Genetic Risk Score Enhances Coronary Artery Disease Risk Prediction in Individuals With Type 1 Diabetes

FinnDiane Study Group

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Genetic risk score enhances coronary artery disease risk prediction in individuals with type 1 diabetes

Running title: Genetic risk score for CAD in type 1 diabetes

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Structured abstract

OBJECTIVE Individuals with type 1 diabetes are at a high lifetime risk of coronary artery disease (CAD) calling for early interventions. This study explores the use of a genetic risk score (GRS) for CAD risk prediction, compares it to established clinical markers and investigates its performance according to the age and pharmacological treatment.

RESEARCH DESIGN AND METHODS This study in 3,295 individuals with type 1 diabetes from the Finnish Diabetic Nephropathy Study (467 incident CAD, 14.8 years follow-up) employed three risk scores: a GRS, a validated clinical score and their combined score. Hazard ratios (HR) were calculated with Cox regression and model performances compared with Harrel's C-index.

RESULTS A HR of 6.7 for CAD was observed between the highest and the lowest 5th percentile of the GRS (P=1.8×10^{-6}). The performance of GRS (C-index [C] 0.562) was similar to HbA_{1c} (C=0.563, p-value for difference 0.96), HDL (C=0.571, P=0.6) and total cholesterol (C=0.594, P=0.1). The GRS was not correlated with the clinical score (r=-0.013, P=0.5). The combined score outperformed the clinical score (C=0.813 vs C=0.820, P=0.003). The GRS performed better in individuals below the median age (38.6 years) compared to those above (C=0.637 vs C=0.546).

CONCLUSIONS A GRS identified individuals at high risk of CAD and worked better in younger individuals. GRS was also an independent risk factor for CAD with a predictive power comparable to that of HbA_{1c}, HDL and total cholesterol and, when incorporated into a clinical model, modestly improved the predictions. The GRS promises early risk stratification in clinical practice by enhancing the prediction of CAD.

Despite advances in insulin therapy, delivery systems and glucose monitoring (1), a significant number of individuals with type 1 diabetes develops diabetic complications which can substantially reduce their quality of life (2), shorten their life span (3) and impose high health care costs (4). Coronary artery disease (CAD) is currently the leading cause of morbidity and mortality in type 1 diabetes. Notably, CAD is more common, occurs 10 to 15 years earlier in life, and the protective effect of women is lost in individuals with type 1 diabetes compared to the non-diabetic population (5). Mainly attributed to cardiovascular causes of death, the life expectancy is still approximately 12 years shorter in individuals with type 1 diabetes than in the general population (3).

The conventional modifiable risk factors for CAD, including poor glycemic control, elevated blood pressure (BP), dyslipidemia, and smoking are well established to increase CAD risk in type 1 diabetes (6). Improved treatment of these risk factors by statin therapy, BP control and lifestyle modifications have led to a remarkable decrease in the incidence of CAD during recent decades (7). Nonetheless, individuals with type 1 diabetes continue to have an increased risk of cardiovascular events and death compared to the general population (6).

Several cardiovascular disease (CVD) risk prediction models, such as the Framingham Risk Score (8) or U.K. Prospective Diabetes Study (UKPDS) Risk Engine model (9), have been developed to improve CVD risk stratification. These models, however, underestimate the predicted risk of CVD events in type 1 diabetes (10). Therefore, prediction models, including The Swedish National Diabetes Register risk equation (11) and The Steno Type 1 Risk Engine (12) have been developed. These models have been derived from large cohorts of type 1 diabetes individuals and have shown comparable performance regarding CVD risk prediction (12). However, these models are all age-dependent and can only be applied after clinical risk

factors appear (13) and are, thus, inadequate to identify high-risk individuals at the very early stage. Therefore, better risk stratification for early identification and intervention is urgently needed for type 1 diabetes.

Genetics is also known to contribute to the development of CAD. To date, 163 genetic variants have been genome-wide significantly associated with CAD in the general population (14). Of note, although research on type 1 diabetes specific CAD risk variants has been scarce, there has been evidence for some variants to increase CAD risk only in individuals with type 1 diabetes (15-17). Notably, CAD risk stratification by genetic risk scores (GRSs) has been shown to discriminate high and low risk individuals for CAD in the general population (18-20). In fact, Khera et al. (20) reported a large area under curve value (AUC 0.81) for a genome-wide polygenic risk score (PRS) in CAD prediction. Moreover, there is evidence from the general population that in those with the highest GRS, lifestyle modification or statin therapy reduce the risk of CAD by approximately 50% and are more effective when initiated at the early stages of the disease (21, 22). Furthermore, recent studies have shown similarities between the genetic architecture of CAD in individuals with and without diabetes, also specifically type 1 diabetes by observing correlated effect estimates on the known loci in genome-wide association studies (GWAS) (15, 16, 23).

Therefore, in type 1 diabetes, genetic risk stratification based on GRSs by using the general population CAD risk variants, which can be applied at any age, may offer a potential for earlier risk screening and ultimately primary prevention. Furthermore, GRSs have been suggested to complement the conventional risk factors for the identification of high-risk individuals (19). However, there is evidence that combining GRSs with conventional risk factors has only modestly improved the CAD risk prediction in the general population (18).

This study investigates the potential of such a GRS for CAD risk prediction in individuals with type 1 diabetes, both separately and combined with traditional risk factors, and its performance according to age and pharmacological treatment.

Research Design and Methods

The Study Cohort

This study is a part of the Finnish Diabetic Nephropathy (FinnDiane) study: an ongoing nationwide multicenter study aiming to identify risk factors for diabetic complications in individuals with type 1 diabetes. A more detailed description of the study has been reported elsewhere (24). In short, the study was launched in 1997 and to date 5,496 adult individuals with type 1 diabetes have been recruited from ≥80 hospitals and health centers throughout Finland (Supplemental Table S1). Type 1 diabetes was defined by age of onset ≤ 40 years and insulin treatment initiated within one year from diagnosis. The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Non-fatal CAD events were identified from the Finnish Care Register for Health Care and deaths, including fatal CAD events, from the Causes of Death Register. CAD events included myocardial infarction (MI) (ICD-8/9 410, 412, ICD-10 I21-I23), coronary bypass graft surgery and coronary angioplasty based on the Nordic Classification of Surgical Procedures (Supplemental Table S2). A clinical risk score for CAD was calculated based on a validated 5-year CVD risk model in type 1 diabetes (11). The model has eight predictors: diabetes duration, onset age of diabetes, total cholesterol/HDL cholesterol ratio, HbA_{1c}, systolic BP, smoking

status, macroalbuminuria, and previous CVD (11). Diabetic nephropathy (DN) status was defined by urinary albumin excretion rate (AER) or albumin-to-creatinine ratio (ACR) in two out of three timed overnight or 24h urine collections or in morning spot urine samples for ACR. Normal AER was defined as AER <20 µg/min or <30 mg/24h or ACR <2.5 mg/mmol for men and <3.5 mg/mmol for women; microalbuminuria as an AER ≥20 and <200 µg/min or ≥30 and <300 mg/24h or ACR ≥2.5 and <25 mg/mmol for men and ≥3.5 and <35 mg/mmol for women; and macroalbuminuria as AER ≥200 µg/min or ≥300 mg/24h or ACR ≥25 for men and ≥35 mg/mmol for women. End-stage renal disease was defined as dialysis or kidney transplantation. eGFR was calculated using the Chronic Kidney Disease Collaboration (CKD-EPI) formula (25). Individuals were classified into five stages according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (26). LDL cholesterol was calculated with the equation from Sampson et al (27).

We selected individuals from a recent GWAS on CAD in 4,869 individuals with type 1 diabetes in the FinnDiane cohort (16). We excluded 1,420 individuals with missing clinical data, and 154 individuals with a CAD event prior to the baseline. Overall, 3,295 individuals with type 1 diabetes were included in this study (467 incident cases) (Supplemental Fig. S1A). Participants were followed until an initial CAD event or death, or otherwise until the end of follow-up date 31 December 2015.

Genetic and combined risk scores

GWAS genotyping and imputation procedures, as well as GRS calculation have been described elsewhere (16). In short, genotyping was performed at the University of Virginia with HumanCoreExome Bead arrays 12-1.0, 12-1.1, and 24-1.0 113 (Illumina, San Diego, CA, USA), and genotypes were called with zCall software (28). GWAS imputation was performed

with minimac3 software (29) using 1000 Genomes phase 3 reference panel (Hg37). In this study, we calculated an allelic GRS for the study participants with 156 of the currently known 163 general population CAD risk variants (14) available in our GWAS data. We defined the GRS for an individual as the mean of the variant dosages weighted by their corresponding natural logarithmic OR from original studies (16),

$$GRS = \frac{\sum_{i=1}^{156} \ln(OR_i) \times Dosage_i}{156}.$$

The genetic and clinical risk scores were combined by summing up their contributions weighted by respective survival model Harrel's C-indexes – from unadjusted models with standardized scores – which were transformed according to [*(C-index – 0.5) x 2*] for the weighting of parameters to vary between 0 and 1,

$$Combination\ score = [(C\text{-}index_{GRS} - 0.5) \times 2] \times GRS + [(C\text{-}index_{Clinical\ score} - 0.5) \times 2] \times Clinical\ score.$$

Finally, we studied a genome-wide PRS designed by Khera et al. (20) for the general population. We calculated the score with plink2 (https://www.cog-genomics.org/plink/2.0/) using publicly available score weights for the roughly six million variants of which five million were available in our data (https://cvd.hugeamp.org/).

Pharmacological treatment

To estimate the value of GRS in those with pharmacological treatment, the FinnDiane data were linked to the Finnish Drug Prescription Register data (maintained by the National Social Insurance Institution since 1994), available for 3241 individuals. From the register information on purchases of antihypertensive (ATC codes C02, C03, C07-C09) and lipid-lowering drugs (ATC code C10) were obtained until the end of 2015. First, baseline medication status was defined as any purchase of these drugs 180 days before and after the FinnDiane baseline visit. Moreover, to confirm stable medication status at each medication group, refill adherences for

antihypertensive and lipid-lowering drugs were calculated for both drugs separately during the follow-up. The acceptable refill period was set to 180 days between two purchases (at least two prescriptions) of these drugs and if exceeded, uncovered days were calculated from baseline until the end of follow-up. A similar approach used by other researchers (30), was adopted to define adherence thresholds: ≥0.80 was considered satisfactory, while adherence <0.50 was considered poor. We divided individuals into four subgroups based on the baseline medication status and these refill adherence thresholds (Supplemental Fig. S1B): antihypertensive drugs only, lipid-lowering drug only, both antihypertensive and lipid-lowering drugs, and none of these drugs.

