitative traits (e.g. SBP, DBP and body height) were tested respectively by logistic and linear regression adjusted for sex, age, duration of diabetes and PCs in each cohort. Odds ratios (OR) or hazard ratios (HR) with their 95% confidence intervals (CI), or β ± SE were calculated in these analyses. Results from individual cohorts were combined by inverse-variance weighted meta-analysis using a fixed effects model. Cochran's Q-test was used to assess the heterogeneity of effect between studies. We accounted for potential population stratification and relatedness of the individuals by adjustment for PCs in all association analysis and subsequent genomic control correction in GWAS analysis.

To test for the gene-(ABC achievement) interaction effects on new-onset diabetes cardiovascular endpoints (i.e. CHD and MI), we performed Cox regression based on the model including two main effects (i.e. the achievement of each ABC target at baseline ('yes' [coded as 1] vs. 'no' [coded as 0]), and the lead SNP), the interaction (product) term of main effects and covariates in a combined cohort of Chinese patients with T2D (HKDR Study, HKDB Phase 1 and 2 Studies). For each significant interaction effect, a subgroup analysis was performed by Cox regression to examine the association between the goal attainment and endpoint, stratified by different genotypes. In both interaction and subgroup analyses, we adjusted for study cohorts (i.e. HKDR Study, HKDB Phase 1 and 2 Studies), enrolment year, sex, age, duration of diabetes, and PCs.

Supplementary results

Biological insight of the newly identified variant rs10171703

We looked up our genome-wide significant locus using the GTEx-v8 expression eQTL data in 47 tissues (n = 73 – 706). The major C-allele of the lead variant rs10171703 was significantly associated with increased expression of the *PDE1A* gene in both subcutaneous adipose (n = 581; NES ± SE = 0.110 ± 0.028; $P = 1.1\times10^{-4}$) and sun exposed skin tissues (n = 605; NES ± SE = 0.091 ± 0.025; $P = 2.0\times10^{-4}$), after considering false discovery rate (Supplementary Figures S2 and S3). The variant rs10171703 moderately correlated (was in partial LD) with the peak eQTL SNP (i.e. rs4091077) at *PDE1A* gene in subcutaneous adipose tissue (r^2 = 0.511) but did not correlate with (independent of) the eQTL peak (i.e. rs934260) in the sun exposed skin tissue (r^2 = 0.021) (Supplementary Table S12). Meta-analysis of all the 47 tissues available in GTEx-v8 yielded a p-value of 2.6×10^{-11} for association between rs10171703 and *PDE1A* expression under a random effects model (Supplementary Figures S2).

We further performed multi-tissue TWAS analysis to test whether the genetic variants exert effects on CHD risk through regulating tissue-specific expression of causal gene. Using our meta-analysis summary statistics within the *PDE1A* region and the GTEx-v8 eQTL data in S-PrediXcan, *PDE1A* showed genetically-mediated differential expression in the tissues of thyroid ($P = 8.0\times10^{-3}$) and muscularis of esophagus (P = 0.019) (Supplementary Table S13). However, such observation was not seen in the subcutaneous adipose (P = 0.807) and sun exposed skin (P = 0.957) tissues (Supplementary Table 13).

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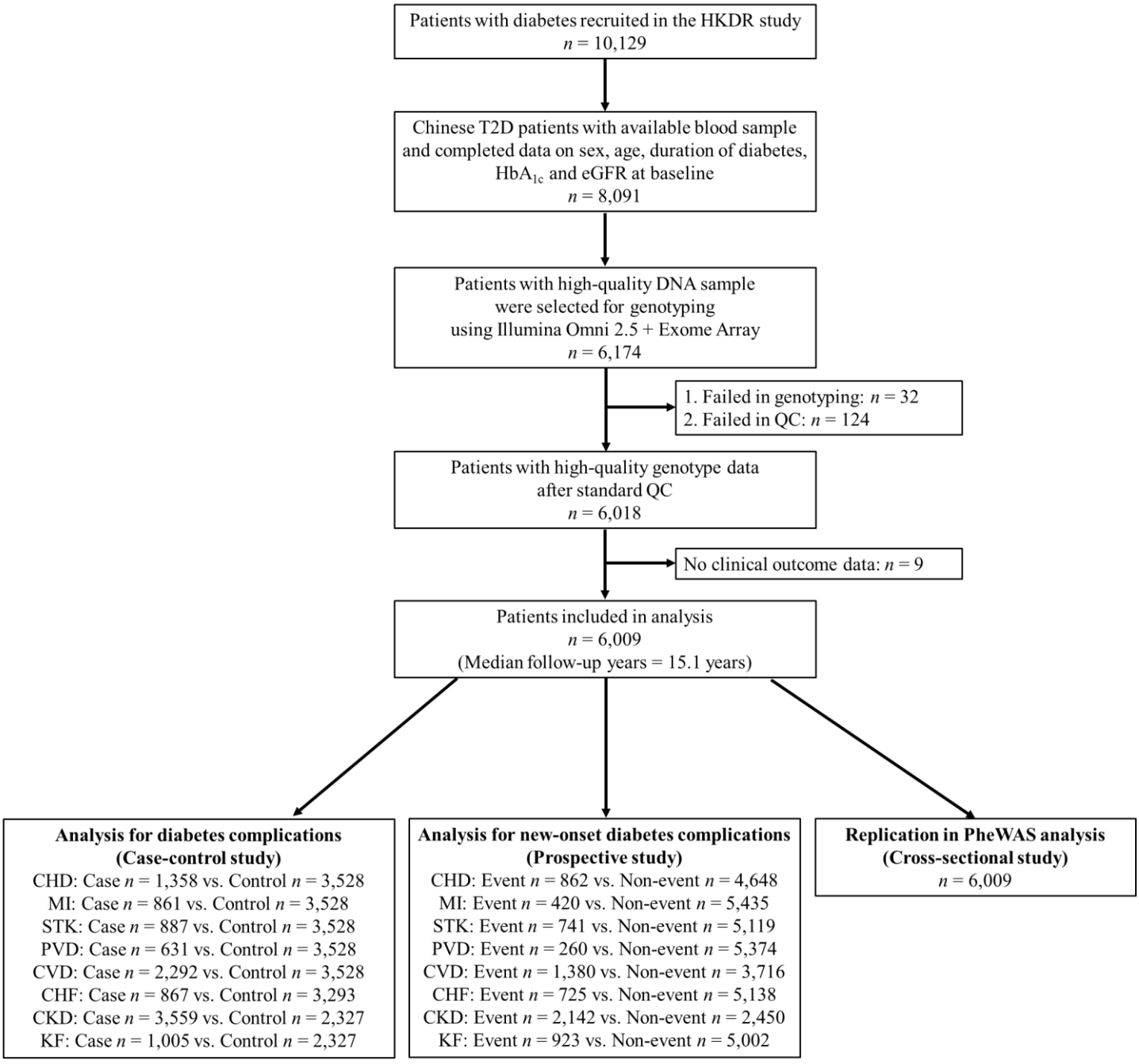
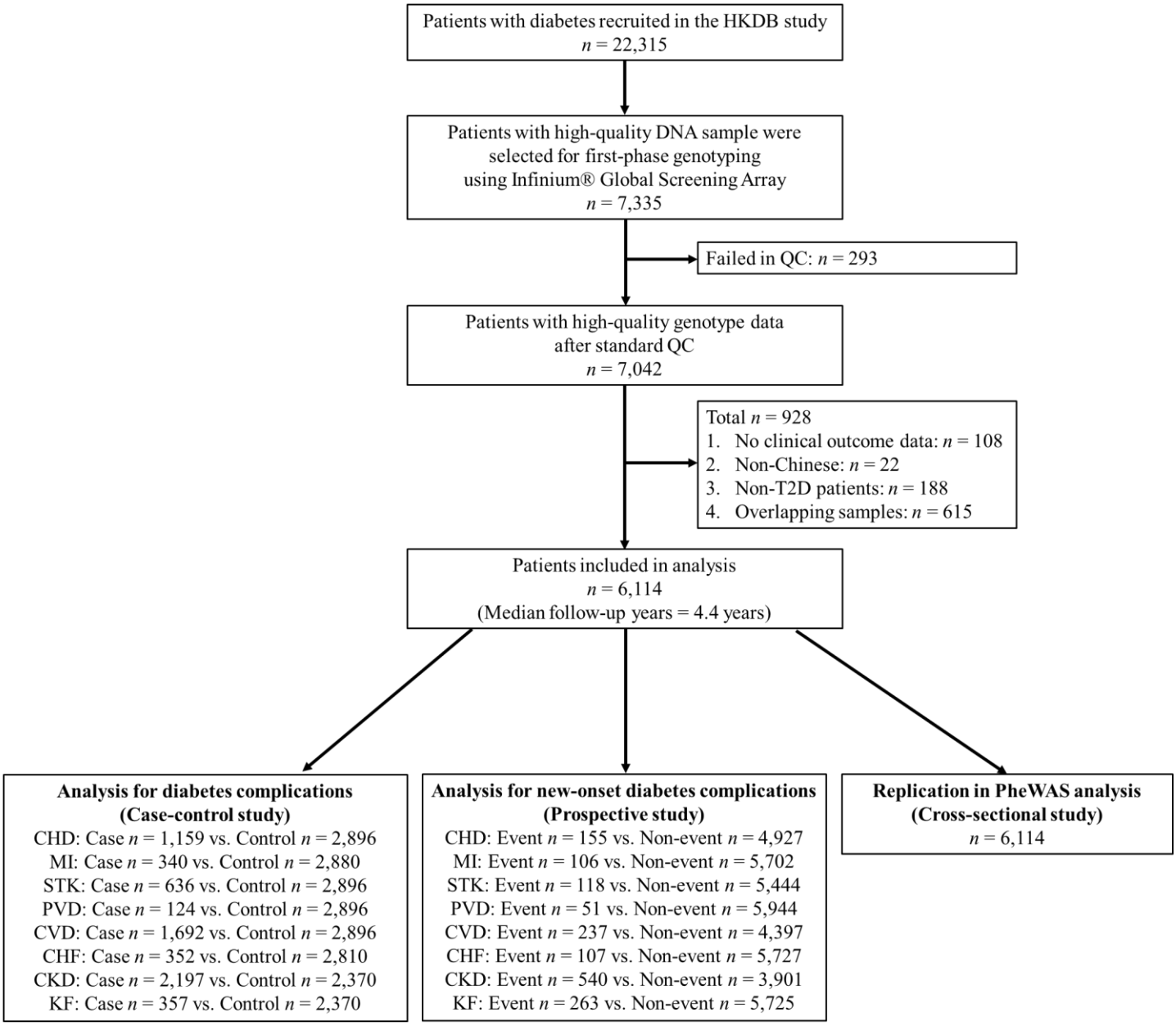
Supplementary Figure S1. Number of individuals included in A) the HKDR Study, B) the HKDB Phase 1 Study], and C) the HKDB Phase 2 Study. Each of the cardio-renal outcome was defined based on the discharge principle diagnoses of hospital admissions and mortality until 31st December, 2019. Hospital discharge principal diagnoses were coded by the International Classification of Diseases (ICD), version 9 and were used to identify the outcome events, which occurred either at baseline (i.e. history of outcome) or during follow-up (i.e. incidence of outcome). In the case-control analysis, patients who had a particular outcome either at baseline or during follow-up were enrolled in the group of cases. The counterpart controls for each outcome were defined as patients who 1) had duration of diabetes >10 years, and 2) were free from cardiovascular (chronic kidney) disease for the analysis of cardiovascular (renal) outcomes. In the prospective analysis, we included the patients who had no history but incidence of a particular outcome in the event group, while patients without both history and incidence of the outcome were included in the non-event group.

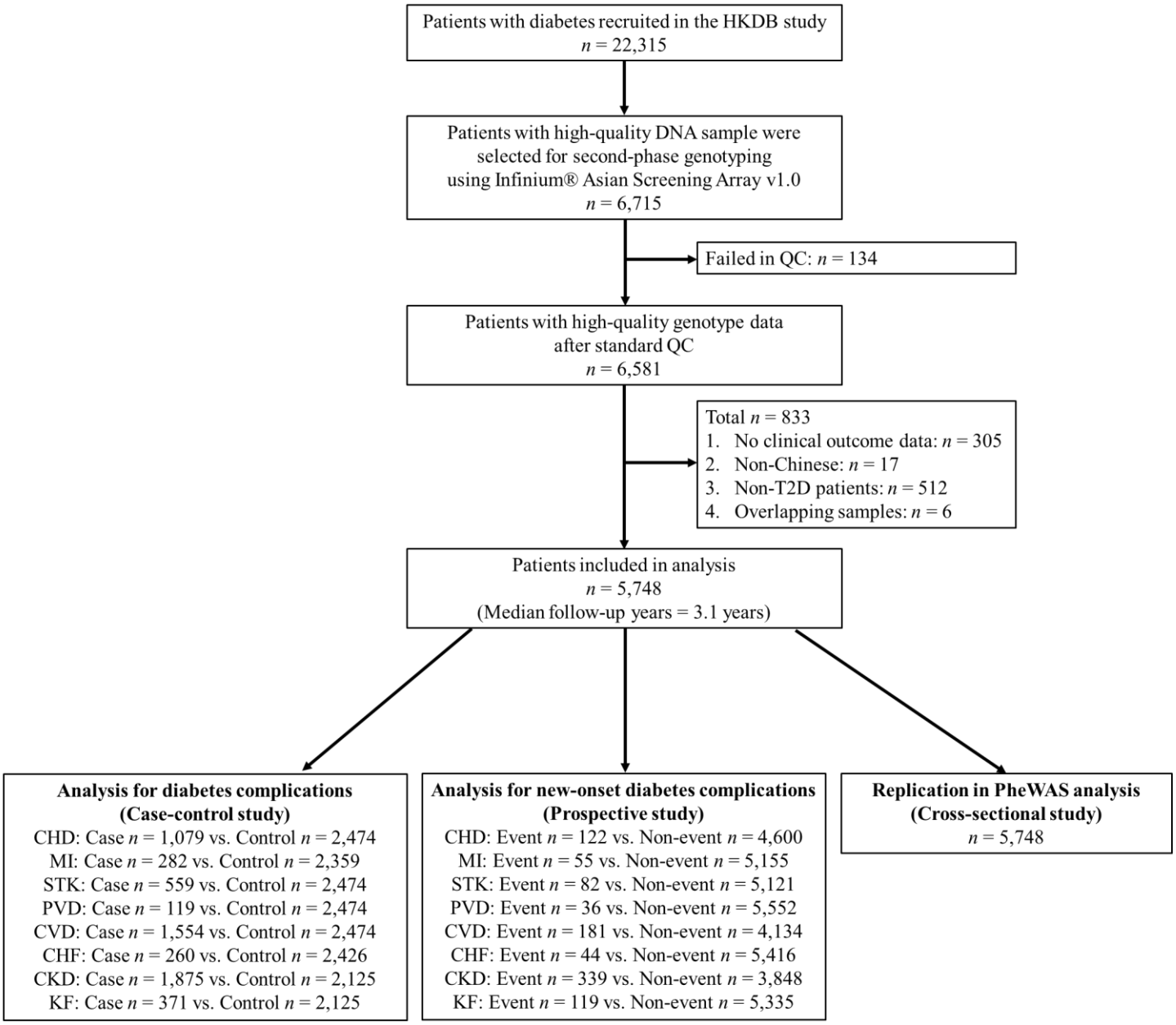
A


Patients with diabetes recruited in the HKDR study
n = 10,129
Chinese T2D patients with available blood sample and completed data on sex, age, duration of diabetes, HbA1c and eGFR at baseline
n = 8,091
Patients with high-quality DNA sample were selected for genotyping using Illumina Omni 2.5 + Exome Array
n = 6,174
1. Failed in genotyping: n = 32
2. Failed in QC: n = 124
Patients with high-quality genotype data after standard QC
n = 6,018
No clinical outcome data: n = 9
Patients included in analysis
n = 6,009
(Median follow-up years = 15.1 years)
Analysis for diabetes complications (Case-control study)
CHD: Case n = 1,358 vs. Control n = 3,528
MI: Case n = 861 vs. Control n = 3,528
STK: Case n = 887 vs. Control n = 3,528
PVD: Case n = 631 vs. Control n = 3,528
CVD: Case n = 2,292 vs. Control n = 3,528
CHF: Case n = 867 vs. Control n = 3,293
CKD: Case n = 3,559 vs. Control n = 2,327
KF: Case n = 1,005 vs. Control n = 2,327
Analysis for new-onset diabetes complications (Prospective study)
CHD: Event n = 862 vs. Non-event n = 4,648
MI: Event n = 420 vs. Non-event n = 5,435
STK: Event n = 741 vs. Non-event n = 5,119
PVD: Event n = 260 vs. Non-event n = 5,374
CVD: Event n = 1,380 vs. Non-event n = 3,716
CHF: Event n = 725 vs. Non-event n = 5,138
CKD: Event n = 2,142 vs. Non-event n = 2,450
KF: Event n = 923 vs. Non-event n = 5,002
Replication in PheWAS analysis (Cross-sectional study)
n = 6,009