Statistical analysis

Continuous covariates are described with mean ±SD for normally distributed variables, and as median with interquartile range (IQR) for non-normally distributed values. Differences between the groups were tested with t-test or Wilcox signed rank test, for normally and non-normally distributed variables, respectively. Binary variables are expressed as frequency (%) and differences in distributions were tested with Pearson's chi-squared test or two-tailed Fisher exact test, as appropriate. In addition, the correlation structure between the clinical variables was calculated with Spearman rank correlation. We compared individuals in the top and bottom score distribution percentiles with Cox proportional hazard (PH) regression models adjusted for sex and the calendar year of type 1 diabetes onset; and presented results as hazard ratios (HR) with 95% CIs. Triglycerides and clinical risk score were $\log_e$-transformed in all analyses. Furthermore, Cox PH regression models were built for each clinical variable (i.e. sex, smoking, DN status, calendar year of type 1 diabetes onset, age, systolic BP, diastolic BP, waist-to-height ratio, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and HbA_{1c}) and risk score (i.e. GRS, genome-wide PRS, clinical and combined scores). All studied risk scores and

clinical variables were standardized to zero mean and unit standard deviation. Model performances were compared with Harrel's C-index (31). Statistical significances of the differences were evaluated as suggested by Kang et al. (32). Finally, Cox PH regression models were built with standardized clinical covariates and GRS as separate covariates in one model. Statistical analyses were performed in R statistical software (https://www.r-project.org).

3. Results

Cohort characteristics

The study comprised 3,295 individuals with type 1 diabetes, 51% of whom were men. The mean age was 39.1 ± 11.2 years, and mean duration of diabetes was 22.9 ± 11.7 years at baseline. During a median of 14.8 (IQR 11.6–16.8) follow-up years (43,691 person-years), 467 individuals developed CAD (250 non-fatal MI, 38 fatal MI and 179 coronary revascularization). The characteristics of the cases, who developed CAD and the control subjects, who did not, are shown in Table 1 (Distributions of each clinical variable between cases and controls are plotted in Supplemental Fig. S2 and S3). As could be expected, cases were older, and they had longer duration of diabetes. They had also more often signs of traditional clinical risk factors (i.e. reduced renal function and albuminuria, elevated systolic BP, worse lipid profile and glycemic control) for CAD than controls. Consequently, the previously validated clinical risk score also indicated higher clinical risk for CAD in cases than in controls (Table 1).

Genetic risk score and CAD

The GRS differed significantly between those individuals that developed CAD and those that did not (P=7.7×10^{-7}), although the mean difference was small (Table 1, Supplemental Fig. S4). We found a clear difference in CAD risk when we compared individuals within the high and

low GRS percentiles. These differences were most pronounced when comparing the extreme ends of the GRS distribution. Individuals in the highest 5th percentile showed 6.7-fold increased risk of CAD compared to those in the lowest 5th percentile (Supplemental Table S4). The increase in risk was more modest but remained steep for the decile (HR 2.99 [95% CI 1.98, 4.50]), for the quintile (HR 2.21 [95% CI 1.64, 2.98]) and for the 30th percentile (HR 1.76 [95% CI 1.39, 2.24]) group comparisons (Supplemental Table S4). There was also a clear difference in the risk when comparing the top and the bottom percentiles of the clinical and combined risk scores (Supplemental Table S4, Supplemental Fig. S5). Although combining the clinical and genetic risk scores improved the 30th percentile comparison HR from the clinical risk score alone only slightly, the combination score already outperformed the clinical risk score in the quintile comparisons (HR 75.42 [95% CI 25.80, 220.48] vs HR 85.48 [95% CI 29.67, 246.26], respectively).

Survival model GRS performance (C-index 0.562 [95% CI 0.535, 0.589]) was comparable to the traditional clinical risk factors HbA_{1c} (C-index 0.563, *P*=1.0), HDL cholesterol (C-index 0.571, *P*=0.6), LDL cholesterol (C-index 0.598, *P*=0.064) and total cholesterol (C-index 0.594, *P*=0.1) (Fig. 1). Furthermore, the GRS significantly outperformed sex (C-index 0.520, *P*=0.02), while we noticed a non-significant improvement from smoking (C-index 0.527, *P*=0.05) and diastolic BP (C-index 0.529, *P*=0.1) in survival model risk prediction. However, other clinical variables, i.e. triglycerides (C-index 0.629, *P*= 0.0007), DN status (C-index 0.698, $P=5.0\times10^{-12}$), systolic BP (C-index 0.700, $P=2.8\times10^{-12}$), age (C-index 0.748, $P<1.00\times10^{-12}$) and calendar year of type 1 diabetes onset (C-index 0.770, $P<1.00\times10^{-12}$), significantly outperformed the GRS. Furthermore, the genome-wide PRS did not outperform the allelic GRS based on 156 variants (C-index 0.571 vs 0.562, *P=0.46*) (Fig. 1). Thus, the subsequent analyses were performed with the GRS with variant effect similarities previously assessed in type 1 diabetes

(16). When we combined the genetic and clinical risk scores into a combination score, we saw a modestly improved risk stratification of the individuals over the clinical risk score (C-index for clinical score 0.813 vs for combined score 0.820, *P*=0.003). Of note, when we inspected the performance of a multivariable survival model (sex, smoking, DN status, calendar year of type 1 diabetes onset, age, systolic- and diastolic BP, waist-to-height ratio, total- and HDL cholesterol, triglycerides and HbA_{1c}), we noticed a similar trend with respect to GRS addition (C-index for multivariable clinical model 0.829 vs for multivariable clinical model with GRS 0.836).

In further analyses, we split individuals according to their median age at baseline into two groups (age <38.6 years and age ≥38.6 years). The performance of GRS was better in the younger age group (C-index 0.637 [0.580, 0.695]) than in the older age group (C-index 0.546 [0.516, 0.577]). In the younger age group, the GRS outperformed sex, smoking and waist-to-height ratio, and was comparable to most of the clinical risk factors, while only DN status outperformed it (Supplemental Fig. S6A). In contrast, in the older age group most of the clinical variables outperformed the GRS (Supplemental Fig. S6B).

Finally, a multivariable Cox PH model with all clinical variables found that the strongest predictors were age (HR 1.78 [95% CI 1.56–2.03]), calendar year of type 1 diabetes onset (HR 0.62 [95% CI 0.54-0.72]), DN status (HR 1.64 [95% CI 1.49-1.81]) and GRS (HR 1.31 [95% CI 1.19-1.44]) (Fig. 2). In addition, HDL cholesterol, systolic BP and HbA_{1c} reached statistical significance after Bonferroni correction, although with more modest effect sizes. Thus, unlike many important clinical variables, such as waist-to-height ratio and total cholesterol, the GRS attained a highly significant association with incident CAD events when adjusted for clinical risk factors. Although the clinical variables strongly correlated with each other, GRS only

weakly correlated with HDL-, LDL- and total cholesterol (Supplemental Fig. S7), which may explain the clear association between GRS and CAD events in a strongly adjusted model. Of note, no correlation was observed between GRS and clinical risk score (-0.013, *P*=0.5).

Pharmacological treatment and CAD

As antihypertensive and lipid-lowering medications are an important part of preventing and treating CAD, we estimated the value of GRS in those who were already medicated at baseline and continuously thereafter. As expected, individuals with none of these drugs (n=1,258) had a shorter duration of diabetes and a better clinical profile, compared to those with antihypertensive drugs only (n=559), or both antihypertensive and lipid-lowering drugs (n=282; Supplementary Table S5). No differences in CAD risk were observed between the top and the bottom quintiles in those who were taking both antihypertensive and lipid-lowering drugs (HR 0.99 [95% CI 0.54, 1.84]). On the contrary, there was a clear difference in CAD risk between the top and the bottom GRS quintiles in those on continuous antihypertensive drug treatment only (HR 2.23 [95% CI 1.24, 3.98]). Notably, the HR between the top and the bottom quintiles was almost fourfold (HR 3.78 [95% CI 1.63, 8.78]) in those with none of these drugs (Supplemental Table S6, Supplemental Fig. S8). The results did not change after adjustment for the clinical risk score.

Conclusions

Our findings from a representative cohort of individuals with type 1 diabetes illustrate that a general population GRS, built with 156 established CAD risk variants, successfully identified individuals at high risk for CAD. Notably, the GRS was comparable to the risk imposed by traditional risk factors such as HbA_{1c}, HDL- and total cholesterol. The GRS combined with a validated clinical score for individuals with type 1 diabetes discriminated high and low risk

individuals with high accuracy and modestly improved CAD risk prediction over the clinical risk score. Furthermore, within a multivariable survival model with several clinical risk variables, the GRS stands out as one of the strongest predictors of CAD events, which may be attributable to the GRS not being strongly correlated with the clinical risk factors. Importantly, the GRS showed better performance in the younger age group than in the older age group, suggesting that the GRS is particularly important for the younger individuals. Moreover, our data also demonstrated that among participants without antihypertensive or lipid-lowering medication (mean age 33.6 years), those within the highest GRS quintile had nearly fourfold risk of CAD compared with those in the lowest GRS quintile, which also points towards the utility of the GRS in the early prediction of CAD.

Only a few studies have considered the association between GRSs and incidence of CAD in individuals with diabetes (33-35). Findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study in type 2 diabetes (35) showed that a GRS, derived from 204 variants identified in the general population, predicted CAD (area under ROC 0.567, HR per SD 1.27 [1.18, 1.37]) comparably to our study; thus, providing further evidence for the known risk loci to impact individuals with type 1 diabetes equally. Moreover, addition of further genetic factors, such as the haptoglobin genotype (17), or diabetes-specific genetic findings (15, 16), which are not included in our score, might further enhance the risk stratification of individuals with type 1 diabetes at increased risk of CAD. In line with the findings from the ACCORD study, the risk stratification improved modestly, but significantly, when an allelic GRS was added to the clinical model.

Over the past decade, research on the potential of genetic information to improve CAD risk prediction have expanded from a few candidate genes (14) to genome-wide studies with PRSs

constructed with thousands or millions of genetic variants (19, 20). In the current study, the allelic GRS with 156 established risk variants already provided significant improvement with respect to survival model performance. We also examined a general population PRS with five million variants, but found no significant improvement compared to the allelic GRS. The genetic background of CAD on a genome-wide level most likely differs for individuals with type 1 diabetes, therefore, using variant weights optimized in the general population even at diabetes specific genetic loci might cause unnecessary noise and decrease PRS performance. We call for further research on diabetes specific CAD genome-wide PRS. In fact, in the general population, genome-wide PRSs of almost 500,000 adults (19) have shown great predictive ability of CAD events (C-index 0.623). Moreover, advances in microarray technologies may provide standardized genetic risk tools which can be applied to clinical use. Meanwhile, an allelic GRS may be helpful to identify individuals with type 1 diabetes with high genetic risk for CAD and to carry out randomized clinical trials to test if these high-risk individuals are, similarly to the general population (21, 22), more likely to benefit from early intervention.

Of note, we observed no difference in CAD risk between the top and the bottom quintile of the GRS among individuals with both antihypertensive and lipid-lowering drugs. Our results are consistent with previous *post hoc* analyses of clinical trial data, which have illustrated that high genetic risk of CAD may be mitigated by statin therapy (22, 36). However, our findings may only partly be explained by the use of statins. Foremost, the number of individuals using statins without antihypertensive treatment was too low to be able to draw any firm conclusions from that group. Additionally, our data show that individuals with antihypertensive and lipid-lowering treatment had already a worse clinical risk profile at baseline compared to those without pharmacological intervention throughout the follow-up. Following medical guidelines, antihypertensive and lipid-lowering drugs have been prescribed predominantly to those with

the worst prognosis. Among these high-risk individuals with established clinical risk indications the GRS no longer seems clinically useful.

Although our data on the GRS after manifestation of clinical symptoms and pharmacological interventions are inconclusive, the GRS is a life-long non-modifiable risk factor for CAD and therefore, high-risk individuals with respect to CAD could be identified prior to the manifestation of any clinical risk factor (37). Thus, a GRS may be a novel and independent biomarker for clinical use in CAD event prediction in the younger individuals with type 1 diabetes, and allows preventative action and early intervention steps to be taken at an early stage among high-risk individuals (38).

The strengths of our study include its large representative cohort of individuals with type 1 diabetes. All participants were also carefully characterized and linked to the Finnish national administrative registers, covering all CAD events (39) and all outpatient prescriptions for antihypertensive and lipid-lowering drugs. Some limitations, however, need to be considered. Although, we have one of the largest GWAS data sets for individuals with type 1 diabetes, this study might still suffer from limited power due to moderate GWAS size. Even though we used a validated clinical risk score developed for type 1 diabetes, the score was designed to predict CVD events, while we evaluated CAD as the primary outcome. Of note, this validated score does not include all verified clinical risk factors, such as LDL cholesterol (40). Due to the observational design and limited power to match medicated and non-medicated individuals with similar disease severity, we were not able to conclusively assess the effect of lipid-lowering medications.

In conclusion, our study showed that a general population GRS discriminates those individuals with type 1 diabetes, who have high risk of CAD. Importantly, the GRS is an independent risk factor and comparable to the risk imposed by the traditional risk factors such as HbA_{1c}, HDL and total cholesterol. Furthermore, the GRS modestly improved risk stratification when incorporated into the validated clinical risk model specific for individuals with type 1 diabetes. Notably, GRS is a particularly important risk factor among younger individuals, similarly to those with no medication, but seems to be no longer of clinical use in individuals with the worst clinical profile, who are treated with both antihypertensive and lipid-lowering medications. As the GRS is a life-long risk factor and established well before the clinical risk manifests, we envision the main benefit in future clinical practice to be the early identification of younger individuals at a high risk for CAD.

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Author contributions

R.L. and A.A. designed and carried out the data analyses, interpreted the results, wrote the manuscript, and reviewed/edited the manuscript. S.M. designed the analysis, contributed to it

and its interpretation and revised the manuscript. V.H. contributed to the acquisition of data and revised the manuscript. E.V. contributed to the analysis and revised the manuscript. C.F., N.S. and P.-H.G. contributed to discussion, and reviewed/edited the manuscript. P.-H.G. has full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analyses. All authors gave their final approval of this version of the manuscript.

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Duality of Interest

P-H.G. has received lecture honoraria from Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, EloWater, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Peer Voice, Sanofi and Sciarc. P-H.G. is an advisory board member for AbbVie, Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk and Sanofi. P-H.G. has received investigator-initiated grants from Eli Lilly and Roche. No other potential conflicts of interest relevant to this article

were reported. The funding sources were not involved in the design or conduct of the study. All other authors declare that there is no duality of interest associated with this manuscript.

Data availability

No data are available. The ethical statement and the informed consent do not allow for free data availability.

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Table 1. Baseline clinical characteristics of the cases who developed CAD and controls who did not during the follow-up.

	Cases	Controls	*P* value
N	467	2,828	
Age (years)	46.8 ± 9.7	37.8 ± 10.9	3.0×10^{-60}
Males, n (%)	252 (54.0)	1,422 (50.3)	0.2
Duration of diabetes (years)	31.5 ± 9.8	21.4 ± 11.4	2.2×10^{-71}
Median age at onset of diabetes (years)	13.5 (8.8–20.9)	14.4 (9.5–22.7)	0.01
Median calendar year of type 1 diabetes onset	1967 (1962–1974)	1980 (1972–1988)	5.0×10^{-83}
Diabetic nephropathy status n (%)			1.1×10^{-61}
Normal AER	160 (34.3)	1925 (68.1)	NA
Microalbuminuria	66 (14.1)	399 (14.1)	NA
Macroalbuminuria	155 (33.2)	369 (13.0)	NA
End-stage renal disease	86 (18.4)	135 (4.8)	NA
Median eGFR (ml/min/1.73 m^2)	71.0 (24.8–99.6)	101.2 (83.5–113.8)	6.6×10^{-55}
CKD (ml/min/1.73 m^2)			1.4×10^{-57}
1 eGFR >90	164 (35.1)	1,917 (67.8)	NA
2 eGFR 60-89	116 (24.8)	569 (20.1)	NA
3 eGFR 30-59	62 (13.3)	136 (4.8)	NA
4 eGFR 15-29	29 (6.2)	52 (1.8)	NA
5 eGFR <15	96 (20.6)	154 (5.4)	NA
Systolic BP (mmHg)	146 ± 20	133 ± 18	6.6×10^{-33}
Diastolic BP (mmHg)	81 ± 10	80 ± 10	0.08
Waist-to-height ratio	0.52 ± 0.06	0.50 ± 0.06	9.3×10^{-11}
Total cholesterol (mmol/l)	5.28 ± 1.13	4.88 ± 0.93	5.7×10^{-13}
HDL cholesterol (mmol/l)	1.25 ± 0.37	1.36 ± 0.39	9.4×10^{-10}
LDL cholesterol (mmol/l)	3.39 ± 0.95	3.01 ± 0.86	3.8×10^{-15}
Median triglycerides (mmol/l)	1.23 (0.92–1.79)	0.98 (0.74–1.39)	1.1×10^{-19}
HbA_{1c} (%)	8.7 ± 1.5	8.3 ± 1.4	2.3×10^{-6}
HbA_{1c} (mmol/mol)	70 ± 16	67 ± 16	2.3×10^{-6}
Current or history of smoking, n (%)	239 (51.2)	1,293 (45.7)	0.03
Previous stroke, n (%)	28 (6.0)	42 (1.5)	1.1×10^{-9}
Deceased until 2015, n (%)	192 (41.1)	286 (10.1)	5.7×10^{-69}
GRS	0.0086 ± 0.0032	0.0078± 0.0032	7.7×10^{-7}
Median clinical risk score	8.17 (4.58–15.44)	2.16 (0.89–4.88)	5.5×10^{-100}

Data are mean ± SD, median (IQR), or %. NA, not applicable, GRS, genetic risk score

Figure legends

Figure 1. C-indexes with 95% CI for clinical covariates, as well as for the genetic, clinical and combined risk scores. PRS, polygenic risk score

Figure 2. Forest plot for clinical variables and genetic risk score as separate covariates in one multivariable Cox regression model. All covariates were standardized.

Supplementary Material

Lithovius R, Antikainen AA, Mutter S ,Valo E, Forsblom C, Harjutsalo V, Sandholm N, Groop PH, on behalf of the FinnDiane Study Group. Genetic risk score enhances coronary artery disease risk prediction in individuals with type 1 diabetes

Contents

Supplemental Tables

Supplemental Table S1. Physicians and nurses at each of the FinnDiane centers participating in patient recruitment and characterization