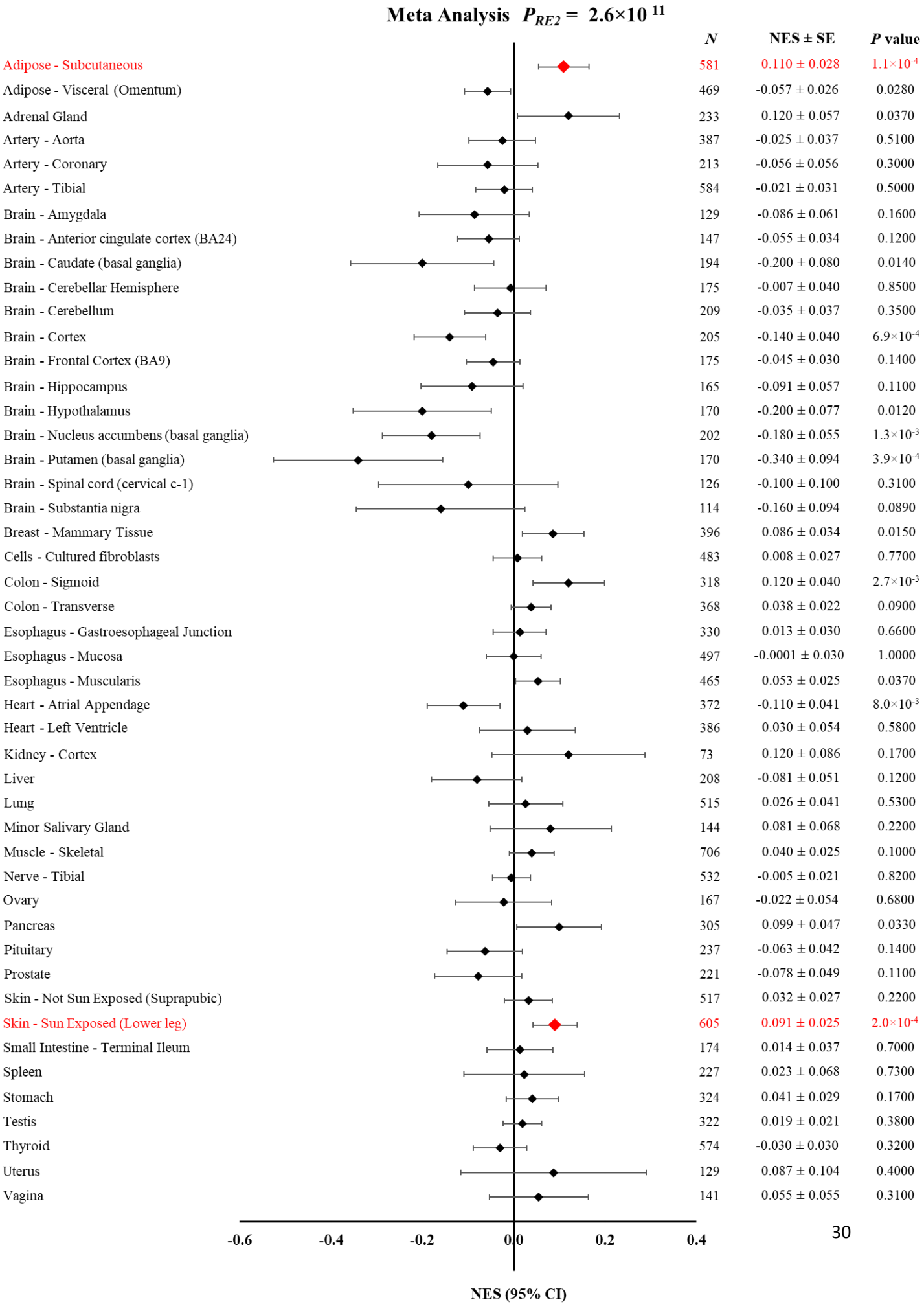
B


Patients with diabetes recruited in the HKDB study
n = 22,315
Patients with high-quality DNA sample were selected for first-phase genotyping using Infinium® Global Screening Array
n = 7,335
Failed in QC: n = 293
Patients with high-quality genotype data after standard QC
n = 7,042
Total n = 928
1. No clinical outcome data: n = 108
2. Non-Chinese: n = 22
3. Non-T2D patients: n = 188
4. Overlapping samples: n = 615
Patients included in analysis
n = 6,114
(Median follow-up years = 4.4 years)
Analysis for diabetes complications (Case-control study)
CHD: Case n = 1,159 vs. Control n = 2,896
MI: Case n = 340 vs. Control n = 2,880
STK: Case n = 636 vs. Control n = 2,896
PVD: Case n = 124 vs. Control n = 2,896
CVD: Case n = 1,692 vs. Control n = 2,896
CHF: Case n = 352 vs. Control n = 2,810
CKD: Case n = 2,197 vs. Control n = 2,370
KF: Case n = 357 vs. Control n = 2,370
Analysis for new-onset diabetes complications (Prospective study)
CHD: Event n = 155 vs. Non-event n = 4,927
MI: Event n = 106 vs. Non-event n = 5,702
STK: Event n = 118 vs. Non-event n = 5,444
PVD: Event n = 51 vs. Non-event n = 5,944
CVD: Event n = 237 vs. Non-event n = 4,397
CHF: Event n = 107 vs. Non-event n = 5,727
CKD: Event n = 540 vs. Non-event n = 3,901
KF: Event n = 263 vs. Non-event n = 5,725
Replication in PheWAS analysis (Cross-sectional study)
n = 6,114

C

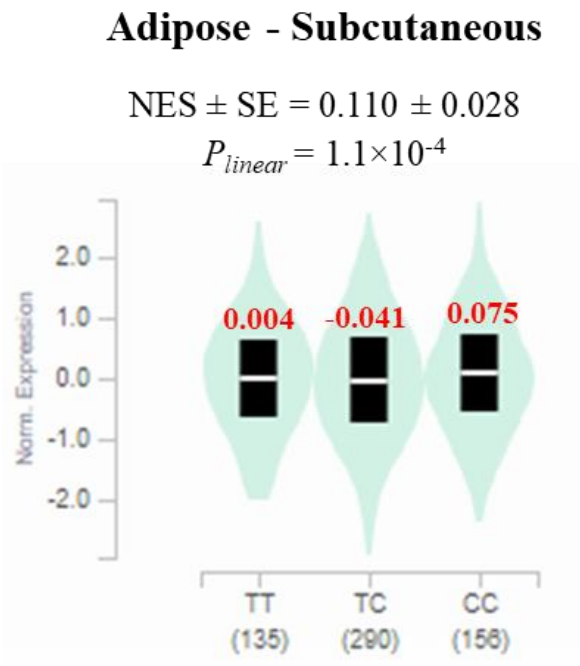

Patients with diabetes recruited in the HKDB study
n = 22,315
Patients with high-quality DNA sample were selected for second-phase genotyping using Infinium® Asian Screening Array v1.0
n = 6,715
Failed in QC: n = 134
Patients with high-quality genotype data after standard QC
n = 6,581
Total n = 833
1. No clinical outcome data: n = 305
2. Non-Chinese: n = 17
3. Non-T2D patients: n = 512
4. Overlapping samples: n = 6
Patients included in analysis
n = 5,748
(Median follow-up years = 3.1 years)
Analysis for diabetes complications (Case-control study)
CHD: Case n = 1,079 vs. Control n = 2,474
MI: Case n = 282 vs. Control n = 2,359
STK: Case n = 559 vs. Control n = 2,474
PVD: Case n = 119 vs. Control n = 2,474
CVD: Case n = 1,554 vs. Control n = 2,474
CHF: Case n = 260 vs. Control n = 2,426
CKD: Case n = 1,875 vs. Control n = 2,125
KF: Case n = 371 vs. Control n = 2,125
Analysis for new-onset diabetes complications (Prospective study)
CHD: Event n = 122 vs. Non-event n = 4,600
MI: Event n = 55 vs. Non-event n = 5,155
STK: Event n = 82 vs. Non-event n = 5,121
PVD: Event n = 36 vs. Non-event n = 5,552
CVD: Event n = 181 vs. Non-event n = 4,134
CHF: Event n = 44 vs. Non-event n = 5,416
CKD: Event n = 339 vs. Non-event n = 3,848
KF: Event n = 119 vs. Non-event n = 5,335
Replication in PheWAS analysis (Cross-sectional study)
n = 5,748

Supplementary Figure S2. Multi-tissue eQTL comparison between *PDE1A* expression and rs10171703. The tissues include those with >70 samples, and with matched gene expression and genotype data in the Genotype Tissue Expression (GTEx) database (http://www.gtexportal.org/home/). The estimate corresponds to the normalized effect size (NES) of the eQTL, which is defined as the slope (i.e. β-coefficient) of the linear regression between genotype and expression, and is computed as the effect of the alternative C-allele relative to the reference T-allele. The *p*-values were obtained for each variant-gene pair by testing the null hypothesis that NES is equal to zero. A false discovery rate (FDR) threshold of ≤0.05 was applied to identify genes with a significant eQTL (highlighted in red colour). To combine gene expression data across many tissues, meta-analysis was conducted using a random effects model named "RE2" in Metasoft (35).

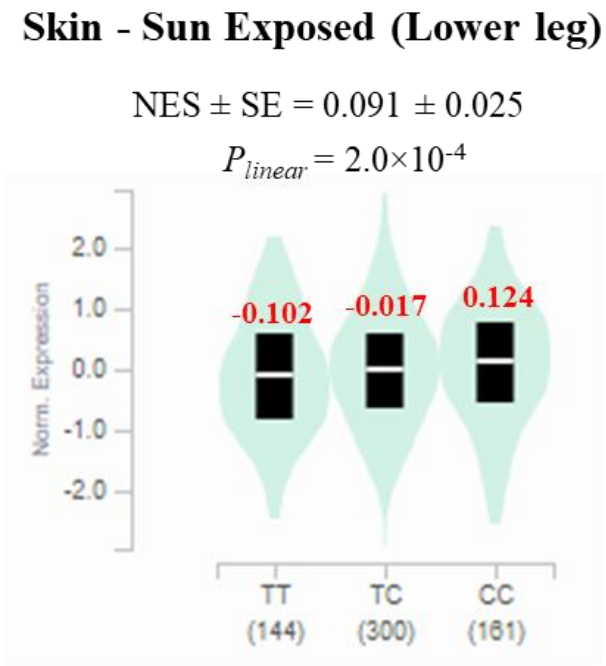

Meta Analysis $P_{RE2} = 2.6\times10^{-11}$
N
NES ± SE
P value
Adipose - Subcutaneous 581 0.110 ± 0.028 1.1×10-4
Adipose - Visceral (Omentum) 469 -0.057 ± 0.026 0.0280
Adrenal Gland 233 0.120 ± 0.057 0.0370
Artery - Aorta 387 -0.025 ± 0.037 0.5100
Artery - Coronary 213 -0.056 ± 0.056 0.3000
Artery - Tibial 584 -0.021 ± 0.031 0.5000
Brain - Amygdala 129 -0.086 ± 0.061 0.1600
Brain - Anterior cingulate cortex (BA24) 147 -0.055 ± 0.034 0.1200
Brain - Caudate (basal ganglia) 194 -0.200 ± 0.080 0.0140
Brain - Cerebellar Hemisphere 175 -0.007 ± 0.040 0.8500
Brain - Cerebellum 209 -0.035 ± 0.037 0.3500
Brain - Cortex 205 -0.140 ± 0.040 6.9×10-4
Brain - Frontal Cortex (BA9) 175 -0.045 ± 0.030 0.1400
Brain - Hippocampus 165 -0.091 ± 0.057 0.1100
Brain - Hypothalamus 170 -0.200 ± 0.077 0.0120
Brain - Nucleus accumbens (basal ganglia) 202 -0.180 ± 0.055 1.3×10-3
Brain - Putamen (basal ganglia) 170 -0.340 ± 0.094 3.9×10-4
Brain - Spinal cord (cervical c-1) 126 -0.100 ± 0.100 0.3100
Brain - Substantia nigra 114 -0.160 ± 0.094 0.0890
Breast - Mammary Tissue 396 0.086 ± 0.034 0.0150
Cells - Cultured fibroblasts 483 0.008 ± 0.027 0.7700
Colon - Sigmoid 318 0.120 ± 0.040 2.7×10-3
Colon - Transverse 368 0.038 ± 0.022 0.0900
Esophagus - Gastroesophageal Junction 330 0.013 ± 0.030 0.6600
Esophagus - Mucosa 497 -0.0001 ± 0.030 1.0000
Esophagus - Muscularis 465 0.053 ± 0.025 0.0370
Heart - Atrial Appendage 372 -0.110 ± 0.041 8.0×10-3
Heart - Left Ventricle 386 0.030 ± 0.054 0.5800
Kidney - Cortex 73 0.120 ± 0.086 0.1700
Liver 208 -0.081 ± 0.051 0.1200
Lung 515 0.026 ± 0.041 0.5300
Minor Salivary Gland 144 0.081 ± 0.068 0.2200
Muscle - Skeletal 706 0.040 ± 0.025 0.1000
Nerve - Tibial 532 -0.005 ± 0.021 0.8200
Ovary 167 -0.022 ± 0.054 0.6800
Pancreas 305 0.099 ± 0.047 0.0330
Pituitary 237 -0.063 ± 0.042 0.1400
Prostate 221 -0.078 ± 0.049 0.1100
Skin - Not Sun Exposed (Suprapubic) 517 0.032 ± 0.027 0.2200
Skin - Sun Exposed (Lower leg) 605 0.091 ± 0.025 2.0×10-4
Small Intestine - Terminal Ileum 174 0.014 ± 0.037 0.7000
Spleen 227 0.023 ± 0.068 0.7300
Stomach 324 0.041 ± 0.029 0.1700
Testis 322 0.019 ± 0.021 0.3800
Thyroid 574 -0.030 ± 0.030 0.3200
Uterus 129 0.087 ± 0.104 0.4000
Vagina 141 0.055 ± 0.055 0.3100
-0.6
-0.4
-0.2
0.0
0.2
0.4
NES (95% CI)

Supplementary Figure S3. Gene expression level of *PDE1A* according to the genotypes of rs10171703 in the A) adipose (*n* = 581) and B) skin tissues (*n* = 605), using data from the GTEx portal (http://www.gtexportal.org/home/). The normalized effect size (NES) of the eQTL, is defined as the slope (i.e. β-coefficient) of the linear regression between genotype and expression, and is computed as the effect of the alternative C-allele relative to the reference T-allele. The *p*-values were obtained for each variant-gene pair by testing the null hypothesis that NES is equal to zero.