The Finnish Diabetic Nephropathy Study Center	Physicians and nurses
Anjalankoski Health Center	S.Koivula, T.Uggeldahl
Central Finland Central Hospital, Jyväskylä	T.Forslund, A.Halonen, A.Koistinen, P.Koskiaho, M.Laukkanen, J.Saltevo, M.Tiihonen
Central Hospital of Åland Islands, Mariehamn	M.Forsen, H.Granlund, A.-C.Jonsson, B.Nyroos
Central Hospital of Kanta-Häme, Hämeenlinna	P.Kinnunen, A.Orvola, T.Salonen, A.Vähänen
Central Hospital of Kymenlaakso, Kotka	R.Paldanius, M.Riihelä, L.Ryysy
Central Hospital of Länsi-Pohja, Kemi	H.Laukkanen, P.Nyländen, A.Sademies
Central Ostrobothnian Hospital District, Kokkola	S.Anderson, B.Asplund, U.Byskata, P.Liedes, M.Kuusela, T.Virkkala
City of Espoo Health Center:	
Espoonlahti	A.Nikkola, E.Ritola
Tapiola	M.Niska, H.Saarinen
Samaria	E.Oukko-Ruponen, T.Virtanen
Viherlaakso	A.Lyytinen
City of Helsinki Health Center:	
Puistola	H.Kari, T.Simonen
Suutarila	A.Kaprio, J.Kärkkäinen, B.Rantaeskola
Töölö	P.Kääriäinen, J.Haaga, A-L.Pietiläinen
City of Hyvinkää Health Center	S.Klemetti, T.Nyandoto, E.Rontu, S.Satuli-Autere
City of Vantaa Health Center:	
Korso	R.Toivonen, H.Virtanen
Länsimäki	R.Ahonen, M.Ivaska-Suomela, A.Jauhiainen
Martinlaakso	M.Laine, T.Pellonpää, R.Puranen
Myyrmäki	A.Airas, J.Laakso, K.Rautavaara
Rekola	M.Erola, E.Jatkola
Tikkurila	R.Lönnblad, A.Malm, J.Mäkelä, E.Rautamo
Heinola Health Center	P.Hentunen, J.Lagerstam
Helsinki University Central Hospital, Department of Medicine, Division of Nephrology	M.Feodoroff, D.Gordin, O.Heikkilä, K.Hietala, J.Fagerudd, M.Korolainen, L.Kyllönen, J.Kytö, S.Lindh, K.Pettersson-Fernholm, M.Rosengård-Bärlund, A.Sandelin, L.Thorn, J.Tuomikangas, T.Vesisenaho, J.Wadén
Herttoniemi Hospital, Helsinki	V.Sipilä
Hospital of Lounais-Häme, Forssa	T.Kalliomäki, J.Koskelainen, R.Nikkanen, N.Savolainen, H.Sulonen, E.Valtonen
Hyvinkää Hospital	L. Norvio, A.Hämäläinen
Iisalmi Hospital	E.Toivanen
Jokilaakso Hospital, Jämsä	A.Parta, I.Pirttiniemi
Jorvi Hospital, Helsinki University Central Hospital	S.Aranko, S.Ervasti, R.Kauppinen-Mäkelin, A.Kuusisto, T.Leppälä, K.Nikkilä, L.Pekkonen
Jyväskylä Health Center, Kyllö	K.Nuorva, M.Tiihonen
Kainuu Central Hospital, Kajaani	S.Jokelainen, K.Kananen, M.Karjalainen, P.Kemppainen, A-M.Mankinen, A.Reponen M.Sankari
Kerava Health Center	H.Stuckey, P.Suominen
Kirkkonummi Health Center	A.Lappalainen, M.Liimatainen, J.Santaholma
Kivelä Hospital, Helsinki	A.Aimolahti, E.Huovinen
Koskela Hospital, Helsinki	V.Ilkka, M.Lehtimäki
Kotka Health Center	E.Pälikkö-Kontinen, A.Vanhanen
Kouvola Health Center	E.Koskinen, T.Siitonen
Kuopio University Hospital	E.Huttunen, R.Ikäheimo, P.Karhapää, P.Kekäläinen, M.Laakso, T.Lakka, E.Lampainen, L.Moilanen, S. Tanskanen, L.Niskanen, U.Tuovinen, I.Vauhkonen, E.Voutilainen
Kuusamo Health Center	T.Kääriäinen, E.Isopoussu
Kuusankoski Hospital	E.Kilkki, I.Koskinen, L.Riihelä
Laakso Hospital, Helsinki	T.Meriläinen, P.Poukka, R.Savolainen, N.Uhlenius
Lahti City Hospital	A.Mäkelä, M.Tanner
Lapland Central Hospital, Rovaniemi	L.Hyvärinen, K.Lampela, S.Pöykkö, T.Rompasaari, S.Severinkangas, T.Tulokas
Lappeenranta Health Center	P. Erola, L.Härkönen, P.Linkola, T.Pekkanen, I.Pulli, E.Repo
Lohja Hospital	T.Granlund, K.Hietanen, M.Porrassalmi, M.Saari, T.Salonen, M.Tiikkainen,
Länsi-Uusimaa Hospital, Tammisaari	I.-M.Jousmaa, J.Rinne
Loimaa Health Center	A.Mäkelä, P.Eloranta
Malmi Hospital, Helsinki	H.Lanki, S.Moilanen, M.Tilly-Kiesi
Mikkeli Central Hospital	A.Gynther, R.Manninen, P.Nironen, M.Salminen, T.Vänttinen
Mänttä Regional Hospital	I.Pirttiniemi, A-M.Hänninen
North Karelian Hospital, Joensuu	U-M.Henttula, P.Kekäläinen, M.Pietarinen, A.Rissanen, M.Voutilainen
Nurmijärvi Health Center	A.Burgos, K.Urtamo
Oulaskangas Hospital, Oulainen	E.Jokelainen, P-L.Jylkkä, E.Kaarlela, J.Vuolaspuro
Oulu Health Center	L.Hiltunen, R.Häkkinen, S.Keinänen-Kiukaanniemi
Oulu University Hospital	R.Ikäheimo
Päijät-Häme Central Hospital	H.Haapamäki, A.Helanterä, S.Hämäläinen, V.Ilvesmäki, H.Miettinen
Palokka Health Center	P.Sopanen, L.Welling
Pieksämäki Hospital	V.Sevtsenko, M.Tamminen
Pietarsaari Hospital	M-L.Holmbäck, B.Isomaa, L.Sarelin

Pori City Hospital	P.Ahonen, P.Merisalo, E.Muurinen, K.Sävelä
Porvoo Hospital	M.Kallio, B.Rask, S.Rämö
Raahe Hospital	A.Holma, M.Honkala, A.Tuomivaara, R.Vainionpää
Rauma Hospital	K.Laine, K.Saarinen, T.Salminen
Riihimäki Hospital	P.Aalto, E.Immonen, L.Juurinen
Salo Hospital	A.Alanko, J.Lapinleimu, P.Rautio, M.Virtanen
Satakunta Central Hospital, Pori	M.Asola, M.Juhola, P.Kunelius, M.-L.Lahdenmäki, P.Pääkkönen, M.Rautavirta
Savonlinna Central Hospital	T.Pulli, P.Sallinen, M.Taskinen, E.Tolvanen, T.Tuominen, H.Valtonen, A.Vartia, S-L. Viitanen
Seinäjoki Central Hospital	O.Antila, E.Korpi-Hyövälti, T.Latvala, E.Leijala, T.Leikkari, M.Punkari, N.Rantamäki, H.Vähävuori
South Karelia Central Hospital, Lappeenranta	T.Ensala, E.Hussi, R.Härkönen, U.Nyholm, J.Toivanen
Tampere Health Center	A.Vaden, P.Alarotu, E.Kujansuu, H.Kirkkopelto-Jokinen, M.Helin, S.Gummerus, L.Calonius, T.Niskanen, T.Kaitala, T.Vatanen
Tampere University Hospital	P. Hannula, I.Ala-Houhala, R.Kannisto, T.Kuningas, P.Lampinen, M.Määttä, H.Oksala, T.Oksanen, A.Putila, H.Saha, K.Salonen, H.Tauriainen, S.Tulokas
Tiirismaa Health Center, Hollola	T.Kivelä, L.Petlin, L.Savolainen
Turku Health Center	A.Artukka, I.Hämäläinen, L.Lehtinen, E.Pyysalo, H.Virtamo, M.Viinikkala, M.Vähätalo
Turku University Central Hospital	K.Breitholz, R.Eskola, K.Metsärinne, U.Pietilä, P.Saarinen, R.Tuominen, S.Äyräpää
Vaajakoski Health Center	K.Mäkinen, P.Sopanen
Valkeakoski Regional Hospital	S.Ojanen, E.Valtonen, H.Ylönen, M.Rautiainen,T.Immonen
Vammala Regional Hospital	I.Isomäki, R.Kroneld, L.Mustaniemi, M.Tapiolinna-Mäkelä
Vaasa Central Hospital	S.Bergkulla, U.Hautamäki, V-A.Myllyniemi, I.Rusk

Supplemental Table S2. ICD and procedure codes used for ascertaining coronary artery disease (CAD) during the whole study period (by the end of 2015) and ICD codes used for ascertaining previous stroke events prior to the FinnDiane baseline visit (for the clinical risk score calculation)

Code type	Register	Codes	Explanation
ICD-10	Finnish Causes of Death Register and Finnish Care Register for Health Care (Hospital Discharge Register until 1993)	I21, I22, I23	myocardial infraction
		I60, I61, I62, I63, I64	stroke
ICD-9		410, 412	myocardial infraction
		430, 431, 432, 433, 434	stroke
Procedure code	Care Register for Health Care (Hospital Discharge Register until 1993)	FNA01, FNA02, FNA03, FNA04, FNA05, FNA10, FNA20, FNA96 FNB01, FNB02, FNB20, FNB96 FNC10, FNC20, FNC30, FNC40, FNC50, FNC60, FNC96 FND10, FND20, FND96 FNE01, FNE02, FNE03, FNE10, FNE11, FNE20, FNE21, FNE96	coronary bypass surgery (GABG)
	Care Register for Health Care (Hospital Discharge Register until 1993)	FN1AT, FN1BT, FN1YT TFN40,TFN50	coronary balloon angioplasty (PTCA/PCI)
	Care Register for Health Care (Hospital Discharge Register until 1993)	5311, 5312, 5313, 5314, 5315, 5329	coronary operations (coronary bypass surgery or balloon angioplasty) before 1996

CAD was defined as a hard CAD event (myocardial infarction or coronary bypass surgery or coronary balloon angioplasty) and controls were individuals without hard CAD events. In the original study cohort (1) only 5% of cases had CAD event before age of 35 years, and thus, controls with age <35 years (N = 322) or diabetes duration <15 years (N = 151) were excluded from the case–control CAD analysis (1). Stroke was defined as a hard stroke event prior to the FinnDiane baseline visit.