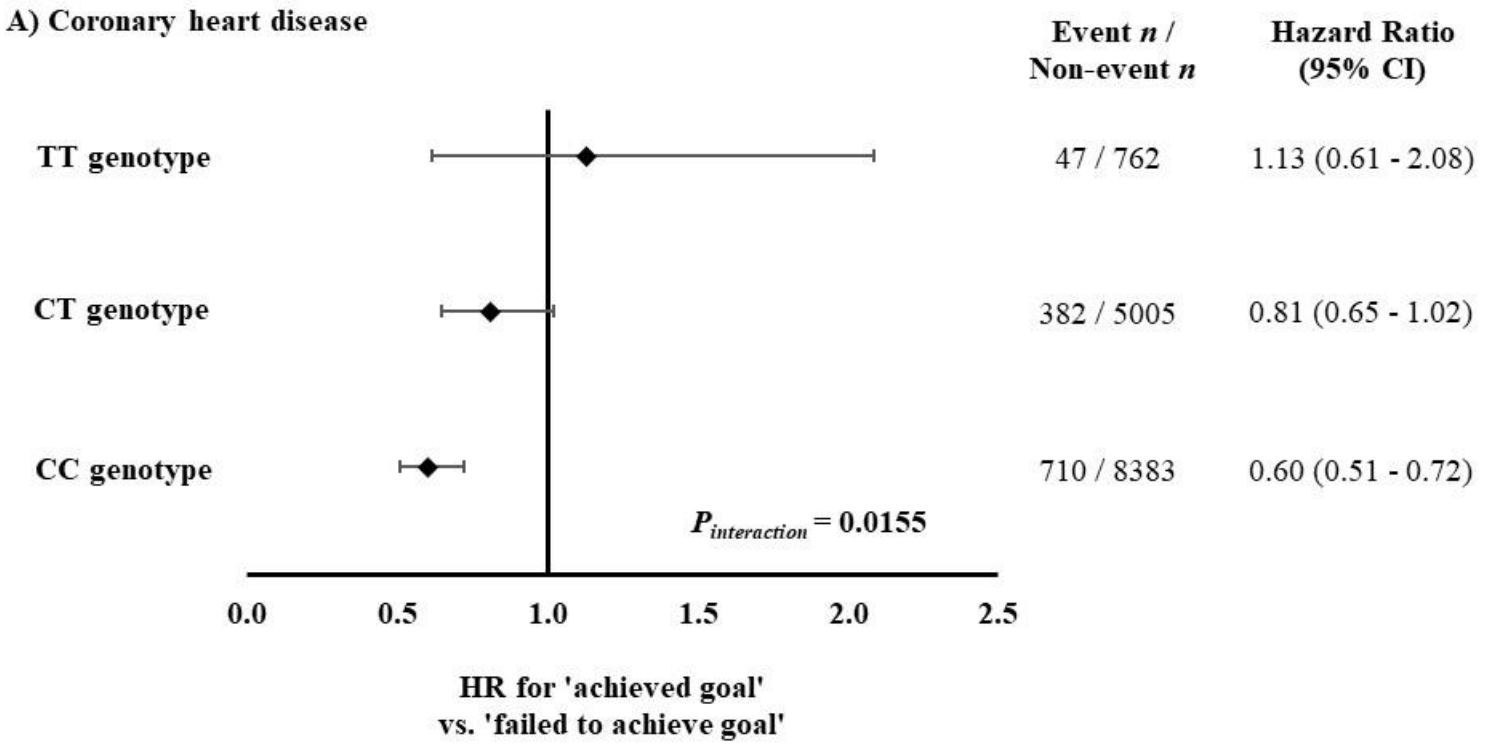
A)

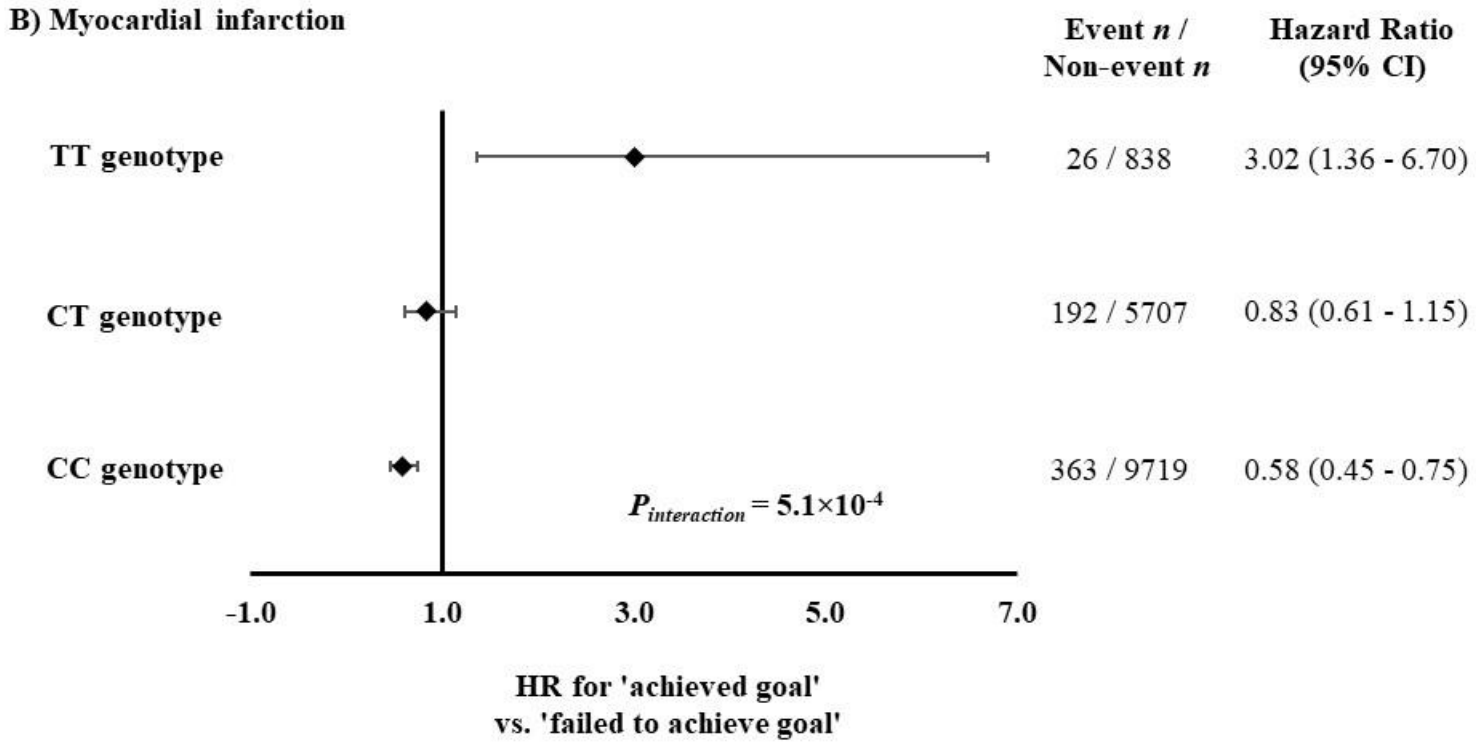


B)

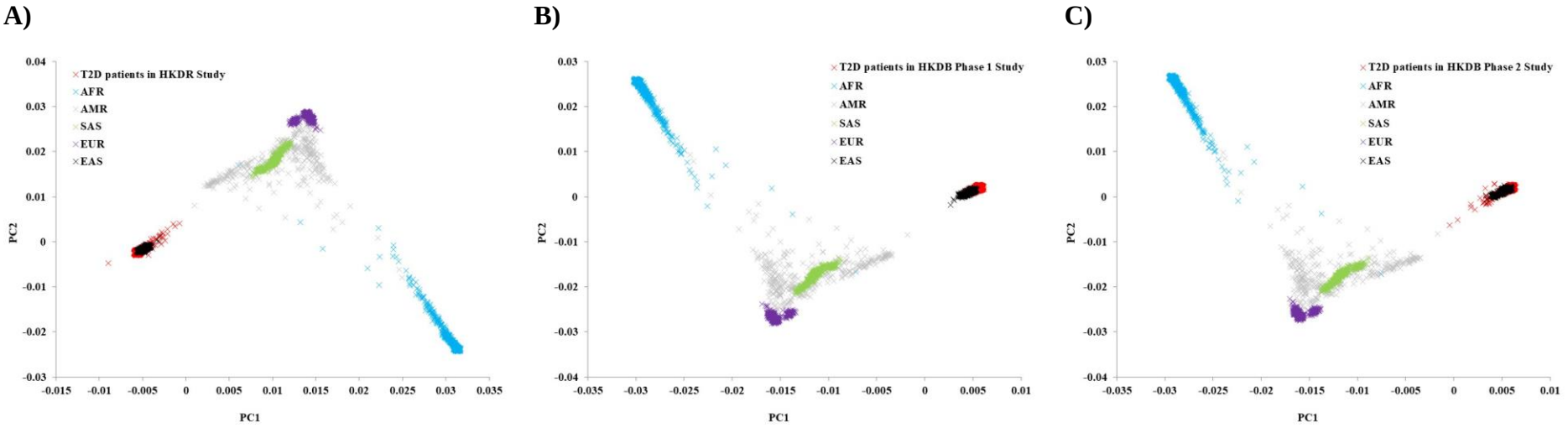


Supplementary Figure S4. Association of blood pressure goal attainment with new-onset coronary heart disease (A) and myocardial infarction (B) according to *PDE1A* rs10171703 genotype among Chinese patients with type 2 diabetes. These analyses were conducted in the combined cohort of the HKDR Study, the HKDB Phase 1 and 2 Studies. $P_{interaction}$ was the *p*-value of the interaction term obtained from the Cox regression model including two main effects (e.g. *PDE1A* rs10171703 and achievement of blood pressure goal [i.e. SBP <130 mmHg and DBP <80 mmHg]), the interaction term of main effects, and the covariates (i.e. study cohorts [HKDR Study, HKDB Phase 1 and 2 Studies], enrolment year, sex, age, duration of diabetes, and principal components [PCs]). Hazard ratio (HR) and 95% CI were obtained from the Cox regression model assessing the association between the achievement of blood pressure goal ('yes' [coded as 1] vs. 'no' [coded as 0]) and incidence of diabetes cardiovascular complications, adjusting for study cohorts (HKDR Study, HKDB Phase 1 and 2 Studies), enrolment year, sex, age, duration of diabetes, and PCs. Event: patients had no history but incidence of outcome; non-event: patients had neither history nor incidence of outcome.




B) Myocardial infarction
Event n / Non-event n
Hazard Ratio (95% CI)
TT genotype
26 / 838
3.02 (1.36 - 6.70)
CT genotype
192 / 5707
0.83 (0.61 - 1.15)
CC genotype
363 / 9719
0.58 (0.45 - 0.75)
$P_{interaction} = 5.1 \times 10^{-4}$
-1.0
1.0
3.0
5.0
7.0
HR for 'achieved goal' vs. 'failed to achieve goal'

Supplementary Figure S5. Principal component analysis (PCA) in the HKDR Study, and the HKDB Phase 1 and 2 Studies. The PCA plots show the first two principal components, based on genotype data of 26 different populations from the 1000 Genomes Project, as well as each cohort of Chinese patients with type 2 diabetes (T2D) in this study [(A) 6,009 patients with T2D from the HKDR Study; (B) 6,114 patients with T2D from the HKDB Phase 1 Study; and (C) 5,748 patients with T2D from the HKDB Phase 2 Study]. The 26 populations from the 1000 Genomes Project have been divided into 5 super populations: 1) African (AFR) includes Yoruba in Ibadan, Nigeria, Luhya in Webuye, Kenya, Gambian in Western Divisions in the Gambia, Mende in Sierra Leone, Esan in Nigeria, Americans of African Ancestry in SW USA, and African Caribbeans in Barbados; 2) Ad Mixed American (AMR) includes Mexican Ancestry from Los Angeles USA, Puerto Ricans from Puerto Rico, Colombians from Medellin, and Colombia, Peruvians from Lima, Peru; 3) South Asian (SAS) includes Gujarati Indian from Houston, Texas, Punjabi from Lahore, Pakistan, Bengali from Bangladesh, Sri Lankan Tamil from the UK, and Indian Telugu from the UK; 4) European (EUR) includes Utah Residents (CEPH) with Northern and Western European Ancestry, Toscani in Italia, Finnish in Finland, British in England and Scotland, and Iberian Population in Spain; and 5) East Asian (EAS) includes Han Chinese in Beijing, China, Japanese in Tokyo, Japan, Southern Han Chinese, Chinese Dai in Xishuangbanna, China, and Kinh in Ho Chi Minh City, Vietnam.



Supplementary Table S1. Clinical characteristics for all Chinese patients with type 2 diabetes included in the two-stage GWAS analysis, stratified by the status of coronary heart disease.

	CHD status in HKDR Study Cohort for genome-wide scan Enrolment year: 1994 - 2007 Genotyping platform: Illumina Omni 2.5 + Exome Array			**CHD status in HKDB Phase 1 Study Cohort for genome-wide scan Enrolment year: 2013 - 2019 Genotyping platform: Infinium® Global Screening Array**			**CHD status in HKDB Phase 2 Study Cohort for follow-up of top signals Enrolment year: 2014 - 2019 Genotyping platform: Infinium® Asian Screening Array v1.0**		
Phenotype	**Yes (*n* = 1,358)**	**No (*n* = 3,528)**	***P***	**Yes (*n* = 1,159)**	**No (*n* = 2,896)**	***P***	**Yes (*n* = 1,079)**	**No (*n* = 2,474)**	***P***
Clinical characteristics at baseline									
Male % (*N*)	51.4% (698)	41.3% (1,458)	<0.0001	74.2% (860)	54.4% (1,574)	<0.0001	75.9% (819)	53.7% (1,328)	<0.0001
Age (years)	61.7 ± 11.4	53.8 ± 13.1	<0.0001	65.5 ± 9.31	61.9 ± 10.1	<0.0001	64.9 ± 9.09	61.5 ± 10.2	<0.0001
Age Onset (years)	52.8 ± 11.6	47.0 ± 12.1	<0.0001	52.8 ± 10.8	47.2 ± 10.2	<0.0001	52.2 ± 10.9	45.5 ± 10.3	<0.0001
Duration of diabetes (years)	8.78 ± 7.03	6.67 ± 6.40	<0.0001	12.6 ± 8.79	14.7 ± 6.96	<0.0001	12.7 ± 9.05	16.0 ± 6.83	<0.0001
Follow-up time (years)	8.21 (3.37 - 13.6)	17.5 (14.2 - 21.8)	<0.0001	4.19 (3.38 - 4.65)	4.44 (4.09 - 4.85)	<0.0001	2.84 (2.41 - 3.33)	3.14 (2.76 - 3.51)	<0.0001
Smoking status % (*N*)	--	--	<0.0001	--	--	<0.0001	--	--	<0.0001
Non-smoker	63.7% (865)	75.3% (2,655)	--	53.2% (617)	72.0% (2,085)	--	50.8% (548)	69.8% (1,727)	--
Ex-smoker	22.2% (302)	12.8% (452)	--	33.6% (389)	18.4% (534)	--	35.2% (380)	19.3% (477)	--
Current smoker	14.0% (190)	11.7% (413)	--	13.2% (153)	9.50% (276)	--	14.0% (151)	10.8% (266)	--
Body height (m)	1.58 ± 0.08	1.58 ± 0.08	0.7005	1.63 ± 0.08	1.62 ± 0.09	<0.0001	1.63 ± 0.08	1.61 ± 0.09	<0.0001
Body weight (kg)	63.5 (56.0 - 71.5)	62.0 (54.7 - 70.0)	0.0003	70.0 (62.0 - 78.7)	66.6 (58.7 - 76.4)	<0.0001	71.1 (63.0 - 79.8)	67.0 (58.6 - 77.0)	<0.0001
BMI (kg/m^2)	25.3 (23.0 - 27.6)	24.7 (22.4 - 27.4)	<0.0001	26.1 (23.8 - 28.9)	25.6 (22.9 - 28.5)	<0.0001	26.5 (24.3 - 29.3)	25.7 (23.2 - 28.8)	<0.0001
Waist circumference (cm)									
Males	89.9 ± 9.11	87.9 ± 10.1	<0.0001	95.2 ± 10.2	93.4 ± 10.5	<0.0001	95.3 ± 10.3	93.4 ± 10.7	<0.0001
Females	85.6 ± 9.66	82.6 ± 9.88	<0.0001	89.3 ± 10.6	88.8 ± 11.2	0.4596	89.1 ± 10.4	88.5 ± 11.6	0.4415
Hip circumference (cm)	96.9 ± 7.78	96.4 ± 8.19	0.0664	96.6 ± 8.14	96.3 ± 8.24	0.3492	97.6 ± 7.51	96.9 ± 8.31	0.0338
Waist-hip-ratio	0.91 ± 0.07	0.88 ± 0.07	<0.0001	0.97 ± 0.07	0.95 ± 0.07	<0.0001	0.96 ± 0.07	0.94 ± 0.07	<0.0001
HbA_{1C} (%)	7.60 (6.60 - 8.90)	7.10 (6.30 - 8.30)	<0.0001	7.30 (6.70 - 8.30)	7.50 (6.80 - 8.40)	<0.0001	7.40 (6.70 - 8.40)	7.70 (6.90 - 8.60)	<0.0001
Total cholesterol (mmol/l)	5.14 (4.50 - 6.00)	5.10 (4.40 - 5.80)	0.0055	3.91 (3.44 - 4.53)	4.25 (3.76 - 4.80)	<0.0001	3.79 (3.30 - 4.40)	4.18 (3.67 - 4.75)	<0.0001
Triglycerides (mmol/l)	1.52 (1.09 - 2.25)	1.32 (0.92 - 2.00)	<0.0001	1.37 (0.98 - 2.00)	1.29 (0.91 - 1.89)	<0.0001	1.40 (1.00 - 2.02)	1.33 (0.92 - 1.97)	0.0047
HDL-cholesterol (mmol/l)	1.20 (1.00 - 1.42)	1.28 (1.09 - 1.54)	<0.0001	1.09 (0.92 - 1.31)	1.20 (1.01 - 1.46)	<0.0001	1.07 (0.90 - 1.28)	1.17 (0.99 - 1.41)	<0.0001
LDL-cholesterol (mmol/l)	3.10 (2.44 - 3.80)	3.00 (2.41 - 3.65)	0.0354	2.07 (1.63 - 2.58)	2.31 (1.90 - 2.76)	<0.0001	1.95 (1.55 - 2.41)	2.24 (1.82 - 2.71)	<0.0001
Systolic blood pressure (mmHg)	140 ± 21.2	132 ± 19.4	<0.0001	137 ± 18.2	135 ± 17.4	0.0002	136 ± 18.3	134 ± 16.8	<0.0001
Diastolic blood pressure (mmHg)	75.7 ± 11.3	75.3 ± 10.6	0.2470	74.9 ± 10.9	74.0 ± 10.9	0.0237	73.9 ± 11.5	72.9 ± 10.9	0.0149

Albumin-creatinine-ratio (mg/mmol)	3.70 (1.09 - 24.2)	1.50 (0.70 - 6.06)	<0.0001	4.00 (1.10 - 18.1)	2.60 (1.00 - 11.9)	<0.0001	3.95 (1.10 - 20.7)	2.90 (1.00 - 12.2)	0.0021
eGFR (min/ml per 1.73 m^2)	71.6 ± 25.2	86.7 ± 23.8	<0.0001	68.0 ± 24.9	78.5 ± 23.3	<0.0001	67.3 ± 25.7	77.4 ± 24.3	<0.0001
Treatment at baseline									
Lipid lowering % (*N*)	30.6% (415)	13.6% (480)	<0.0001	87.7% (1,004)	71.5% (2,042)	<0.0001	89.3% (958)	70.5% (1,724)	<0.0001
Blood pressure anti-hypertensive % (*N*)	63.2% (858)	37.1% (1,310)	<0.0001	89.9% (1,029)	77.6% (2,210)	<0.0001	88.7% (950)	75.2% (1,839)	<0.0001
ACE inhibitor % (*N*)	30.9% (420)	17.2% (608)	<0.0001	--	--	--	--	--	--
Oral glucose lowering % (*N*)	69.1% (938)	65.7% (2,319)	0.0265	84.1% (430)	93.0% (1,121)	<0.0001	88.5% (897)	93.6% (2,177)	<0.0001
Insulin treatment % (*N*)	24.1% (327)	13.8% (486)	<0.0001	35.9% (405)	40.4% (1,139)	0.0085	35.2% (373)	47.2% (1,147)	<0.0001
History of cardio-renal complications at baseline									
Coronary heart disease % (*N*)	36.5% (495)	0.00% (0)	<0.0001	86.6% (1,004)	0.00% (0)	<0.0001	88.7% (957)	0.00% (0)	<0.0001
Myocardial infarction % (*N*)	35.9% (488)	0.00% (0)	<0.0001	20.4% (234)	0.00% (0)	<0.0001	22.3% (228)	0.00% (0)	<0.0001
Peripheral vascular disease (*N*)	3.40% (46)	0.00% (0)	<0.0001	12.0% (139)	0.00% (0)	<0.0001	12.1% (131)	0.00% (0)	<0.0001
Stroke % (*N*)	9.80% (133)	0.00% (0)	<0.0001	2.40% (28)	0.00% (0)	<0.0001	2.70% (29)	0.00% (0)	<0.0001
Cardiovascular diseases % (*N*)	43.4% (589)	0.00% (0)	<0.0001	89.2% (1,034)	0.00% (0)	<0.0001	90.7% (979)	0.00% (0)	<0.0001
Congestive heart failure % (*N*)	7.00% (95)	0.60% (22)	<0.0001	12.5% (145)	1.80% (53)	<0.0001	12.3% (133)	1.30% (33)	<0.0001
Chronic kidney disease % (*N*)	34.7% (471)	14.6% (516)	<0.0001	43.0% (498)	26.7% (773)	<0.0001	41.7% (450)	26.9% (665)	<0.0001
Kidney Failure % (*N*)	2.10% (29)	0.70% (25)	<0.0001	3.10% (36)	1.00% (28)	<0.0001	6.60% (71)	3.30% (82)	<0.0001
Incident cardio-renal complications during follow-up (without history)									
Coronary heart disease % (*N*)	63.5% (863)	0.00% (0)	<0.0001	13.4% (155)	0.00% (0)	<0.0001	11.3% (122)	0.00% (0)	<0.0001
Myocardial infarction % (*N*)	27.5% (373)	0.00% (0)	<0.0001	9.30% (106)	0.00% (0)	<0.0001	5.40% (55)	0.00% (0)	<0.0001
Peripheral vascular disease (*N*)	16.0% (217)	0.00% (0)	<0.0001	2.80% (32)	0.00% (0)	<0.0001	1.90% (20)	0.00% (0)	<0.0001
Stroke % (*N*)	6.80% (92)	0.00% (0)	<0.0001	1.50% (17)	0.00% (0)	<0.0001	1.30% (14)	0.00% (0)	<0.0001
Cardiovascular diseases % (*N*)	56.6% (769)	0.00% (0)	<0.0001	10.8% (125)	0.00% (0)	<0.0001	9.30% (100)	0.00% (0)	<0.0001
Congestive heart failure % (*N*)	25.4% (345)	6.00% (213)	<0.0001	4.40% (51)	1.10% (33)	<0.0001	1.80% (19)	0.60% (15)	0.0012
Chronic kidney disease % (*N*)	43.2% (586)	32.6% (1,149)	<0.0001	10.9% (126)	9.00% (260)	0.0634	7.00% (75)	6.50% (160)	0.5938
Kidney Failure % (*N*)	24.2% (328)	10.3% (363)	<0.0001	7.00% (81)	3.90% (114)	<0.0001	3.30% (36)	2.40% (60)	0.1235

Data were expressed as mean ± SD or median (Q1-Q3). Between-group comparisons were performed by chi-squared test for categorical variables, and unpaired Student's t-test or the Wilcoxon Rank Sum test for continuous variables.

Supplementary Table S2. Clinical characteristics for the European patients with type 2 diabetes included in the FIELD study and stratified by the status of coronary heart disease (Replication I study).

Phenotype	CHD status in the FIELD Study Replication I cohort Enrolment year: 1998 - 2000 Genotyping platform: Affymetrix Axiom Array Yes (*n* = 764)	No (*n* = 4276)	*P*
Clinical characteristics at baseline			
Male % (*N*)	78.8% (602)	59.6% (2,547)	<0.0001
Age (years)	64.4 ± 6.50	62.0 ± 6.90	<0.0001
Age Onset (years)	56.3 ± 8.70	55.9 ± 8.10	0.2515
Duration of diabetes (years)	6.00 (3.00 - 12.0)	4.00 (2.00 - 9.00)	<0.0001
Follow-up time (years) [a]	5.33 (4.77 - 6.01)	5.01 (4.74 - 5.77)	<0.0001
Smoking status % (*N*)			<0.0001
Non-smoker	30.0% (229)	40.2% (1,718)	
Ex-smoker	58.2% (445)	51.1% (2,185)	
Current smoker	11.8% (90)	8.70% (373)	
Body height (m)	171.1 ± 8.60	169.1 ± 9.40	<0.0001
Body weight (kg)	88.3 ± 16.4	88.1 ± 17.4	0.8060
BMI (kg/m^2)	30.2 ± 5.10	30.8 ± 5.80	0.0023
Waist circumference (cm)			
Males	105.3 ± 12.2	105.3 ± 12.6	0.9107
Females	102.5 ± 14.2	101.3 ± 14.2	0.3111
Hip cirumference (cm)	110.4 ± 11.7	111.7 ± 12.5	0.0080
Waist-hip-ratio	0.90 ± 0.10	0.90 ± 0.10	<0.0001
HbA_{1C} (%)	7.00 (6.20 - 7.90)	6.70 (6.00 - 7.60)	<0.0001
Total cholesterol (mmol/l)	5.00 (4.50 - 5.50)	5.10 (4.60 - 5.60)	0.1666
Triglycerides (mmol/l)	1.80 (1.40 - 2.50)	1.70 (1.30 - 2.30)	0.0530
HDL-cholesterol (mmol/l)	1.00 (0.80 - 1.10)	1.10 (0.90 - 1.20)	<0.0001
LDL-cholesterol (mmol/l)	3.10 (2.70 - 3.60)	3.10 (2.60 - 3.60)	0.5265
Systolic blood pressure (mmHg)	141.1 ± 15.1	139.0 ± 14.6	0.0002
Diastolic blood pressure (mmHg)	80.9 ± 8.80	81.4 ± 8.30	0.1069
Albumin-creatinine-ratio (mg/mmol)	1.60 (0.80 - 5.30)	1.00 (0.60 - 2.60)	<0.0001
eGFR (min/ml per 1.73 m^2)	81.2 ± 14.5	86.1 ± 14.0	<0.0001
Treatment at baseline			
Lipid lowering % (N)†	0.30% (2)	0.00% (2)	0.1115
Blood pressure anti-hypertensive % (*N*)	68.7% (525)	55.1% (2,358)	<0.0001
ACE inhibitor % (*N*)	38.2% (292)	32.9% (1,405)	0.0039
Oral glucose lowering % (*N*)	63.7% (487)	60.1% (2,572)	0.0610
Insulin treatment % (*N*)	18.2% (139)	9.60% (410)	<0.0001
History of cardio-renal complications at baseline			
Coronary heart disease % (*N*)	46.6% (356)	0.00% (2)	<0.0001
Myocardial infarction % (*N*)	32.2% (246)	0.00% (2)	<0.0001

Peripheral vascular disease (*N*)	17.3% (132)	6.40% (274)	<0.0001
Stroke % (*N*)	6.00% (46)	3.00% (128)	<0.0001
Cardiovascular diseases % (*N*)	60.2% (460)	14.3% (610)	<0.0001
Congestive heart failure % (*N*)	6.80% (52)	1.90% (82)	<0.0001
Chronic kidney disease % (*N*) [b]	9.40% (72)	4.90% (211)	<0.0001
Kidney Failure % (*N*) [c] †	0.10% (1)	0.02% (1)	0.2802
Incident cardio-renal complications during follow-up (without history)			
Coronary heart disease % (N) [d]	66.6% (509)	0.0% (0)	<0.0001
Coronary heart disease (first ever) % (N)	53.4% (408)	0.0% (0)	<0.0001
Myocardial infarction % (N) [e]	27.9% (213)	0.0% (0)	<0.0001
Myocardial infarction (first ever) % (N)	23.7% (181)	0.0% (0)	<0.0001
Peripheral vascular disease % (N) [f]	5.8% (44)	1.7% (73)	<0.0001
Peripheral vascular disease (first ever) % (N)	2.7% (21)	0.9% (40)	<0.0001
Stroke % (N) [g]	6.3% (48)	2.6% (111)	<0.0001
Stroke (first ever) % (N)	5.4% (41)	2.3% (99)	<0.0001
Cardiovascular diseases % (N) [h]	68.2% (521)	3.1% (131)	<0.0001
Cardiovascular diseases (first ever) % (N)	39.8% (304)	2.1% (90)	<0.0001
Congestive heart failure % (N) [i]	7.9% (60)	1.3% (55)	<0.0001
Congestive heart failure (first ever) % (N)	5.9% (45)	1.1% (46)	<0.0001
Chronic kidney disease % (N) [j]	11.9% (91)	3.9% (168)	<0.0001
Chronic kidney disease (first ever) % (N)	7.6% (58)	3.0% (129)	<0.0001
Kidney Failure % (N) [k]	6.0% (46)	1.5% (64)	<0.0001
Kidney Failure (first ever) % (N)	5.9% (45)	1.5% (63)	<0.0001

Data were expressed as mean ± SD or median (Q1-Q3). Between-group comparisons were performed by chi-squared test for categorical variables, and unpaired Student's t-test or the Wilcoxon Rank Sum test for continuous variables.
† Between-group comparisons were performed by Fisher exact test.
[a] Follow-up time was calculated using a reverse Kaplan-Meier approach,
[b] eGFR<60 or ICD-10 code indicating renal failure/disease prior to visit 3 (active run-in period),
[c] eGFR<30 or ICD-10 code indicating renal failure prior to visit 3 (active run-in period),
[d] Includes 101 that also had coronary heart disease at baseline
[e] Includes 32 that had a MI prior to the study
[f] Includes 56 with history of peripheral vascular disease prior to the study
[g] Includes 19 that had a stroke prior to the study
[h] Includes 258 with cardiovascular disease prior to the study
[i] Includes 24 with CHF prior to randomisation
[j] Includes 72 with chronic kidney disease at baseline
[k] Includes 2 patients with kidney failure diagnosed prior to randomisation.

Supplementary Table S3. Associations of lead variants from 13 novel loci with coronary heart disease in Chinese patients with type 2 diabetes.