Supplemental Table S3. Variants in the genetic risk score (1, 2)

Variant	Variant position (GRCh37)	Effect allele	Close genes	Known variant EAF	Known variant OR	Reference
rs1333049	9:22125503	C	ANRIL, CDKN2B-AS	0.48	1.36	3
rs2493298	1:3325912	A	PRDM16, PEX10, PLCH2, RER1	0.14	1.06	4
rs3827066	20:44586023	T	PCIF1, ZNF335, NEURL2, PLTP, MMP9	0.14	1.04	4
rs11810571	1:151762308	G	TDRKH, RP11-98D18.9	0.79	1.07	5
rs1317507	13:113631780	A	MCF2L, PCID2, CUL4A	0.26	1.04	4
rs1746048	10:44775824	C	CXCL12	0.87	1.09	6
rs16844401	4:3449652	A	HGFAC, RGS12, MSANTD1	0.07	1.07	4
rs6494488	15:65024204	A	OAZ2, RBPMS2, TRIP4	0.82	1.05	7
rs112635299	14:94838142	G	SERPINA2, SERPINA1	0.98	1.15	4
rs7212798	17:59013488	C	BCAS3	0.15	1.08	8
rs116843064	19:8429323	G	ANGTPL4	0.98	1.16	9
rs2972146	2:227100698	T	LOC646736, IRS1, MIR5702	0.65	1.06	10
rs3825807	15:79089111	A	ADAMTS7	0.57	1.08	6
rs6102343	20:39924279	A	ZHX3, PLCG1, TOP1	0.25	1.04	4
rs6725887	2:203745885	C	WDR12, CARF, FAM117B, ICA1L, NBEAL1	0.15	1.14	6
rs944172	9:110517794	C	KLF4	0.28	1.04	4
rs11099493	4:82587050	A	HNRNPD, RASGEF1B	0.69	1.04	4
rs1250229	2:216304384	T	FN1, ATIC, LOC102724849, ABCA12, LINC00607	0.26	1.07	11
rs3918226	7:150690176	T	NOS3	0.06	1.14	8
rs7623687	3:49448566	A	RHOA, AMT, TCTA, CDHRA, KLHDC8B	0.86	1.07	5
rs7696431	4:169687725	T	PALLD, DDX60L	0.51	1.04	4
rs9501744	6:1617143	C	FOXC1	0.87	1.05	4
rs9982601	21:35599128	T	MRPS6, SLC5A3, KCNE2	0.15	1.18	6
rs2306374	3:138119952	C	MRAS, CEP70	0.18	1.12	6
rs7500448	16:83045790	A	CDH13	0.77	1.07	5
rs8042271	15:89574218	G	MFGE8, RP11-326A19.4, ABHD2	0.90	1.10	8
rs12500824	4:77416627	A	SHROOM3, SEPT11, FAM47E, STBD1	0.36	1.04	4
rs1412444	10:91002927	T	LIPA	0.42	1.09	12
rs2023938	7:19036775	C	HDAC9	0.10	1.08	13
rs2107732	7:45077978	G	CCM2, MYO1G	0.91	1.06	4
rs260020	20:57714025	T	ZNF831	0.13	1.05	4
rs2820315	1:201872264	T	LMOD1, IPO9, NAV1, SHISA4, TIMM17A	0.30	1.05	7
rs6700559	1:200646073	C	DDX59, CAMSAP2, KIF14	0.53	1.04	7
rs9319428	13:28973621	A	FLT1	0.32	1.06	13
rs11057830	12:125307053	A	SCARB1	0.15	1.08	14
rs17581137	15:96146414	A	gene desert	0.75	1.04	4
rs35541991	6:22583856	C	HDGFL1	0.31	1.05	5
rs3936511	5:55860781	G	MAP3K1, MIER3	0.18	1.04	4
rs73015714	19:17855763	G	FCHO1, COLGALT1	0.20	1.06	4
rs7947761	11:100624599	G	ARHGAP42	0.28	1.04	4
rs13723	17:27941886	G	CORO6, BLMH, ANKRD13B, GIT1, SSH2, EFCAB5	0.49	1.04	4
rs2252641	2:145801461	C	ZEB2, TEX41	0.46	1.06	13
rs4773144	13:110960712	G	COL4A1, COL4A2	0.44	1.07	6
rs599839	1:109822166	A	SORT1, PSCR1, CELSR2	0.78	1.11	6
rs61776719	1:38461319	A	FHL3, UTP11, SF3A3, MANEAL, INPP5B	0.53	1.04	4
rs663129	18:57838401	A	PMAIP1, MC4R	0.26	1.06	8
rs9367716	6:57160572	G	PRIM2, RAB23, DST, BEND6	0.68	1.04	4
rs11601507	11:5701074	A	TRIM5, TRIM22, TRIM6, OR52N1, OR52B6	0.07	1.09	4
rs12936587	17:17543722	G	Ral1, PEMT, RASD1, SMCR3, TOM1L2	0.56	1.07	6
rs1892094	1:169094459	C	ATP1B1, BLZF1, CCDC181, F5, NME7, SELP, SLC19A2	0.50	1.04	7

rs2145598	14:58794001	G	ARID4A, PSMA3	0.42	1.03	4
rs46522	17:46988597	T	UBE2Z, GIP, ATP5G1	0.53	1.06	6
rs515135	2:21286057	C	APOB	0.83	1.07	13
rs590121	11:75274150	T	SERPINH1	0.30	1.05	7
rs6984210	8:22033615	G	BMP1, SFTPC, DMTN, PHYHIP, DOK2, XPO7	0.06	1.09	4
rs885150	9:124420173	C	DAB2IP	0.27	1.03	4
rs11206510	1:55496039	T	PCSK9	0.82	1.08	6
rs11556924	7:129663496	C	ZC3HC1, KLHDC10	0.62	1.09	6
rs17087335	4:57838583	T	REST, NOA1	0.21	1.06	8
rs1800775	16:56995236	C	CETP	0.51	1.04	14
rs2895811	14:100133942	C	HHIPL1, YY1	0.43	1.07	6
rs3832966	14:75614504	I	TMED10, ZC2HC1C, RPS6KL1, NEK9, EIF2B2e, ACYP1	0.46	1.05	5
rs3851738	16:75387533	C	CFDP1, BCAR1	0.60	1.05	10
rs60154123	1:210468999	T	HHAT, SERTAD4, DIEXF	0.15	1.05	4
rs1050362	16:72130815	A	DHX38, HP, DHODH	0.38	1.04	7
rs1122608	19:11163601	G	LDLR, SMARCA4	0.77	1.14	6
rs12190287	6:134214525	C	TCF21, TARID (EYA4−AS1)	0.62	1.08	6
rs12493885	3:153839866	C	ARHGEF26	0.85	1.08	10
rs17114036	1:56962821	A	PPAP2B	0.91	1.17	6
rs1801251	2:233633460	A	KCNJ13, GIGYF2	0.35	1.05	14
rs1867624	17:62387091	T	PECAM1, DDX5, TEX2	0.61	1.04	7
rs4266144	3:156852592	G	CCNL1, TIPARP	0.32	1.03	4
rs56062135	15:67455630	C	SMAD3	0.79	1.07	8
rs964184	11:116648917	G	APOA1-C3-A4-A5	0.13	1.13	6
rs10841443	12:20220033	G	RP11-664H17.1	0.67	1.05	10
rs11677932	2:238223955	G	COL6A3	0.68	1.03	4
rs1321309	6:36638636	A	CDKN1A, PI16	0.49	1.03	4
rs1508798	5:9556694	T	SEMA5A, TAS2R1	0.81	1.05	4
rs1561198	2:85809989	T	VAMP5, VAMP8, GGCX	0.45	1.06	13
rs1591805	6:126717064	A	CENPW	0.49	1.04	4
rs246600	5:142516897	T	ARHGAP26	0.48	1.05	7
rs264	8:19813180	G	LPL	0.86	1.11	13
rs4252120	6:161143608	T	PLG, LPAL2	0.73	1.07	13
rs4752700	10:124237612	G	HTRA1, PLEKHA1	0.45	1.03	4
rs4845625	1:154422067	T	IL6R, AQP10, ATP8B2, CHTOP, UBAP2L	0.47	1.06	13
rs582384	2:45896437	A	PRKCE, TMEM247	0.53	1.03	4
rs6905288	6:43758873	A	VEGFA, MRPL14, TMEM63B	0.57	1.05	4
rs7199941	16:81906423	A	PLCG2, CENPN	0.40	1.04	4
rs748431	3:14928077	G	FGD5	0.36	1.05	10
rs10840293	11:9751196	A	SWAP70	0.55	1.06	8
rs10947789	6:39174922	T	KCNK5	0.76	1.07	13
rs11172113	12:57527283	C	LRP1, STAT6	0.41	1.06	14
rs11806316	1:115753482	G	NGF, CASQ2	0.63	1.04	4
rs1800449	5:121413208	T	LOX	0.17	1.07	10
rs2706399	5:131867702	G	IL5, RAD50	0.51	1.07	15
rs2832227	21:30533076	G	MAP3K7CL, BACH1	0.18	1.04	4
rs3184504	12:111884608	T	SH2B3, FLJ21127, ATXN2	0.44	1.07	6
rs35879803	4:146782837	C	ZNF827	0.70	1.05	5
rs3775058	4:96117371	A	UNC5C	0.23	1.04	4
rs699	1:230845794	G	AGT, CAPN9, GNPAT	0.42	1.04	4
rs867186	20:33764554	A	PROCR, ASIP, NCOA6, ITGB4BP/EIF6	0.89	1.08	7
rs975722	7:117332914	G	CTTNBP2, CFTR, ASZ1	0.40	1.03	4
rs11042937	11:10745394	T	MRVl1, CTR9	0.49	1.04	14
rs11838267	12:7175872	T	C1S	0.87	1.05	4
rs12526453	6:12927544	C	PHACTR1, EDN1	0.67	1.10	6