						Cohort for genome-wide scan: HKDR Study (1358 cases vs 3528 controls)				Cohort for genome-wide scan: HKDB Phase 1 Study (1159 cases vs 2896 controls)			
SNP	**Chr**	**Position (Build 37)**	**Nearest genes**	**Function**	**Risk/ other alleles**	**RAF in cases**	**RAF in controls**	**OR (95% CI)**	***P***	**RAF in cases**	**RAF in controls**	**OR (95% CI)**	***P***
rs145306069*	1	203765163	*ZC3H11A*	intronic	T/C	0.358	0.320	1.19 (1.08 - 1.31)	4.0E-04	0.354	0.310	1.21 (1.09 - 1.35)	4.9E-04
rs3770911*	2	36638473	*CRIM1*	intronic	G/A	0.155	0.140	1.11 (0.98 - 1.25)	0.1156	0.192	0.154	1.40 (1.22 - 1.60)	1.2E-06
rs13410259*	2	183340241	*PDE1A*	intronic	C/A	0.793	0.758	1.22 (1.09 - 1.36)	4.2E-04	0.787	0.752	1.26 (1.12 - 1.43)	2.1E-04
rs10171703†	2	183343102	*PDE1A*	intronic	C/T	0.793	0.758	1.22 (1.09 - 1.35)	4.3E-04	0.787	0.752	1.26 (1.12 - 1.43)	2.2E-04
rs143122158*	3	22824243	*RP11-1037D22.1*	intergenic	C/T	0.018	0.011	2.01 (1.30 - 3.11)	1.6E-03	0.023	0.016	1.94 (1.28 - 2.95)	1.9E-03
rs62336633*	4	111236309	*ZBED1P1*	intergenic	A/G	0.235	0.209	1.19 (1.07 - 1.33)	1.8E-03	0.251	0.221	1.28 (1.12 - 1.46)	3.7E-04
rs41377244*	5	124669572	*RN7SKP117*	intergenic	T/C	0.961	0.946	1.44 (1.15 - 1.81)	1.5E-03	0.938	0.924	1.65 (1.23 - 2.20)	7.2E-04
rs7029336*	9	4747340	*AK3*	intergenic	A/C	0.188	0.165	1.17 (1.04 - 1.31)	0.0106	0.190	0.152	1.36 (1.19 - 1.55)	4.8E-06
rs2004294*	9	20235881	*AL512635.1*	intergenic	A/C	0.751	0.715	1.23 (1.11 - 1.36)	8.0E-05	0.702	0.675	1.16 (1.03 - 1.30)	0.0123
rs6491536*	13	100548455	*CLYBL*	UTR3	C/A	0.224	0.190	1.23 (1.10 - 1.38)	2.2E-04	0.212	0.189	1.19 (1.05 - 1.35)	6.3E-03
rs12435989*	14	50470952	*C14orf182*	intronic	G/T	0.906	0.884	1.29 (1.11 - 1.50)	1.1E-03	0.910	0.885	1.34 (1.13 - 1.58)	7.0E-04
rs4902371*	14	65619418	*RNU2-14P*	intergenic	G/T	0.328	0.290	1.21 (1.10 - 1.33)	1.5E-04	0.318	0.296	1.16 (1.03 - 1.30)	0.0117
rs305960*	19	41662968	*RPL36P16*	intergenic	G/A	0.315	0.275	1.23 (1.11 - 1.35)	4.9E-05	0.350	0.329	1.15 (1.01 - 1.30)	0.0319
rs4823994*	22	49495277	*RPL35P8*	intergenic	G/A	0.772	0.739	1.19 (1.07 - 1.32)	1.4E-03	0.755	0.719	1.28 (1.13 - 1.45)	1.2E-04

Supplementary Table S3. *Continued.*

		Meta-analysis of two GWASs: HKDR Study + HKDB Phase 1 Study (2517 cases vs 6424 controls)					Cohort for follow-up of top signals: HKDB Phase 2 Study (1079 cases vs 2474 controls)				Meta-analysis in Chinese patients with T2D: HKDR Study + HKDB Phase 1 Study + HKDB Phase 2 Study (3596 cases vs 8898 controls)			
SNP	**Nearest genes**	**OR (95% CI)**	P_{meta}	P_{GC}	P_{het}	**Effects**	**RAF in cases**	**RAF in controls**	**OR (95% CI)**	***P***	**OR (95% CI)**	P_{meta}	P_{het}	**Effects**
rs145306069*	*ZC3H11A*	1.20 (1.12 - 1.29)	6.9E-07	7.7E-07	0.7919	++	0.315	0.307	1.02 (0.90 - 1.16)	0.7551	1.15 (1.08 - 1.23)	8.1E-06	0.0868	+++
rs3770911*	*CRIM1*	1.23 (1.12 - 1.35)	8.6E-06	1.0E-05	0.0124	++	0.148	0.151	1.00 (0.87 - 1.16)	0.9858	1.16 (1.07 - 1.25)	1.7E-04	2.5E-03	+++
rs13410259*	*PDE1A*	1.24 (1.14 - 1.34)	3.5E-07	3.9E-07	0.6544	++	0.781	0.751	1.16 (1.03 - 1.32)	0.0181	1.21 (1.13 - 1.30)	2.7E-08	0.6672	+++
rs10171703†	*PDE1A*	1.24 (1.14 - 1.34)	3.7E-07	4.1E-07	0.6477	++	0.791	0.761	1.17 (1.03 - 1.32)	0.0154	1.21 (1.13 - 1.30)	2.4E-08	0.6777	+++
rs143122158*	*RP11-1037D22.1*	1.98 (1.46 - 2.67)	9.5E-06	1.0E-05	0.9053	++	0.011	0.014	0.55 (0.29 - 1.04)	0.0647	1.56 (1.19 - 2.05)	1.4E-03	1.7E-03	++-
rs62336633*	*ZBED1P1*	1.22 (1.12 - 1.33)	3.0E-06	3.3E-06	0.4357	++	0.217	0.223	0.96 (0.84 - 1.11)	0.5842	1.15 (1.07 - 1.23)	2.0E-04	0.0115	++-
rs41377244*	*RN7SKP117*	1.52 (1.27 - 1.81)	4.6E-06	5.1E-06	0.4811	++	0.940	0.943	0.95 (0.76 - 1.18)	0.6205	1.26 (1.10 - 1.45)	1.1E-03	3.9E-03	++-
rs7029336*	*AK3*	1.25 (1.14 - 1.36)	7.1E-07	8.3E-07	0.0901	++	0.162	0.165	0.97 (0.84 - 1.12)	0.6991	1.17 (1.08 - 1.26)	5.1E-05	3.7E-03	++-
rs2004294*	*AL512635.1*	1.20 (1.11 - 1.29)	4.0E-06	4.2E-06	0.4542	++	0.695	0.708	0.91 (0.81 - 1.03)	0.1446	1.11 (1.04 - 1.18)	1.9E-03	7.8E-04	++-
rs6491536*	*CLYBL*	1.21 (1.12 - 1.32)	4.7E-06	5.0E-06	0.6941	++	0.187	0.190	0.99 (0.87 - 1.14)	0.9075	1.15 (1.07 - 1.23)	1.2E-04	0.0415	++-
rs12435989*	*C14orf182*	1.31 (1.17 - 1.46)	2.7E-06	2.9E-06	0.7452	++	0.892	0.887	1.01 (0.85 - 1.19)	0.9288	1.21 (1.10 - 1.32)	8.0E-05	0.0368	+++
rs4902371*	*RNU2-14P*	1.19 (1.10 - 1.28)	6.2E-06	6.5E-06	0.5896	++	0.278	0.291	0.95 (0.84 - 1.07)	0.3951	1.12 (1.05 - 1.19)	6.3E-04	7.5E-03	++-
rs305960*	*RPL36P16*	1.19 (1.11 - 1.29)	6.3E-06	6.5E-06	0.4025	++	0.324	0.305	1.08 (0.95 - 1.22)	0.2239	1.16 (1.09 - 1.24)	7.6E-06	0.2802	+++
rs4823994*	*RPL35P8*	1.23 (1.13 - 1.33)	8.1E-07	9.1E-07	0.4003	++	0.738	0.753	0.95 (0.84 - 1.07)	0.3583	1.13 (1.06 - 1.21)	3.5E-04	1.4E-03	++-

Nearest Entrez genes within 250 kb

* represents the lead variant for each locus identified in the meta-analysis of GWASs

† represents the lead variant at *PDE1A* locus identified in the meta-analysis of all cohorts with Chinese patients with T2D

Odds ratios (ORs) were estimated according to the risk allele.

P represents the *p*-value obtained from individual cohort using the logistic regression model with the adjustments of sex, age and principal components

P_{meta} represents the *p*-value obtained from the meta-analysis under a fixed effect model

P_{GC} represents the *p*-value obtained from the meta-analysis under a fixed effect model after genomic control

P_{het} represents the *p*-value obtained from the heterogeneity test (Cochran's Q test)

RAF: Risk allele frequency

Supplementary Table S4. Associations of *PDE1A* rs10171703 with coronary heart disease in all discovery and replication cohorts.

Cohort	Population	Covariates	Imputation quality (Rsq)	*N*		Risk allele frequency		Association tests		
				CHD case	Non-CHD control	CHD case	Non-CHD control	OR (95% CI) / HR (95% CI)	$P_{additive}$	P_{het}
Genome-wide scan										
HKDR Study	Chinese T2D patients	sex, age, and PCs	1.0000	1,358	3,528	0.793	0.758	1.22 (1.09 - 1.35)	4.3×10^{-4}	--
HKDB Phase 1 Study	Chinese T2D patients	sex, age, and PCs	0.9036	1,159	2,896	0.787	0.752	1.26 (1.12 - 1.43)	2.2×10^{-4}	--
Meta-analysis of two GWASs	**Chinese T2D patients**	--	--	**2,517**	**6,424**	--	--	**1.24 (1.14 - 1.34)**	$\mathbf{3.7\times10^{-7}}$	**0.6477**
Follow-up of top signals										
HKDB Phase 2 Study	Chinese T2D patients	sex, age, and PCs	0.9997	1,079	2,474	0.791	0.761	1.17 (1.03 - 1.32)	0.0154	--
Meta-analysis in Chinese patients with T2D	**Chinese T2D patients**	--	--	**3,596**	**8,898**	--	--	**1.21 (1.13 - 1.30)**	$\mathbf{2.4\times10^{-8}}$	**0.6777**
Replication I										
FIELD Study	European T2D patients	sex, age, duration of diabetes, and PCs	0.9995	764	4,276	0.523		0.97 (0.82 - 1.14) †	0.6879 §	--
Replication II										
Biobank Japan (BBJ) Project (Ishigaki *et al*. 2020) [1]	Japanese from general populations	sex, age, and PCs	0.9999	29,319	183,134	0.726	0.724	1.02 (1.00 - 1.05)	0.0214	--
Biobank Japan (BBJ) Project (Koyama *et al.* 2020) [2]	Japanese from general populations	sex, age, and PCs	>0.3	25,892	142,336	0.723		1.02 (1.00 - 1.04)	0.1026	--
GWAS in two Japanese Cohorts (Matsunaga *et al*. 2020) [3]	Japanese from general populations	sex, age, and PCs	0.9999	15,302	36,140	--	--	1.07 (1.03 - 1.12)	1.3×10^{-3}	0.4396
CARDIoGRAMplusC4D Consortium and UK Biobank [4]	Europeans from general populations	sex, age, and PCs	--	122,733	424,528	0.510		1.01 (1.00 - 1.02)	0.0716	0.7411
FinnGEN Project [5]	Europeans from general populations	sex, age, PCs, and genotyping batch	info score >0.95	21,012	197,780	0.485	0.479	1.04 (1.01 - 1.07)	3.3×10^{-3}	--
Joint T2D-CHD GWAS and CARDIoGRAMplusC4D [6, 7]	Multi-ethnic general populations	--	--	90,831	169,534	--	--	1.02 (0.99 - 1.04)	0.1854	--

All study cohorts used the case-control study design, except the FIELD study which is a prospective cohort.

ORs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
† HR and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
$P_{additive}$ was obtained from either the logistic regression model with the adjustments of covariates, or the meta-analysis under a fixed effect model
§ $P_{additive}$ was obtained from the Cox regression model with the adjustments of covariates
P_{het} refers to the *p*-value obtained from the heterogeneity test (Cochran's Q test)
PCs: Principal components
Part of the samples included in the Matsunaga *et al.* 2020 Study were recruited from the Biobank Japan Project (n = 12,494 cases and 7,261 controls)
Analysis of the Joint T2D-CHD GWAS included samples from the CARDIoGRAMplusC4D Consortium

References:

[1] Ishigaki K, Akiyama M, Kanai M *et al.* Large-scale genome-wide association study in a Japanese population identifies novel susceptibility loci across different diseases. *Nat Genet. 2020 Jul;52(7):669-679.*
[2] Koyama S, Ito K, Terao C *et al.* Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. *Nat Genet. 2020 Nov;52(11):1169-1177.*
[3] Matsunaga H, Ito K, Akiyama M *et al.* Transethnic Meta-Analysis of Genome-Wide Association Studies Identifies Three New Loci and Characterizes Population-Specific Differences for Coronary Artery Disease. Circ Genom Precis Med. *2020 Jun;13(3):e002670.*
[4] van der Harst P, Verweij N. Identification of 64 Novel Genetic Loci Provides an Expanded View on the Genetic Architecture of Coronary Artery Disease. *Circ Res. 2018 Feb 2;122(3):433-443.*
[5] Kurki MI, Karjalainen J, Palta P *et al.* FinnGen: Unique genetic insights from combining isolated population and national health register data. *medRxiv 2022:2022.2003.2003.22271360*
[6] Zhao W, Rasheed A, Tikkanen E *et al.* Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease. *Nat Genet. 2017 Oct;49(10):1450-1457.*
[7] https://kp4cd.org/node/207

Supplementary Table S5. Sensitivity analysis for the association of *PDE1A* rs10171703 with the risk of coronary heart disease in Chinese patients with type 2 diabetes, with different covariates adjustments.

Covariates	**Cohort**	**Case *N***	**Control *N***	**OR (95% CI)**	$P_{additive}$	P_{het}
PCs, sex, age	HKDR Study	1358	3528	1.22 (1.09 - 1.35)	4.3×10^{-4}	--
	HKDB Phase 1 Study	1159	2896	1.26 (1.12 - 1.43)	2.2×10^{-4}	--
	HKDB Phase 2 Study	1079	2474	1.17 (1.03 - 1.32)	0.0154	--
	Meta-analysis	**3596**	**8898**	**1.21 (1.13 - 1.30)**	$\mathbf{2.4\times10^{-8}}$	**0.6777**
PCs, sex, age, duration of diabetes	HKDR Study	1357	3528	1.21 (1.08 - 1.35)	7.0×10^{-4}	--
	HKDB Phase 1 Study	1152	2896	1.24 (1.09 - 1.39)	6.1×10^{-4}	--
	HKDB Phase 2 Study	1071	2474	1.19 (1.05 - 1.36)	6.4×10^{-3}	--
	Meta-analysis	**3580**	**8898**	**1.21 (1.13 - 1.30)**	$\mathbf{3.3\times10^{-8}}$	**0.9294**
PCs, sex, age, duration of diabetes, smoking status	HKDR Study	1356	3520	1.21 (1.09 - 1.36)	6.5×10^{-4}	--
	HKDB Phase 1 Study	1152	2895	1.23 (1.09 - 1.39)	8.0×10^{-4}	--
	HKDB Phase 2 Study	1071	2470	1.19 (1.05 - 1.35)	8.2×10^{-3}	--
	Meta-analysis	**3579**	**8885**	**1.21 (1.13 - 1.30)**	$\mathbf{5.0\times10^{-8}}$	**0.9256**
PCs, sex, age, duration of diabetes, smoking status, obesity (BMI, waist-hip-ratio)	HKDR Study	1341	3507	1.18 (1.05 - 1.32)	4.2×10^{-3}	--
	HKDB Phase 1 Study	991	2643	1.20 (1.05 - 1.37)	6.0×10^{-3}	--
	HKDB Phase 2 Study	824	1986	1.22 (1.05 - 1.41)	7.1×10^{-3}	--
	Meta-analysis	**3156**	**8136**	**1.20 (1.11 - 1.29)**	$\mathbf{1.7\times10^{-6}}$	**0.9470**
PCs, sex, age, duration of diabetes, smoking status, obesity, hypertension (systolic and diastolic blood pressure, use of anti-hypertensive drugs)	HKDR Study	1341	3504	1.14 (1.01 - 1.28)	0.0361	--
	HKDB Phase 1 Study	980	2602	1.18 (1.03 - 1.35)	0.0147	--
	HKDB Phase 2 Study	818	1964	1.20 (1.04 - 1.39)	0.0129	--
	Meta-analysis	**3139**	**8070**	**1.17 (1.08 - 1.26)**	$\mathbf{5.9\times10^{-5}}$	**0.8201**
PCs, sex, age, duration of diabetes, smoking status, obesity, hypertension, glycaemic control (HbA1c,	HKDR Study	1341	3504	1.13 (1.01 - 1.28)	0.0381	--

use of oral glucose lowering drugs, insulin treatment)	HKDB Phase 1 Study	422	1021	1.12 (0.90 - 1.38)	0.3139	--
	HKDB Phase 2 Study	705	1695	1.17 (1.00 - 1.37)	0.0544	--
	Meta-analysis	**2468**	**6220**	**1.14 (1.05 - 1.25)**	**2.9×10^{-3}**	**0.9332**
PCs, sex, age, duration of diabetes, smoking status, obesity, hypertension, glycaemic control, dyslipidemia (triglyceride levels, HDL cholesterol, LDL cholesterol, use of lipid lowering drugs)	HKDR Study	1265	3354	1.15 (1.02 - 1.31)	0.0271	--
	HKDB Phase 1 Study	414	989	1.15 (0.92 - 1.44)	0.2123	--
	HKDB Phase 2 Study	693	1632	1.17 (0.99 - 1.38)	0.0649	--
	Meta-analysis	**2372**	**5975**	**1.16 (1.06 - 1.27)**	**1.7×10^{-3}**	**0.9914**
PCs, sex, age, duration of diabetes, smoking status, obesity, hypertension, glycaemic control, dyslipidemia, renal function (albumin-creatinine-ratio, eGFR)	HKDR Study	1223	3214	1.15 (1.01 - 1.31)	0.0368	--
	HKDB Phase 1 Study	380	840	1.11 (0.88 - 1.40)	0.3664	--
	HKDB Phase 2 Study	588	1393	1.19 (0.99 - 1.42)	0.0614	--
	Meta-analysis	**2191**	**5447**	**1.15 (1.05 - 1.27)**	**3.6×10^{-3}**	**0.9104**

Association between *PDE1A* rs10171703 and CHD risk was assessed by logistic regression with adjustments for different covariates measured at baseline.
Results obtained from the individual cohorts were meta-analysed under a fixed effect model
ORs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
P_{het} refers to the *p*-value obtained from the heterogeneity test (Cochran's Q test)
PC: Principal components

Supplementary Table S6. Associations of *PDE1A* rs10171703 with the risks of cardio-renal complications in Chinese patients with type 2 diabetes.