rs17465637	1:222823529	C	MIA3, AIDA, C1orf58	0.74	1.14	6
rs1878406	4:148393664	T	EDNRA	0.15	1.10	13
rs216172	17:2126504	C	SMG6, SRR	0.37	1.07	6
rs2571445	2:218683154	A	TNS1, CXCR2, RUFY4	0.39	1.04	7
rs974819	11:103660567	T	PDGFD	0.32	1.07	12
rs11509880	7:12261911	A	TMEM106B, THSD7A	0.36	1.04	4
rs12897	3:172115902	G	FNDC3B	0.41	1.04	4
rs17608766	17:45013271	C	GOSR2, MYL4, ARL17A	0.14	1.07	7
rs2244608	12:121416988	G	HNF1A, OASL, C12orf43	0.35	1.06	5
rs2505083	10:30335122	C	KIAA1462	0.38	1.07	12
rs667920	3:136069472	T	STAG1, MSL2, NCK1, PPP2R3A	0.78	1.05	4
rs7633770	3:46688562	A	ALS2CL, RTP3	0.41	1.03	4
rs10237377	7:139757136	G	PARP12, TBXAS1	0.65	1.05	7
rs17680741	10:82251514	T	TSPAN14, MAT1A, FAM213A	0.72	1.05	4
rs4918072	10:105693644	A	STN1, SH3PXD2A	0.27	1.04	4
rs579459	9:136154168	C	ABO, SURF6, GBGT1	0.21	1.10	6
rs6997340	8:18286997	T	NAT2	0.31	1.04	4
rs7692387	4:156635309	G	GUCY1A1	0.81	1.08	13
rs10857147	4:81181072	T	PRDM8, FGF5	0.29	1.06	10
rs11057401	12:124427306	T	CCDC92	0.69	1.06	10
rs12413409	10:104719096	G	CYP17A1, CNNM2, NT5C2	0.89	1.12	6
rs1964272	19:46190268	G	SNRPD2, GIPR	0.51	1.05	11
rs2074158	17:40257163	C	DHX58, KAT2A, RAB5, NKIRAS2, DNAJC7, KCNH4, HCRT, GHDC	0.18	1.05	4
rs2075650	19:45395619	G	APOE, APOC1, TOMM40, PVRL2, COTL1	0.14	1.14	15
rs76954792	17:30033514	T	COPRS, RAB11FIP4	0.22	1.04	4
rs12801636	11:65391317	G	PCNX3, POLA2, RELA, SIPA1	0.77	1.05	7
rs12999907	2:164957251	A	FIGN	0.82	1.06	4
rs17080091	6:150997401	C	PLEKHG1, IYD	0.92	1.05	4
rs61848342	10:12303813	C	CDC123, NUDT5, OPTN	0.36	1.04	4
rs7116641	11:43696917	G	HSD17B12	0.31	1.03	4
rs10093110	8:106565414	G	ZFPM2	0.58	1.03	4
rs10512861	3:132257961	G	DNAJC13, NPHP3, ACAD11, UBA5	0.86	1.04	4
rs1351525	11:13301548	T	ARNTL	0.67	1.05	5
rs10267593	7:1937261	G	MAD1L1	0.80	1.04	4
rs273909	5:131667353	G	SLC22A4	0.14	1.07	13
rs2954029	8:126490972	A	TRIB1	0.55	1.06	13
rs9591012	13:33058333	G	N4BP2L2, PDS5B	0.66	1.04	4
rs10953541	7:107244545	C	BCAP29, GPR22	0.80	1.08	12
rs17609940	6:35034800	G	ANKS1A, UHRF1BP1	0.75	1.07	6
rs111245230	9:113169775	C	SVEP1	0.04	1.14	9
rs4613862	6:82612271	A	FAM46A	0.53	1.03	4
rs6544713	2:44073881	T	ABCG5, ABCG8	0.29	1.06	11
rs9964304	18:47229717	C	ACAA2, RPL17	0.28	1.04	4
rs17514846	15:91416550	A	FURIN, FES	0.44	1.07	13
rs3130683	6:31888367	T	C2, C4A	0.86	1.09	14
rs7617773	3:48193515	T	CDC25A, SPINK8, MAP4, ZNF589	0.67	1.04	4
rs840616	2:188196469	C	CALCRL, TFPI	0.65	1.04	4
rs7306455	12:95355541	G	NDUFA12, FGD6	0.90	1.05	4
rs142695226	3:124475201	G	UMPS, ITGB5	0.14	1.08	5
rs12976411	19:32882020	A	ZNF507, LOC400684	0.91	1.05	8
rs11170820	12:54513915	G	HOXC4	0.08	1.10	5

Supplemental Table S4. Cox proportional hazards models according to the low and high genetic, clinical and combined risk score percentile comparisons. Models are adjusted for diabetes onset year and sex.

Percentiles (Low / High)	Low Cases / Controls	High Cases / Controls	*P* value*	HR (95% CI)†	*P* value
GRS 5 / 95	8 / 157	35 / 130	2.1×10^{-5}	6.72 (3.08, 14.70)	1.8×10^{-6}
GRS 10 / 90	34 / 296	76 / 254	1.9×10^{-5}	2.99 (1.98, 4.50)	1.7×10^{-7}
GRS 20 / 80	66 / 593	126 / 533	4.1×10^{-6}	2.21 (1.64, 2.98)	2.2×10^{-7}
GRS 30 / 70	114 / 875	174 / 815	0.0002	1.76 (1.39, 2.24)	2.9×10^{-6}
Clinical risk score 20 / 80	4 / 655	243 / 416	2.5×10^{-63}	75.42 (25.80, 220.48)	2.8×10^{-15}
Clinical risk score 30 / 70	17 / 972	330 / 659	5.7×10^{-76}	15.98 (9.05, 28.22)	1.3×10^{-21}
Combined risk score 20 / 80	4 / 655	255 / 404	2.8×10^{-67}	85.48 (29.67, 246.26)	1.7×10^{-16}
Combined risk score 30 / 70	15 / 974	327 / 662	2.4×10^{-76}	16.92 (9.38, 30.50)	5.2×10^{-21}

**P* values represent comparisons of numbers of cases and controls between the top and the bottom percentiles and are calculated with χ^2 test, †All models adjusted for sex and type 1 diabetes onset year; GRS, genetic risk score

Supplemental Table S5. Characteristics of the individuals according to the medication status

Medication status	No antihypertensive or lipid-lowering drugs (A)	Antihypertensive drugs only (B)	Both antihypertensive and lipid-lowering drugs (C)	Lipid-lowering drugs only (D)	*P* value A vs. B	*P* value A vs. C	*P* value A vs. D	*P* value B vs. C
n	1,258	559	282	40				
Age (years)	33.6 ± 9.9	42.3 ± 10.5	47.3 ± 9.3	50.2 ± 8.4	5.9×10^{-55}	1.5×10^{-72}	1.8×10^{-15}	4.9×10^{-12}
Duration of diabetes (years)	16.9 ± 10.3	27.7 ± 9.8	31.9 ± 9.3	29.0 ± 12.5	4.7×10^{-85}	4.1×10^{-82}	3.8×10^{-7}	2.4×10^{-9}
Median type 1 diabetes onset year	1985 (1977–1991)	1973 (1965–1979)	1969 (1962–1976)	1974 (1965–1982)	2.7×10^{-86}	6.4×10^{-66}	3.7×10^{-7}	0.0003
Men n (%)	551 (43.8)	301 (53.8)	167 (59.2)	15 (37.5)	9.2×10^{-5}	3.7×10^{-6}	0.5	0.2
Median age at diabetes onset (years)	15.5 (10.1–22.7)	13.2 (8.6–19.4)	13.5 (9.0–21.3)	24.1 (14.0–28.1)	4.2×10^{-7}	0.01	0.003	0.2
Genetic risk score	0.0077 ± 0.0031	0.0079 ± 0.0032	0.0083 ± 0.0032	0.0070 ± 0.0028	0.3	0.01	0.1	0.09
Median clinical risk score	1.11 (0.63–2.19)	4.42 (2.17–9.22)	8.99 (4.65–16.28)	4.22 (2.81–10.16)	3.8×10^{-114}	2.7×10^{-115}	4.0×10^{-15}	1.8×10^{-20}
Diabetic nephropathy status n (%)					2.8×10^{-195}	4.2×10^{-160}	0.01	1.3×10^{-5}
Normal AER	1186 (94.3)	164 (29.3)	63 (22.3)	38 (95.0)	NA	NA	NA	NA
Microalbuminuria	61 (4.8)	153 (27.4)	47 (16.7)	0 (0.0)	NA	NA	NA	NA
Macroalbuminuria	8 (0.6)	165 (29.5)	125 (44.3)	0 (0.0)	NA	NA	NA	NA
ESRD	3 (0.2)	77 (13.8)	47 (16.7)	2 (5.0)	NA	NA	NA	NA
Chronic kidney disease n (%)					2.4×10^{-92}	1.1×10^{-139}	9.9×10^{-5}	6.9×10^{-7}
1 eGFR >90 (ml/min/1.73 m^2)	1037 (82.4)	251 (44.9)	86 (30.5)	23 (57.5)	NA	NA	NA	NA
2 eGFR 60 - 89	211 (16.8)	138 (24.7)	56 (19.9)	14 (35.0)	NA	NA	NA	NA
3 eGFR 30 - 59	6 (0.5)	65 (11.6)	55 (19.5)	1 (2.5)	NA	NA	NA	NA
4 eGFR 15 - 29	1 (0.1)	18 (3.2)	24 (8.5)	0 (0.0)	NA	NA	NA	NA
5 eGFR <15	3 (0.2)	87 (15.6)	61 (21.6)	2 (5.0)	NA	NA	NA	NA
Median eGFR (ml/min/1.73 m^2)	108.6 (95.8 – 118.6)	84.4 (47.4 – 105.2)	60.4 (19.0 – 94.3)	96.6 (80.1 – 104.3)	3.6×10^{-72}	2.1×10^{-84}	8.7×10^{-7}	1.5×10^{-8}
HbA_{1c} (%)	8.1 ± 1.4	8.4 ± 1.4	8.6 ± 1.4	8.1 ± 1.1	7.2×10^{-6}	4.9×10^{-9}	0.9	0.02
HbA_{1c} (mmol/mol)	65 ± 16	68 ± 16	71 ± 16	65 ± 12	7.2×10^{-06}	4.9×10^{-9}	0.9	0.02
Total cholesterol (mmol/l)	4.62 ± 0.81	4.96 ± 0.91	5.13 ± 1.09	4.99 ± 0.93	1.6×10^{-13}	8.2×10^{-13}	0.02	0.02
HDL cholesterol (mmol/l)	1.38 ± 0.37	1.34 ± 0.40	1.28 ± 0.40	1.42 ± 0.41	0.07	0.0004	0.5	0.06
Median Triglycerides (mmol/l)	0.88 (0.69 – 1.17)	1.02 (0.77 – 1.50)	1.32 (0.96 – 1.90)	1.00 (0.81 – 1.33)	4.0×10^{-13}	7.6×10^{-35}	0.06	1.96×10^{-10}
LDL cholesterol (mmol/l)	2.81 ± 0.76	3.09 ± 0.84	3.17 ± 0.98	3.11 ± 0.99	1.1×10^{-11}	1.4×10^{-8}	0.06	0.2
Systolic BP (mmHg)	126 ± 14	142 ± 19	148 ± 20	134 ± 14	4.6×10^{-62}	2.65×10^{-50}	0.0006	6.7×10^{-6}
Diastolic BP (mmHg)	77 ± 9	82 ± 10	82 ± 11	76 ± 8	5.0×10^{-24}	8.8×10^{-13}	0.6	0.9
Waist to height ratio	0.48 ± 0.05	0.51 ± 0.06	0.55 ± 0.07	0.53 ± 0.07	5.6×10^{-28}	1.4×10^{-44}	6.1×10^{-5}	2.6×10^{-12}
Current or history of smoking n (%)	510 (40.5)	279 (49.9)	159 (56.4)	17 (42.5)	0.0002	1.7×10^{-6}	0.9	0.09
CAD at the end of follow-up n (%)	67 (5.3)	132 (23.6)	93 (33.0)	7 (17.5)	2.7×10^{-30}	2.1×10^{-12}	0.006	0.005
Previous stroke n (%)	4 (0.3)	18 (3.2)	20 (7.1)	4 (10.0)	9.6×10^{-7}	5.3×10^{-12}	5.0×10^{-5}	0.02
Deceased, n (%)	57 (4.5)	161 (28.8)	92 (32.6)	6 (15.0)	2.2×10^{-48}	1.8×10^{-46}	0.01	0.3