Diabetic complication	Cohort	Case-control analysis							Prospective analysis						
		N		RAF		Logistic regression			*N*		RAF		Cox regression		
		Case	Control	Case	Control	OR (95% CI)	$P_{additive}$	P_{het}	Event	Non-event	Event	Non-event	HR (95% CI)	$P_{additive}$	P_{het}
CHD	HKDR study	1,358	3,528	0.793	0.758	1.22 (1.09 - 1.35)	4.3×10^{-4}	--	862	4,648	0.789	0.761	1.14 (1.01 - 1.28)	0.0270	--
	HKDB phase 1 study	1,159	2,896	0.787	0.752	1.26 (1.12 - 1.43)	2.2×10^{-4}	--	155	4,927	0.817	0.772	1.38 (1.03 - 1.85)	0.0296	--
	HKDB phase 2 study	1,079	2,474	0.791	0.761	1.17 (1.03 - 1.32)	0.0154	--	122	4,600	0.770	0.773	0.96 (0.72 - 1.29)	0.8003	--
	Meta-analysis	**3,596**	**8,898**	--	--	**1.21 (1.13 - 1.30)**	$\mathbf{2.4\times10^{-8}}$	**0.6777**	**1,139**	**14,175**	--	--	**1.14 (1.03 - 1.27)**	$\mathbf{9.3\times10^{-3}}$	**0.2315**
MI	HKDR study	861	3,528	0.789	0.758	1.19 (1.04 - 1.35)	9.0×10^{-3}	--	420	5,435	0.779	0.767	1.05 (0.90 - 1.24)	0.5279	--
	HKDB phase 1 study	340	2,880	0.794	0.751	1.36 (1.10 - 1.67)	4.1×10^{-3}	--	106	5,702	0.827	0.775	1.46 (1.02 - 2.10)	0.0406	--
	HKDB phase 2 study	282	2,359	0.796	0.762	1.19 (0.96 - 1.48)	0.1199	--	55	5,155	0.791	0.775	1.08 (0.68 - 1.71)	0.7473	--
	Meta-analysis	**1,483**	**8,767**	--	--	**1.22 (1.11 - 1.35)**	$\mathbf{5.5\times10^{-5}}$	**0.5413**	**581**	**16,292**	--	--	**1.11 (0.96 - 1.28)**	**0.1489**	**0.2711**
Any stroke	HKDR study	887	3,528	0.783	0.758	1.15 (1.02 - 1.31)	0.0270	--	741	5,119	0.788	0.766	1.10 (0.98 - 1.25)	0.1160	--
	HKDB phase 1 study	636	2,896	0.788	0.765	1.14 (0.98 - 1.32)	0.0806	--	118	5,444	0.797	0.776	1.13 (0.82 - 1.55)	0.4503	--
	HKDB phase 2 study	559	2,474	0.781	0.761	1.10 (0.94 - 1.28)	0.2448	--	82	5,121	0.831	0.776	1.40 (0.93 - 2.10)	0.1045	--
	Meta-analysis	**2,082**	**8,898**	--	--	**1.13 (1.04 - 1.23)**	$\mathbf{2.6\times10^{-3}}$	**0.8894**	**941**	**15,684**	--	--	**1.13 (1.01 - 1.26)**	**0.0343**	**0.5507**
Any stroke (excluded any CHD cases)	HKDR study	624	3,528	0.782	0.758	1.15 (0.99 - 1.32)	0.0659	--	524	4,024	0.790	0.758	1.18 (1.02 - 1.37)	0.0283	--
	HKDB phase 1 study	465	2,896	0.788	0.765	1.14 (0.97 - 1.35)	0.1182	--	86	4,464	0.791	0.770	1.13 (0.78 - 1.63)	0.5105	--
	HKDB phase 2 study	408	2,474	0.780	0.761	1.09 (0.92 - 1.31)	0.3214	--	62	4,200	0.817	0.773	1.28 (0.82 - 2.01)	0.2791	--
	Meta-analysis	**1,497**	**8,898**	--	--	**1.13 (1.03 - 1.24)**	**0.0100**	**0.9144**	**672**	**12,688**	--	--	**1.18 (1.04 - 1.35)**	**0.0126**	**0.9125**
PVD	HKDR study	631	3,528	0.784	0.758	1.15 (0.99 - 1.33)	0.0632	--	260	5,374	0.788	0.767	1.12 (0.91 - 1.39)	0.2757	--
	HKDB phase 1 study	124	2,896	0.796	0.765	1.25 (0.91 - 1.72)	0.1732	--	51	5,944	0.783	0.777	1.11 (0.69 - 1.80)	0.6658	--
	HKDB phase 2 study	119	2,474	0.787	0.761	1.12 (0.82 - 1.54)	0.4647	--	36	5,552	0.763	0.776	0.94 (0.55 - 1.62)	0.8272	--
	Meta-analysis	**874**	**8,898**	--	--	**1.16 (1.03 - 1.31)**	**0.0182**	**0.8779**	**347**	**16,870**	--	--	**1.10 (0.92 - 1.32)**	**0.3017**	**0.8371**
PVD (excluded any CHD cases)	HKDR study	406	3,528	0.759	0.758	1.00 (0.84 - 1.18)	0.9582	--	169	4,242	0.768	0.762	1.03 (0.80 - 1.33)	0.8207	--
	HKDB phase 1 study	79	2,896	0.791	0.765	1.16 (0.79 - 1.72)	0.4446	--	34	4,844	0.771	0.772	0.96 (0.54 - 1.68)	0.8758	--
	HKDB phase 2 study	76	2,474	0.805	0.761	1.24 (0.83 - 1.86)	0.2877	--	22	4,525	0.739	0.773	0.79 (0.40 - 1.53)	0.4776	--
	Meta-analysis	**561**	**8,898**	--	--	**1.05 (0.91 - 1.21)**	**0.5338**	**0.5143**	**225**	**13,611**	--	--	**0.99 (0.80 - 1.23)**	**0.9217**	**0.7518**
CVD	HKDR study	2,292	3,528	0.786	0.758	1.17 (1.07 - 1.29)	4.6×10^{-4}	--	1,380	3,716	0.784	0.758	1.12 (1.02 - 1.22)	0.0160	--
	HKDB phase 1 study	1,692	2,896	0.797	0.765	1.22 (1.09 - 1.35)	2.6×10^{-4}	--	237	4,397	0.812	0.770	1.33 (1.05 - 1.67)	0.0160	--

	HKDB phase 2 study	1,554	2,474	0.788	0.761	1.15 (1.03 - 1.29)	0.0115	--	181	4,134	0.777	0.772	1.02 (0.79 - 1.30)	0.8986	--
	Meta-analysis	**5,538**	**8,898**	**--**	**--**	**1.18 (1.11 - 1.25)**	**2.0×10^{-8}**	**0.7794**	**1,798**	**12,247**	**--**	**--**	**1.13 (1.04 - 1.22)**	**2.7×10^{-3}**	**0.2650**
CVD	HKDR study	934	3,528	0.777	0.758	1.11 (0.98 - 1.25)	0.0945	--	612	3,715	0.787	0.758	1.15 (1.01 - 1.32)	0.0408	--
(excluded any	HKDB phase 1 study	533	2,896	0.790	0.765	1.16 (0.99 - 1.36)	0.0743	--	112	4,397	0.792	0.770	1.13 (0.82 - 1.56)	0.4508	--
CHD cases)	HKDB phase 2 study	475	2,474	0.783	0.761	1.11 (0.94 - 1.31)	0.2194	--	81	4,134	0.795	0.772	1.12 (0.77 - 1.63)	0.5613	--
	Meta-analysis	**1,942**	**8,898**	**--**	**--**	**1.12 (1.03 - 1.22)**	**6.9×10^{-3}**	**0.9111**	**805**	**12,246**	**--**	**--**	**1.15 (1.02 - 1.29)**	**0.0245**	**0.9840**
CHF	HKDR study	867	3,293	0.787	0.758	1.18 (1.04 - 1.35)	0.0102	--	725	5,138	0.787	0.765	1.11 (0.98 - 1.26)	0.1040	--
	HKDB phase 1 study	352	2,810	0.767	0.766	1.01 (0.84 - 1.21)	0.9120	--	107	5,727	0.771	0.778	0.96 (0.70 - 1.32)	0.8192	--
	HKDB phase 2 study	260	2,426	0.799	0.760	1.20 (0.96 - 1.50)	0.1157	--	44	5,416	0.783	0.775	1.00 (0.60 - 1.67)	0.9880	--
	Meta-analysis	**1,479**	**8,529**	**--**	**--**	**1.14 (1.03 - 1.25)**	**8.5×10^{-3}**	**0.3403**	**876**	**16,281**	**--**	**--**	**1.08 (0.97 - 1.22)**	**0.1637**	**0.6852**
CHF	HKDR study	427	3,293	0.756	0.758	0.99 (0.84 - 1.17)	0.9374		380	4,221	0.761	0.762	0.97 (0.82 - 1.15)	0.7478	--
(excluded any	HKDB phase 1 study	156	2,810	0.763	0.766	0.98 (0.75 - 1.28)	0.9034		56	4,772	0.786	0.772	1.07 (0.69 - 1.68)	0.7585	--
CHD cases)	HKDB phase 2 study	108	2,426	0.780	0.760	1.07 (0.77 - 1.48)	0.6985		25	4,498	0.796	0.773	1.13 (0.57 - 2.27)	0.7238	--
	Meta-analysis	**691**	**8,529**	**--**	**--**	**1.00 (0.88 - 1.14)**	**0.9732**	**0.9186**	**461**	**13,491**	**--**	**--**	**0.99 (0.85 - 1.16)**	**0.9117**	**0.8562**
CKD	HKDR study	3,559	2,327	0.775	0.758	1.11 (1.02 - 1.21)	0.0168	--	2,142	2,450	0.772	0.759	1.06 (0.99 - 1.14)	0.0896	--
	HKDB phase 1 study	2,197	2,370	0.793	0.760	1.22 (1.10 - 1.34)	1.4×10^{-4}	--	540	3,901	0.799	0.769	1.22 (1.05 - 1.41)	0.0101	--
	HKDB phase 2 study	1,875	2,125	0.778	0.768	1.04 (0.94 - 1.16)	0.4365	--	339	3,848	0.786	0.776	1.06 (0.88 - 1.27)	0.5316	--
	Meta-analysis	**7,631**	**6,822**	**--**	**--**	**1.12 (1.06 - 1.19)**	**4.8×10^{-5}**	**0.1154**	**3,021**	**10,199**	**--**	**--**	**1.09 (1.02 - 1.16)**	**6.9×10^{-3}**	**0.2732**
CKD	HKDR study	2,502	2,045	0.767	0.754	1.08 (0.98 - 1.19)	0.1325	--	1,556	2,149	0.763	0.755	1.04 (0.96 - 1.13)	0.3751	--
(excluded any	HKDB phase 1 study	1,572	2,012	0.790	0.754	1.24 (1.11 - 1.39)	1.8×10^{-4}	--	414	3,370	0.803	0.763	1.28 (1.08 - 1.52)	4.5×10^{-3}	--
CHD cases)	HKDB phase 2 study	1,341	1,789	0.774	0.759	1.07 (0.95 - 1.20)	0.2721	--	265	3,297	0.782	0.773	1.06 (0.87 - 1.30)	0.5611	--
	Meta-analysis	**5,415**	**5,846**	**--**	**--**	**1.12 (1.05 - 1.19)**	**3.0×10^{-4}**	**0.1101**	**2,235**	**8,816**	**--**	**--**	**1.08 (1.01 - 1.16)**	**0.0342**	**0.0953**
KF	HKDR study	1,005	2,327	0.798	0.758	1.27 (1.12 - 1.45)	2.4×10^{-4}	--	923	5,002	0.794	0.763	1.17 (1.05 - 1.31)	6.2×10^{-3}	--
	HKDB phase 1 study	357	2,370	0.786	0.760	1.16 (0.96 - 1.41)	0.1240	--	263	5,725	0.789	0.777	1.09 (0.89 - 1.35)	0.4112	--
	HKDB phase 2 study	371	2,125	0.775	0.768	1.05 (0.87 - 1.26)	0.6398	--	119	5,335	0.778	0.777	1.00 (0.74 - 1.36)	0.9999	--
	Meta-analysis	**1,733**	**6,822**	**--**	**--**	**1.19 (1.08 - 1.30)**	**2.9×10^{-4}**	**0.2302**	**1,305**	**16,062**	**--**	**--**	**1.14 (1.03 - 1.25)**	**7.7×10^{-3}**	**0.5864**
KF	HKDR study	648	2,045	0.791	0.754	1.24 (1.07 - 1.45)	5.4×10^{-3}	--	596	3,998	0.787	0.757	1.16 (1.01 - 1.33)	0.0373	--
(excluded any	HKDB phase 1 study	239	2,012	0.780	0.754	1.16 (0.93 - 1.46)	0.1908	--	182	4,690	0.776	0.771	1.02 (0.80 - 1.30)	0.8771	--
CHD cases)	HKDB phase 2 study	255	1,789	0.771	0.759	1.08 (0.87 - 1.35)	0.4928	--	84	4,371	0.789	0.773	1.13 (0.77 - 1.64)	0.5347	--
	Meta-analysis	**1,142**	**5,846**	**--**	**--**	**1.18 (1.06 - 1.32)**	**2.9×10^{-3}**	**0.5891**	**862**	**13,059**	**--**	**--**	**1.12 (1.00 - 1.26)**	**0.0466**	**0.6754**

In the case-control analysis, associations were assessed by logistic regression with the adjustments for sex, age and principal components.
In the prospective analysis, associations were assessed by Cox regression with the adjustments for sex, age, duration of diabetes and principal components.
Results obtained from the individual cohorts were meta-analysed under a fixed effect model.
ORs/HRs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703.
P_{het} refers to the *p*-value obtained from the heterogeneity test (Cochran's Q test).
Cardiovascular complications include coronary heart disease, myocardial infarction, stroke, peripheral vascular disease, cardiovascular disease, and congestive heart failure
Renal complications include chronic kidney disease, and kidney failure
In the case-control analysis for a particular outcome, patients with either history or incidence of outcome were enrolled in the group of cases. The counterpart controls for each outcome were defined as patients who 1) had duration of diabetes >10 years, and 2) were free from cardiovascular (chronic kidney) disease for the analysis of cardiovascular (renal) outcomes.
In the prospective analysis for a particular outcome, we included the patients who had no history but incidence of that outcome in the event group, while patients without both history and incidence of the outcome were included in the non-event group.
CHD: Coronary heart disease
MI: Myocardial infarction
PVD: Peripheral vascular disease
CVD: Cardiovascular disease
CHF: Congestive heart failure
CKD: Chronic kidney disease
KF: Kidney failure
RAF: Risk allele frequency

Supplementary Table S7. Associations of *PDE1A* rs10171703 with the risks of cardio-renal complications in replication cohorts (data from public domains).