Data are mean ± SD, median (IQR), or %. NA, not applicable

Supplemental Table S6. Cox proportional hazards models according to the low and the high genetic risk score (GRS) quintiles at each medication group

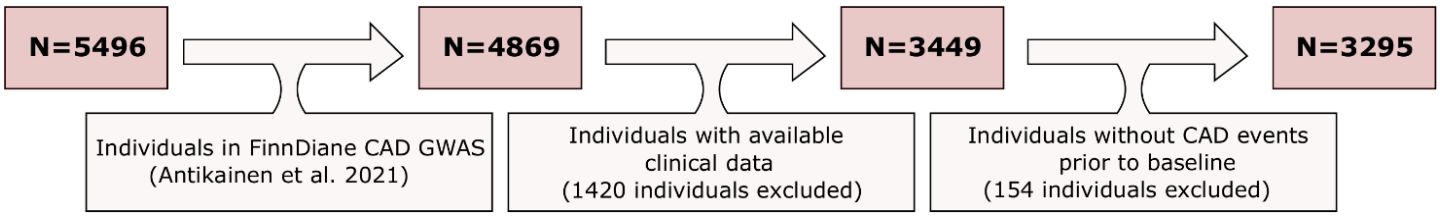
GRS Quintiles (%)	Low (0-20)	High (80-100)		Model 1†		Model 2‡	
	Cases/ Controls	Cases/ Controls	*P* value *	HR (95% CI)	*P* value	HR (95% CI)	*P* value
No antihypertensive or lipid-lowering drugs	7 / 245	25 /227	0.002	3.78 (1.63, 8.78)	0.002	3.68 (1.58, 8.56)	0.002
Antihypertensive drugs only	19 / 93	34 / 78	0.03	2.23 (1.24, 3.98)	0.007	2.69 (1.45, 5.00)	0.002
Both antihypertensive and lipid-lowering drugs	20 / 37	22 / 35	0.8	0.99 (0.54, 1.84)	0.99	1.06 (0.56, 1.97)	0.86

**P* values (calculated with the χ^2test) present comparisons of the numbers of cases and controls between low and high quintiles, †Adjusted for sex and type 1 diabetes onset year, ‡Adjusted for sex, type 1 diabetes onset year and clinical risk score.

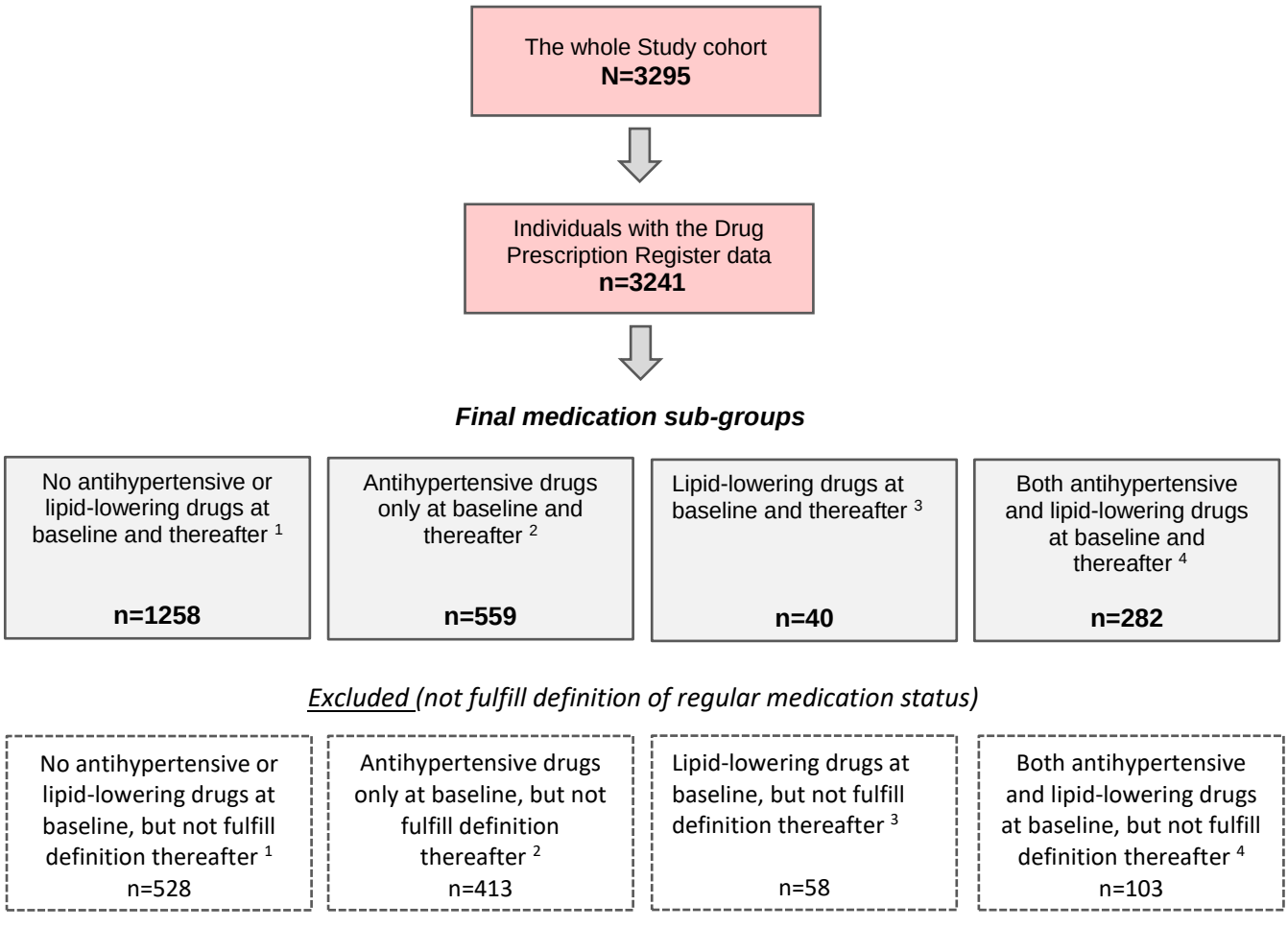
Supplementary Figures

Supplemental Figure S1. Flow chart of the study cohort inclusion process starting from the entire FinnDiane cohort (N=5496) (**A**) and sub-cohort selection process according to the pharmacological treatment (**B**)