Diabetic complication	Cohort	Population	Covariates	*N*		RAF		Logistic regression	
				Case	Control	Case	Control	OR (95% CI)	$P_{additive}$
MI	Biobank Japan Project [1]	Japanese from general populations	age, age^2, sex, age × sex, age^2 × sex, and PCs	14,992	146,214	0.728	0.724	1.04 (1.01 - 1.07)	0.0127
	FinnGEN Project [2]	Europeans from general populations	sex, age, PCs, and genotyping batch	12,801	187,840	0.488	0.479	1.04 (1.01 - 1.07)	8.2×10^{-3}
	Meta-analysis of UK Biobank and CARDIoGRAMplusC4D GWAS [3]	Europeans from general populations	sex, age, PCs, and genotyping array	61,505	577,716	0.496		1.02 (1.01 - 1.04)	4.7×10^{-3}
Any stroke	MEGASTROKE Consortium [4]	Europeans	sex, age, and other study-specific covariates	40,585	406,111	0.4941		1.03 (1.01 - 1.04)	6.5×10^{-3}
	MEGASTROKE Consortium [4]	Transethnic meta-analysis	sex, age, and other study-specific covariates	67,162	454,450	0.4713		1.02 (1.00 - 1.04)	0.0113
CKD	SUMMIT Consortium [5]	Transethnic meta-analysis in T2D patients	age, sex and duration of diabetes	3,094	2,906	0.500		1.00 (0.92 - 1.09)	0.8900
	CKDGen consortium [6]	Transethnic meta-analysis	sex, age, study site, PCs, relatedness, and other study-specific features	64,164	561,055	0.560		1.01 (0.99 - 1.03)	0.2204
	FinnGEN Project [2]	European from general population	sex, age, PCs, and genotyping batch	3,902	212,841	0.490	0.479	1.04 (1.00 - 1.09)	0.0741
KF	SUMMIT Consortium [5]	Transethnic meta-analysis in T2D patients	age, sex and duration of diabetes	371	4,471	0.490		1.10 (0.94 - 1.29)	0.3300
	FinnGEN Project [2]	European from general population	sex, age, PCs, and genotyping batch	5,951	212,841	0.488	0.479	1.04 (1.00 - 1.08)	0.0674

ORs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
MI: Myocardial infarction
CKD: Chronic kidney disease
KF: Kidney failure
RAF: Risk allele frequency
PC: Principal components

References:

[1] Sakaue S, Kanai M, Tanigawa Y *et al.* A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet. 2021 Oct;53(10):1415-1424.*
[2] Kurki MI, Karjalainen J, Palta P *et al.* FinnGen: Unique genetic insights from combining isolated population and national health register data. *medRxiv 2022:2022.2003.2003.22271360*
[3] Hartiala JA, Han Y, Jia Q *et al.* Genome-wide analysis identifies novel susceptibility loci for myocardial infarction. *Eur Heart J. 2021 Mar 1;42(9):919-933.*
[4] Malik R, Chauhan G, Traylor M *et al.* Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. *Nat Genet. 2018 Apr;50(4):524-537.*
[5] van Zuydam NR, Ahlqvist E, Sandholm N *et al*. A Genome-Wide Association Study of Diabetic Kidney Disease in Subjects With Type 2 Diabetes. *Diabetes. 2018 Jul;67(7):1414-1427.*
[6] Wuttke M, Li Y, Li M *et al*. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet. 2019 Jun;51(6):957-972.*

Supplementary Table S8. Associations of *PDE1A* rs10171703 with blood pressure, and body height in Chinese patients with type 2 diabetes and other populations.

Related traits	Cohort [Ref]	Population	Covariates	Total *N* (Cases)	RAF	β ± SE / OR (95% CI)	*P*	P_{het}
DBP	Meta-analysis of the HKDR Study, the HKDB Phase 1 and 2 studies	Chinese T2D patients	sex, age, duration of diabetes, PCs	17,735	0.769-0.778	0.332 ± 0.153	0.0297	0.9730
	Biobank Japan Project (Kanai et al. 2018) [1]	Japanese	Sex, age, age^2, PCs, affection status of 47 diseases, and smoking status	136,615	0.723	0.013 ± 0.004	2.1×10^{-3}	--
	Biobank Japan Project (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	145,515	0.724	0.013 ± 0.004	6.5×10^{-4}	--
	Meta-analysis of Biobank Japan Project, and UK Biobank (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	485,677	0.513-0.724	0.012 ± 0.002	1.2×10^{-8}	--
SBP	Meta-analysis of the HKDR Study, the HKDB Phase 1 and 2 studies	Chinese T2D patients	sex, age, duration of diabetes, PCs	17,737	0.768-0.778	0.595 ± 0.257	0.0208	0.3844
	Biobank Japan Project (Kanai et al. 2018) [1]	Japanese	Sex, age, age^2, PCs, affection status of 47 diseases, and smoking status	136,597	0.723	0.006 ± 0.004	0.1920	--
	Biobank Japan Project (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	145,505	0.724	0.007 ± 0.004	0.0770	--
	Meta-analysis of Biobank Japan Project, and UK Biobank (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	485,664	0.513-0.724	0.003 ± 0.002	0.1516	--
Hypertension	Meta-analysis of the HKDR Study, the HKDB Phase 1 and 2 studies	Chinese T2D patients	sex, age, duration of diabetes, PCs	17,700 (14,627)	0.753-0.779	1.09 (1.01 - 1.17)	0.0174	0.3368
Hypertension	FinnGEN Project [3]	Europeans	sex, age, PCs, and genotyping batch	218,754 (55,917)	0.479	1.02 (1.00 - 1.03)	0.0785	--
Essential hypertension	FinnGEN Project [3]	Europeans	sex, age, PCs, and genotyping batch	205,694 (42,857)	0.479	1.02 (1.00 - 1.04)	0.0481	--
Body height	Meta-analysis of the HKDR Study, the HKDB Phase 1 and 2 studies	Chinese T2D patients	sex, age, duration of diabetes, PCs	17,712	0.769-0.778	-0.0001 ± 0.001	0.8839	0.356
	Biobank Japan Project (Kanai et al. 2018) [1]	Japanese	Sex, age, age^2, PCs, affection status of 47 diseases, and smoking status	159,095	0.724	-0.003 ± 0.003	0.3300	--

	Biobank Japan Project (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	165,056	0.724	-0.001 ± 0.002	0.5700	--
	Meta-analysis of Biobank Japan Project, and UK Biobank (Sakaue et al. 2021) [2]	Japanese	age, age^2, sex, age × sex, age^2 × sex, and PCs	525,444	0.513-0.724	-0.004 ± 0.001	2.9×10^{-3}	--

For individuals taking anti-hypertensive medications, 15 mmHg was added to SBP and 10 mmHg was added to DBP in the HKDR Study, the HKDB Phase 1 and 2 Studies, and the Biobank Japan Project.
Hypertension was defined as blood pressure at or above 130/80 mmHg, or use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or use of other antihypertensive medications in the HKDR Study, the HKDB Phase 1 and 2 Studies.
Associations of *PDE1A* rs10171703 with body height, systolic and diastolic blood pressure were tested by linear regression adjusted for sex, age, duration of diabetes and PCs in each cohort.
Association between *PDE1A* rs10171703 and hypertension was tested by logistic regression adjusted for sex, age, duration of diabetes and PCs in each cohort.
Results obtained from the individual cohorts were meta-analysed under a fixed effect model.
β ± SE / ORs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
P_{het} refers to the *p*-value obtained from the heterogeneity test (Cochran's Q test)
DBP: Diastolic blood pressure
SBP: Systolic blood pressure
PCs: principal components
RAF: Risk allele frequency

References:

[1] Kanai M, Akiyama M, Takahashi A *et al*. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. *Nat Genet. 2018 Mar;50(3):390-400.*
[2] Sakaue S, Kanai M, Tanigawa Y *et al*. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet. 2021 Oct;53(10):1415-1424.*
[3] Kurki MI, Karjalainen J, Palta P *et al*. FinnGen: Unique genetic insights from combining isolated population and national health register data. *medRxiv 2022:2022.2003.2003.22271360*

Supplementary Table S9. Modification effect of *PDE1A* rs10171703 on the association between ABC goals attainment and new-onset of diabetes cardiovascular complications.

		Testing for the interaction effect between *PDE1A* rs10171703 and each ABC goal			Association between each ABC goal and diabetic complications according to *PDE1A* rs10171703 genotypes				
Diabetic complications	**ABC goals**	**Event *n***	**Non-event *n***	***P*$_{interaction}$**	***Subgroup***	**Event *n***	**Non-event *n***	**HR (95% CI)**	***P***
Coronary heart disease	HbA_{1c} <7%	1,127	13,782	0.8503	TT genoytpe carriers	46	740	0.39 (0.18 - 0.85)	0.0174
					CT genoytpe carriers	376	4,868	0.82 (0.66 - 1.02)	0.0781
					CC genoytpe carriers	705	8,166	0.70 (0.60 - 0.83)	2.1×10^{-5}
	SBP <130 mmHg and DBP <80 mmHg	1,139	14,158	0.0155	TT genoytpe carriers	47	762	1.13 (0.61 - 2.08)	0.6946
					CT genoytpe carriers	382	5,005	0.81 (0.65 - 1.02)	0.0726
					CC genoytpe carriers	710	8,383	0.60 (0.51 - 0.72)	2.9×10^{-8}
	LDL <2.6 mmol/l	1,082	13,675	0.8032	TT genoytpe carriers	44	733	0.67 (0.33 - 1.35)	0.2621
					CT genoytpe carriers	364	4,825	0.80 (0.63 - 1.03)	0.0783
					CC genoytpe carriers	674	8,109	0.75 (0.63 - 0.90)	1.6×10^{-3}
Myocardial infarction	HbA_{1c} <7%	575	15,857	0.6628	TT genoytpe carriers	26	815	0.54 (0.21 - 1.38)	0.1961
					CT genoytpe carriers	191	5,560	0.80 (0.59 - 1.10)	0.1650
					CC genoytpe carriers	358	9,473	0.64 (0.51 - 0.81)	2.2×10^{-4}
	SBP <130 mmHg and DBP <80 mmHg	581	16,273	5.1×10^{-4}	TT genoytpe carriers	26	838	3.02 (1.36 - 6.70)	6.7×10^{-3}
					CT genoytpe carriers	192	5,707	0.83 (0.61 - 1.15)	0.2614
					CC genoytpe carriers	363	9,719	0.58 (0.45 - 0.75)	3.6×10^{-5}
	LDL <2.6 mmol/l	547	15,719	0.3048	TT genoytpe carriers	24	805	0.56 (0.20 - 1.56)	0.2706
					CT genoytpe carriers	179	5,500	0.66 (0.46 - 0.95)	0.0254
					CC genoytpe carriers	344	9,405	0.75 (0.59 - 0.97)	0.0277

These analyses were conducted in the combined cohort of the HKDR Study, the HKDB Phase 1 and 2 Studies.

P$_{interaction}$ was the *p*-value of the interaction term obtained from the Cox regression model including two main effects (e.g. *PDE1A* rs10171703 and achievement of blood pressure target [i.e. SBP <130 mmHg and DBP <80 mmHg]), the interaction term of main effects, and the covariates (i.e. study cohorts [HKDR Study, HKDB Phase 1 and 2 Studies], enrolment year, sex, age, duration of diabetes, and principal components [PCs]).

P, hazard ratio (HR) and 95% CI were obtained from the Cox regression model assessing the association between the achievement of each ABC goal ('yes' [coded as 1] vs. 'no' [coded as 0]) and incidence of diabetes cardiovascular complications, adjusting for study cohorts (HKDR Study, HKDB Phase 1 and 2 Studies), enrolment year, sex, age, duration of diabetes, and PCs.
Event: patients had no history but incidence of outcome
Non-event: patients had neither history nor incidence of outcome

Supplementary Table S10. Sensitivity analysis for the interaction effect of *PDE1A* rs10171703 and blood pressure control on new-onset of diabetes cardiovascular complications.

		Combined cohorts (HKDR Study, HKDB Phase 1 and 2 Studies)							
		Model I				Model II			
Diabetic complications	**Follow-up period**	**Event *n***	**Non-event *n***	**HR (95% CI)**	**$P_{interaction}$**	**Event *n***	**Non-event *n***	**HR (95% CI)**	**$P_{interaction}$**
Coronary heart disease	≤1 year	102	15,195	0.53 (0.27 - 1.06)	0.0738	55	9132	0.78 (0.28 - 2.15)	0.6302
	≤2 year	252	15,045	0.58 (0.37 - 0.90)	0.0152	163	9024	0.65 (0.37 - 1.13)	0.1271
	≤3 year	393	14,904	0.52 (0.36 - 0.75)	5.0E-04	257	8930	0.54 (0.34 - 0.86)	9.5E-03
	≤4 year	497	14,800	0.58 (0.42 - 0.80)	1.0E-03	327	8860	0.63 (0.41 - 0.95)	0.0269
	≤5 year	554	14,743	0.58 (0.42 - 0.80)	7.2E-04	375	8812	0.63 (0.42 - 0.93)	0.0204
	≤6 year	617	14,680	0.62 (0.46 - 0.84)	1.7E-03	430	8757	0.66 (0.46 - 0.95)	0.0268
	≤7 year	655	14,642	0.62 (0.47 - 0.83)	1.3E-03	463	8724	0.64 (0.45 - 0.90)	0.0111
	≤8 year	700	14,597	0.62 (0.47 - 0.82)	7.5E-04	501	8686	0.62 (0.44 - 0.87)	6.2E-03
	≤9 year	742	14,555	0.61 (0.47 - 0.81)	4.2E-04	536	8651	0.60 (0.43 - 0.83)	2.0E-03
	≤10 year	785	14,512	0.64 (0.49 - 0.83)	8.9E-04	574	8613	0.62 (0.46 - 0.85)	3.2E-03
	≤26 year	**1,139**	**14,158**	**0.76 (0.61 - 0.95)**	**0.0155**	**889**	**8298**	**0.77 (0.6 - 0.99)**	**0.0424**
Myocardial infarction	≤1 year	66	16,788	0.35 (0.15 - 0.81)	0.0142	29	10013	0.61 (0.17 - 2.19)	0.4453
	≤2 year	129	16,725	0.37 (0.20 - 0.67)	1.3E-03	67	9975	0.34 (0.15 - 0.80)	0.0139
	≤3 year	190	16,664	0.33 (0.19 - 0.55)	2.9E-05	104	9938	0.26 (0.13 - 0.54)	2.4E-04
	≤4 year	234	16,620	0.40 (0.25 - 0.64)	1.3E-04	131	9911	0.36 (0.19 - 0.67)	1.3E-03
	≤5 year	262	16,592	0.41 (0.26 - 0.63)	7.1E-05	153	9889	0.36 (0.20 - 0.66)	7.6E-04
	≤6 year	280	16,574	0.41 (0.26 - 0.62)	3.7E-05	167	9875	0.37 (0.21 - 0.64)	4.4E-04
	≤7 year	293	16,561	0.43 (0.28 - 0.65)	6.7E-05	179	9863	0.40 (0.24 - 0.69)	8.7E-04
	≤8 year	308	16,546	0.43 (0.28 - 0.65)	6.0E-05	193	9849	0.39 (0.23 - 0.67)	5.9E-04
	≤9 year	327	16,527	0.44 (0.29 - 0.65)	4.4E-05	208	9834	0.39 (0.24 - 0.65)	2.5E-04
	≤10 year	346	16,508	0.44 (0.30 - 0.64)	2.6E-05	224	9818	0.39 (0.24 - 0.62)	1.1E-04
	≤26 year	**581**	**16,273**	**0.58 (0.43 - 0.79)**	**5.1E-04**	**434**	**9608**	**0.56 (0.39 - 0.81)**	**1.7E-03**

Supplementary Table S10. *Continued.*

		HKDR Study							
		Model I				Model II			
Diabetic complications	**Follow-up period**	**Event *n***	**Non-event *n***	**HR (95% CI)**	***P*$_{interaction}$**	**Event *n***	**Non-event *n***	**HR (95% CI)**	***P*$_{interaction}$**
Coronary heart disease	≤1 year	45	5,462	0.57 (0.20 - 1.60)	0.2830	39	4,925	0.83 (0.26 - 2.60)	0.7425
	≤2 year	111	5,396	0.62 (0.31 - 1.21)	0.1587	101	4,863	0.67 (0.33 - 1.37)	0.2740
	≤3 year	179	5,328	0.53 (0.31 - 0.90)	0.0197	163	4,801	0.54 (0.31 - 0.94)	0.0299
	≤4 year	235	5,272	0.62 (0.39 - 1.00)	0.0503	215	4,749	0.62 (0.38 - 1.02)	0.0603
	≤5 year	278	5,229	0.61 (0.39 - 0.94)	0.0271	253	4,711	0.62 (0.39 - 0.98)	0.0423
	≤6 year	340	5,167	0.67 (0.45 - 1.00)	0.0510	308	4,656	0.66 (0.43 - 1.00)	0.0525
	≤7 year	378	5,129	0.67 (0.46 - 0.98)	0.0404	341	4,623	0.63 (0.42 - 0.94)	0.0223
	≤8 year	423	5,084	0.65 (0.46 - 0.94)	0.0219	379	4,585	0.61 (0.42 - 0.90)	0.0121
	≤9 year	465	5,042	0.64 (0.46 - 0.91)	0.0119	414	4,550	0.59 (0.41 - 0.84)	3.9E-03
	≤10 year	508	4,999	0.68 (0.49 - 0.95)	0.0231	452	4,512	0.61 (0.43 - 0.87)	6.1E-03
	≤26 year	**862**	**4,645**	**0.84 (0.65 - 1.08)**	**0.1790**	**767**	**4,197**	**0.78 (0.60 - 1.03)**	**0.0767**
Myocardial infarction	≤1 year	22	5,830	0.30 (0.07 - 1.20)	0.0889	18	5,260	0.49 (0.11 - 2.18)	0.3487
	≤2 year	47	5,805	0.29 (0.11 - 0.78)	0.0146	40	5,238	0.31 (0.10 - 0.91)	0.0338
	≤3 year	69	5,783	0.26 (0.11 - 0.58)	1.0E-03	60	5,218	0.25 (0.11 - 0.62)	2.4E-03
	≤4 year	84	5,768	0.33 (0.16 - 0.69)	2.9E-03	73	5,205	0.33 (0.15 - 0.73)	5.9E-03
	≤5 year	101	5,751	0.29 (0.15 - 0.58)	4.5E-04	87	5,191	0.30 (0.14 - 0.62)	1.3E-03
	≤6 year	119	5,733	0.32 (0.17 - 0.59)	3.0E-04	101	5,177	0.31 (0.15 - 0.61)	6.8E-04
	≤7 year	132	5,720	0.36 (0.20 - 0.65)	7.0E-04	113	5,165	0.36 (0.19 - 0.69)	1.9E-03
	≤8 year	147	5,705	0.36 (0.20 - 0.64)	5.0E-04	127	5,151	0.35 (0.19 - 0.66)	1.2E-03
	≤9 year	166	5,686	0.39 (0.23 - 0.66)	4.8E-04	142	5,136	0.36 (0.20 - 0.65)	6.2E-04
	≤10 year	185	5,667	0.39 (0.23 - 0.65)	2.8E-04	158	5,120	0.35 (0.20 - 0.60)	1.9E-04
	≤26 year	**420**	**5,432**	**0.61 (0.43 - 0.87)**	**6.0E-03**	**368**	**4,910**	**0.57 (0.39 - 0.84)**	**4.4E-03**

Supplementary Table S10. *Continued.*

		HKDB Phase 1 and 2 Studies							
		Model I				Model II			
Diabetic complications	**Follow-up period**	**Event *n***	**Non-event *n***	**HR (95% CI)**	**$P_{interaction}$**	**Event *n***	**Non-event *n***	**HR (95% CI)**	**$P_{interaction}$**
Coronary heart disease	≤1 year	57	9,732	0.48 (0.19 - 1.25)	0.1324	16	4,207	0.78 (0.07 - 8.36)	0.8407
	≤2 year	141	9,648	0.52 (0.29 - 0.95)	0.0322	62	4,161	0.53 (0.21 - 1.33)	0.1759
	≤3 year	214	9,575	0.50 (0.30 - 0.84)	8.4E-03	94	4,129	0.54 (0.23 - 1.25)	0.1477
	≤4 year	262	9,527	0.53 (0.34 - 0.84)	7.1E-03	112	4,111	0.62 (0.28 - 1.34)	0.2240
	≤5 year	276	9,513	0.56 (0.36 - 0.87)	9.7E-03	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤6 year	277	9,512	0.56 (0.36 - 0.88)	0.0109	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤7 year	277	9,512	0.56 (0.36 - 0.88)	0.0109	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤8 year	277	9,512	0.56 (0.36 - 0.88)	0.0109	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤9 year	277	9,512	0.56 (0.36 - 0.88)	0.0109	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤10 year	277	9,512	0.56 (0.36 - 0.88)	0.0109	122	4,101	0.63 (0.30 - 1.31)	0.2161
	≤26 year	**277**	**9,512**	**0.56 (0.36 - 0.88)**	**0.0109**	**122**	**4,101**	**0.63 (0.30 - 1.31)**	**0.2161**
Myocardial infarction	≤1 year	44	10,958	0.38 (0.13 - 1.14)	0.0841	11	4,753	0.59 (0.03 - 11.5)	0.7299
	≤2 year	82	10,920	0.40 (0.18 - 0.89)	0.0239	27	4,737	0.20 (0.04 - 0.99)	0.0481
	≤3 year	121	10,881	0.39 (0.19 - 0.79)	8.9E-03	44	4,720	0.20 (0.05 - 0.80)	0.0231
	≤4 year	150	10,852	0.45 (0.24 - 0.84)	0.0126	58	4,706	0.36 (0.12 - 1.14)	0.0832
	≤5 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤6 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤7 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤8 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤9 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤10 year	161	10,841	0.50 (0.27 - 0.91)	0.0232	66	4,698	0.47 (0.17 - 1.30)	0.1449
	≤26 year	**161**	**10,841**	**0.50 (0.27 - 0.91)**	**0.0232**	**66**	**4,698**	**0.47 (0.17 - 1.30)**	**0.1449**

These analyses were conducted in the combined cohort of the HKDR Study, the HKDB Phase 1 and 2 Studies.
Model I (basic model): study cohorts (HKDR Study, HKDB Phase 1 and 2 Studies), sex, age, duration of diabetes, enrolment year, and principal components.
Model II (full model): study cohorts (HKDR Study, HKDB Phase 1 and 2 Studies), sex, age, duration of diabetes, enrolment year, and principal components, smoking status, body mass index, waist-hip ratio, HBA1C, natural log transformed triglyceride levels, HDL-cholesterol, LDL-cholesterol, natural log transformed albumin-creatinine ratio, estimated glomerular filtration rate, status of hypertension, and drug usage (including lipid lowering drug, oral glucose lowering drugs and insulin treatment)
$P_{interaction}$ was the *p*-value of the interaction term obtained from the Cox regression model including two main effects (i.e. *PDE1A* rs10171703 and achievement of blood pressure target [i.e. SBP <130 mmHg and DBP <80 mmHg]), the interaction term of main effects, and the covariates (i.e. Models I and II).
HR corresponds to the effect of interaction term (hazard ratio) estimated from the Cox regression model
Event: patients had no history but incidence of outcome
Non-event: patients had neither history nor incidence of outcome
Follow-up time was calculated as the period from enrolment to the first outcome event, the date of death or particular follow-up period, whichever came first.

Sensitivity analyses for testing the robustness of the interaction effect:
1) We adjusted for additional potential confounders in the Cox regression model (i.e. compare Model I vs. Model II)
2) Since blood pressure may vary over time, we considered a short-term interaction effect on cardiovascular outcomes (i.e. considered a shorter period of follow-up)
3) To examine the concordance of the interaction effect, we conducted the analysis separately in the HKDR Study and the HKDB Study.

Supplementary Table S11. Associations of *PDE1A* rs10171703 with coronary heart disease and myocardial infarction, conditional on the known myocardial infarction-related variant rs12693302 at *PDE1A* locus in Chinese patients with type 2 diabetes.

SNP (Risk/ other alleles)	RAF EAS	RAF EUR	Conditional SNP	Cohort	LD r^2	*N* Case	*N* Control	RAF Case	RAF Control	Unconditional analysis OR (95% CI)	Unconditional analysis $P_{additive}$	Unconditional analysis P_{het}	Conditional analysis OR (95% CI)	Conditional analysis $P_{additive}$	Conditional analysis P_{het}
Coronary heart disease															
rs10171703	0.782	0.464	rs12693302†	HKDR Study	0.217	1,358	3,528	0.793	0.758	1.22 (1.09 - 1.35)	4.3×10^{-4}	--	1.26 (1.12 - 1.42)	1.7×10^{-4}	--
(C/T)				HKDB Phase 1 Study	0.202	1,159	2,896	0.787	0.752	1.26 (1.12 - 1.43)	2.2×10^{-4}	--	1.23 (1.07 - 1.42)	2.9×10^{-3}	--
				HKDB Phase 2 Study	0.245	1,079	2,474	0.791	0.761	1.17 (1.03 - 1.32)	0.0154	--	1.16 (1.00 - 1.34)	0.0475	--
				Meta-analysis	--	**3,596**	**8,898**	--	--	**1.21 (1.13 - 1.30)**	$\mathbf{2.4\times10^{-8}}$	**0.6777**	**1.22 (1.13 - 1.32)**	$\mathbf{3.2\times10^{-7}}$	**0.6633**
rs12693302†	0.583	0.324	rs10171703	HKDR Study	0.217	1,358	3,528	0.575	0.570	1.02 (0.93 - 1.11)	0.7227	--	0.93 (0.84 - 1.03)	0.1747	--
(G/A)				HKDB Phase 1 Study	0.202	1,159	2,896	0.612	0.587	1.14 (1.02 - 1.27)	0.0186	--	1.05 (0.93 - 1.18)	0.4743	--
				HKDB Phase 2 Study	0.245	1,079	2,474	0.600	0.578	1.08 (0.97 - 1.21)	0.1528	--	1.02 (0.89 - 1.15)	0.8180	--
				Meta-analysis	--	**3,596**	**8,898**	--	--	**1.07 (1.01 - 1.14)**	**0.0227**	**0.2838**	**0.99 (0.92 - 1.06)**	**0.7069**	**0.3221**
Myocardial infarction															
rs10171703	0.782	0.464	rs12693302†	HKDR Study	0.217	861	3,528	0.789	0.758	1.19 (1.04 - 1.35)	9.0×10^{-3}	--	1.22 (1.06 - 1.41)	6.2×10^{-3}	--
(C/T)				HKDB Phase 1 Study	0.202	340	2,880	0.794	0.751	1.36 (1.10 - 1.67)	4.1×10^{-3}	--	1.31 (1.04 - 1.66)	0.0203	--
				HKDB Phase 2 Study	0.245	282	2,359	0.796	0.762	1.19 (0.96 - 1.48)	0.1199	--	1.25 (0.98 - 1.60)	0.0756	--
				Meta-analysis	--	**1,483**	**8,767**	--	--	**1.22 (1.11 - 1.35)**	$\mathbf{5.5\times10^{-5}}$	**0.5413**	**1.25 (1.12 - 1.39)**	$\mathbf{7.3\times10^{-5}}$	**0.8624**
rs12693302†	0.583	0.324	rs10171703	HKDR Study	0.217	861	3,528	0.576	0.570	1.02 (0.92 - 1.14)	0.6976	--	0.95 (0.84 - 1.07)	0.3803	--
(G/A)				HKDB Phase 1 Study	0.202	340	2,880	0.618	0.588	1.19 (0.99 - 1.42)	0.0625	--	1.06 (0.87 - 1.30)	0.5524	--
				HKDB Phase 2 Study	0.245	282	2,359	0.580	0.577	1.00 (0.83 - 1.21)	0.9678	--	0.91 (0.73 - 1.13)	0.3933	--
				Meta-analysis	--	**1,483**	**8,767**	--	--	**1.05 (0.97 - 1.14)**	**0.2377**	**0.3283**	**0.96 (0.88 - 1.06)**	**0.4413**	**0.5330**

Association was assessed by logistic regression with adjustments for sex, age and principal components.
Results obtained from the individual cohorts were meta-analysed under a fixed effect model
ORs and 95% CIs were reported according to the CHD-related risk allele (C-allele) of *PDE1A* rs10171703
P_{het} refers to the *p*-value obtained from the heterogeneity test (Cochran's Q test)
RAF: Risk allele frequency

† **Reference:** Hartiala JA *et al.* Genome-wide analysis identifies novel susceptibility loci for myocardial infarction. *Eur Heart J. 2021 Mar 1;42(9):919-933.*

Supplementary Table S12. Associations between the peak eQTL SNP at *PDE1A* locus and *PDE1A* expression in the adipose (n = 581) and skin tissues (n = 605), using data from the GTEx portal.

	Peak eQTL SNP at *PDE1A*							***PDE1A* rs10171703 (chr2:183343102)**				
Tissue	**SNP**	**Chr**	**Position (Build 37)**	**EA / NEA**	**NES ± SE**	P_{eQTL}	$P_{threshold}$	**EA / NEA**	**NES ± SE**	P_{eQTL}	$P_{threshold}$	**LD r^2 with Peak SNP in EAS**
Adipose - Subcutaneous	rs4091077	2	183312302	G/A	0.120 ± 0.029	3.2×10^{-5}	2.6×10^{-4}	C/T	0.110 ± 0.028	1.1×10^{-4}	2.6×10^{-4}	0.511
Skin - Sun Exposed (Lower leg)	rs934260	2	183377037	G/A	0.190 ± 0.035	6.5×10^{-8}	3.2×10^{-4}	C/T	0.091 ± 0.025	2.0×10^{-4}	3.2×10^{-4}	0.021

EA: effect allele; NEA: non-effect allele

LD: Linkage disequilibrium r^2 between the peak eQTL SNP and the top variant rs10171703 identified in the present study.

The normalized effect size (NES) of the eQTL is defined as the slope (i.e. β-coefficient) of the linear regression between genotype and expression, and is computed as the effect of the alternative C-allele relative to the reference T-allele.

P_{eQTL} were obtained for each variant-gene pair by testing the null hypothesis that NES is equal to zero.

$P_{threshold}$ is the false discovery rate (FDR) threshold applied to identify genes with a significant eQTL.

Supplementary Table S13. Associations of genetically predicted PDE1A expression with CHD risk in GTEx tissue types.

Tissue	***Z-score***	***P-value***
Adipose - Subcutaneous	0.244	0.807
Brain - Cerebellar Hemisphere	-0.136	0.892
Brain - Cortex	0.083	0.933
Brain - Hippocampus	-0.301	0.763
Brain - Hypothalamus	-0.258	0.796
Brain - Nucleus accumbens (basal ganglia)	0.476	0.634
Brain - Spinal cord (cervical c-1)	0.436	0.663
Brain - Substantia nigra	0.513	0.608
Breast - Mammary Tissue	1.119	0.263
Cells - Cultured fibroblasts	-0.244	0.807
Esophagus - Muscularis	2.347	0.019
Heart - Atrial Appendage	-0.244	0.807
Muscle - Skeletal	1.116	0.264
Nerve - Tibial	0.105	0.916
Ovary	-0.054	0.957
Pituitary	-0.244	0.807
Skin - Sun Exposed (Lower leg)	0.054	0.957
Thyroid	-2.645	8.0×10^{-3}
Meta-analysis		**0.035**[†]

Only tissues with valid expression model for *PDE1A* were listed.

[†] Meta-analysis of the associations across the tissues listed while factoring correlation among tissues. Statistical significance was estimated by S-MultiXcan.