A

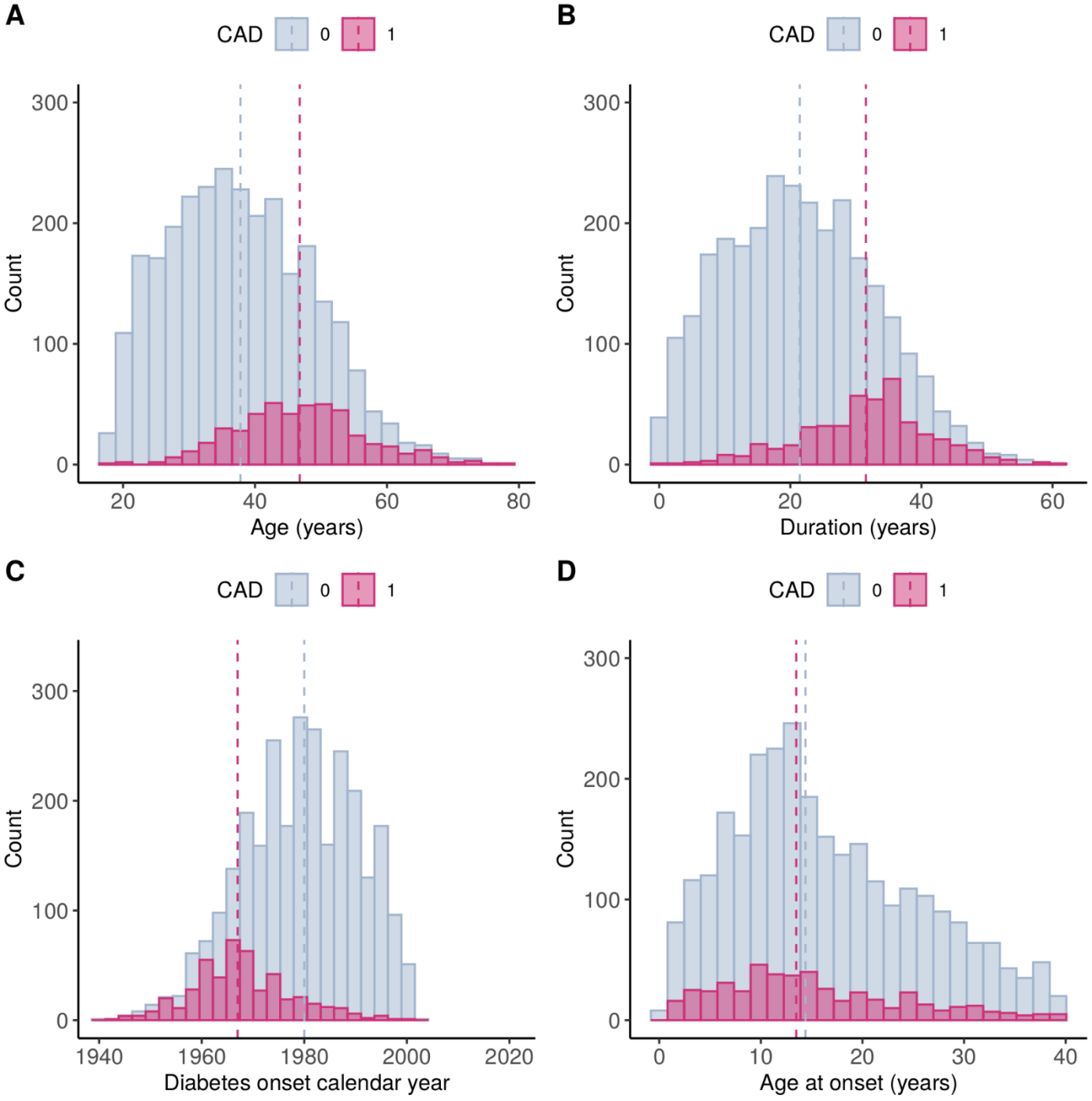


B

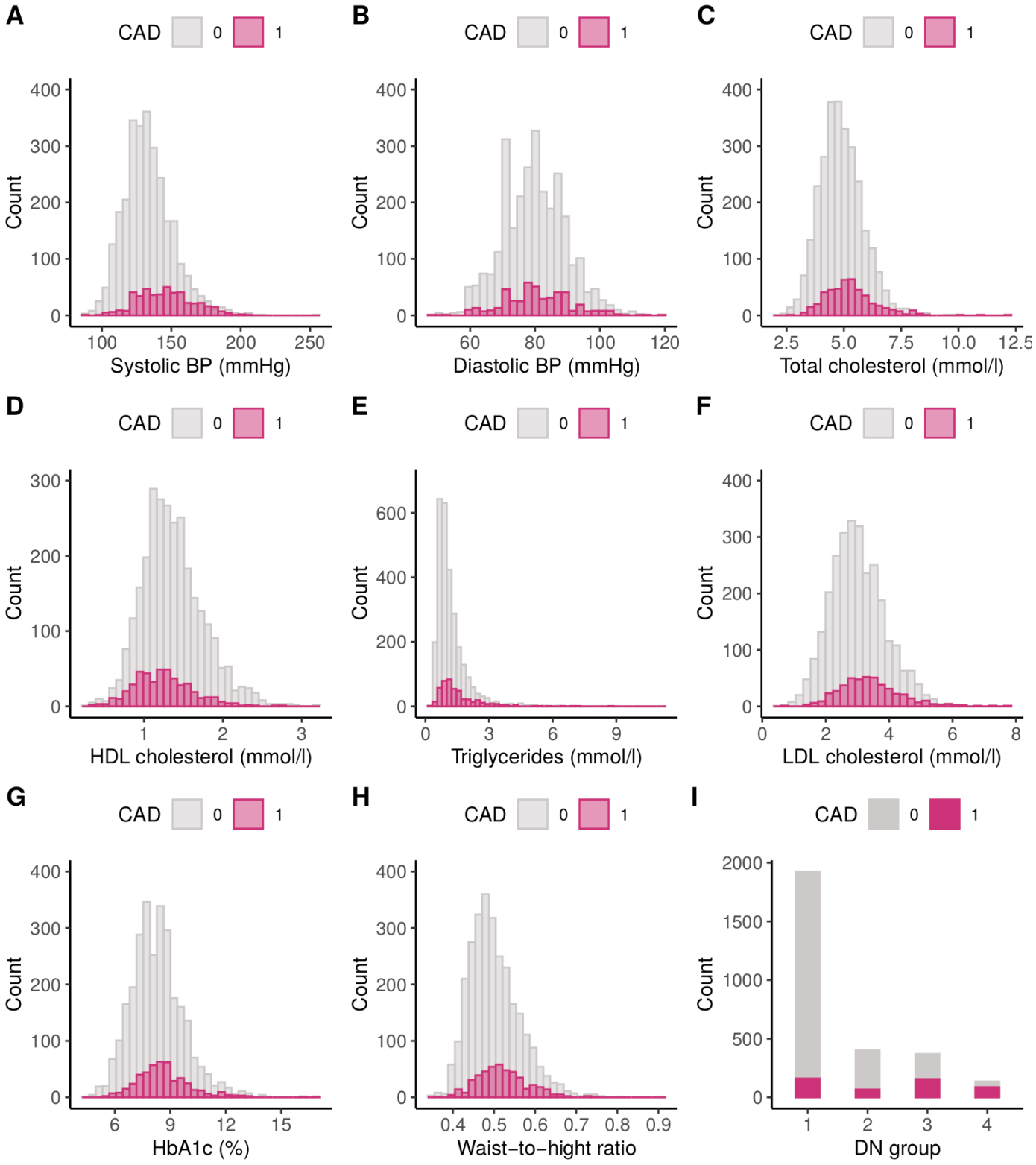


[1] No purchases of antihypertensive and lipid-lowering drugs at baseline and adherence <0.50 for both drugs during the follow-up
[2] Only purchases of antihypertensive drugs at baseline and adherence ≥0.80 for antihypertensive drugs, but <0.50 for lipid-lowering drugs during the follow-up
[3] Only purchases of lipid-lowering drugs at baseline and adherence for lipid-lowering drugs ≥0.80, but <0.50 for antihypertensive drugs during the follow-up
[4] Purchases of antihypertensive and lipid-lowering drugs at baseline and adherence ≥0.80 for both drugs

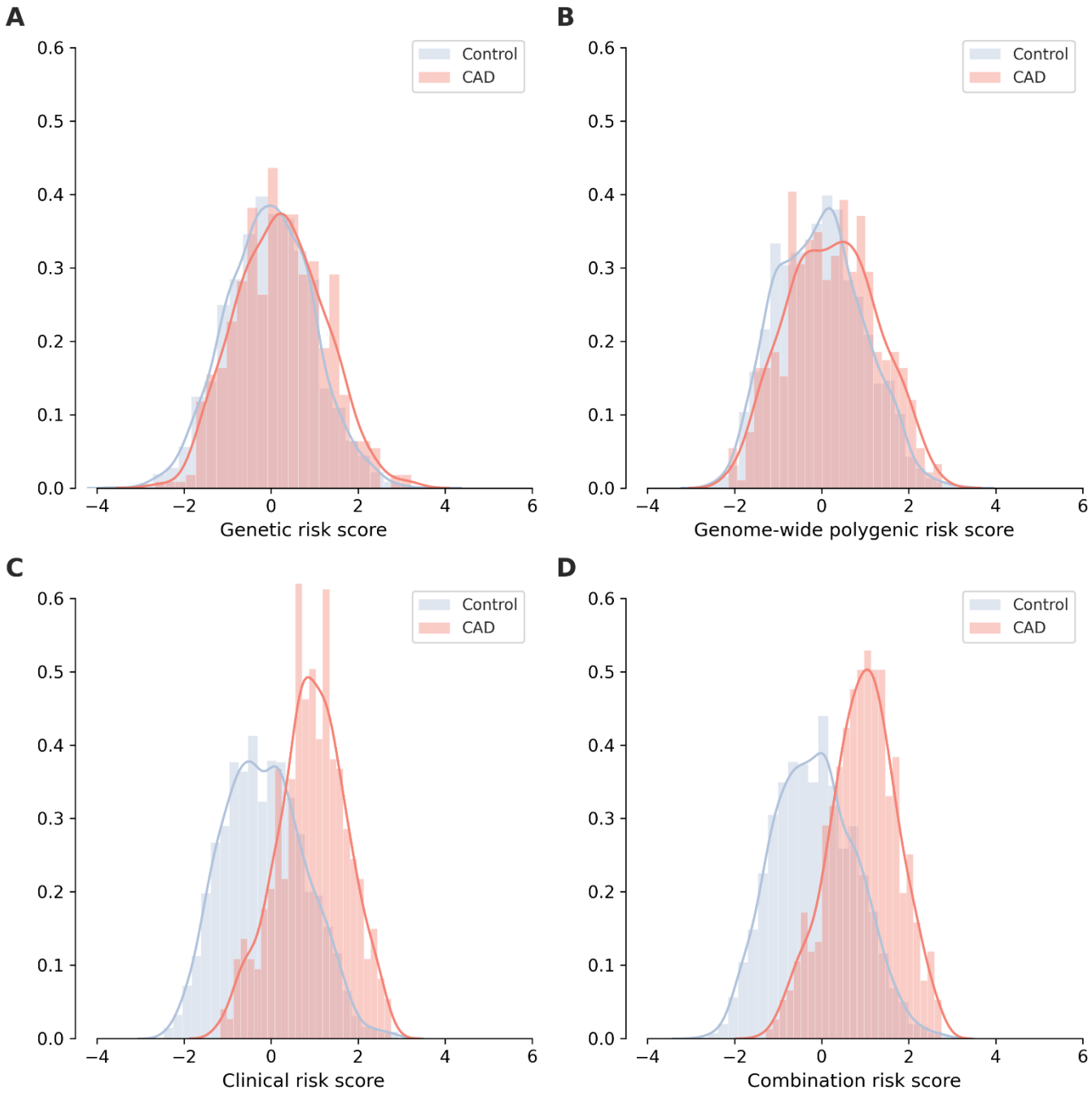
Supplemental Figure S2. Distribution of age (**A**), diabetes duration (**B**), calendar year of type 1 diabetes onset (**C**) and onset age of diabetes (**D**) for 467 CAD cases (red) and for 2,828 controls (grey) at the baseline



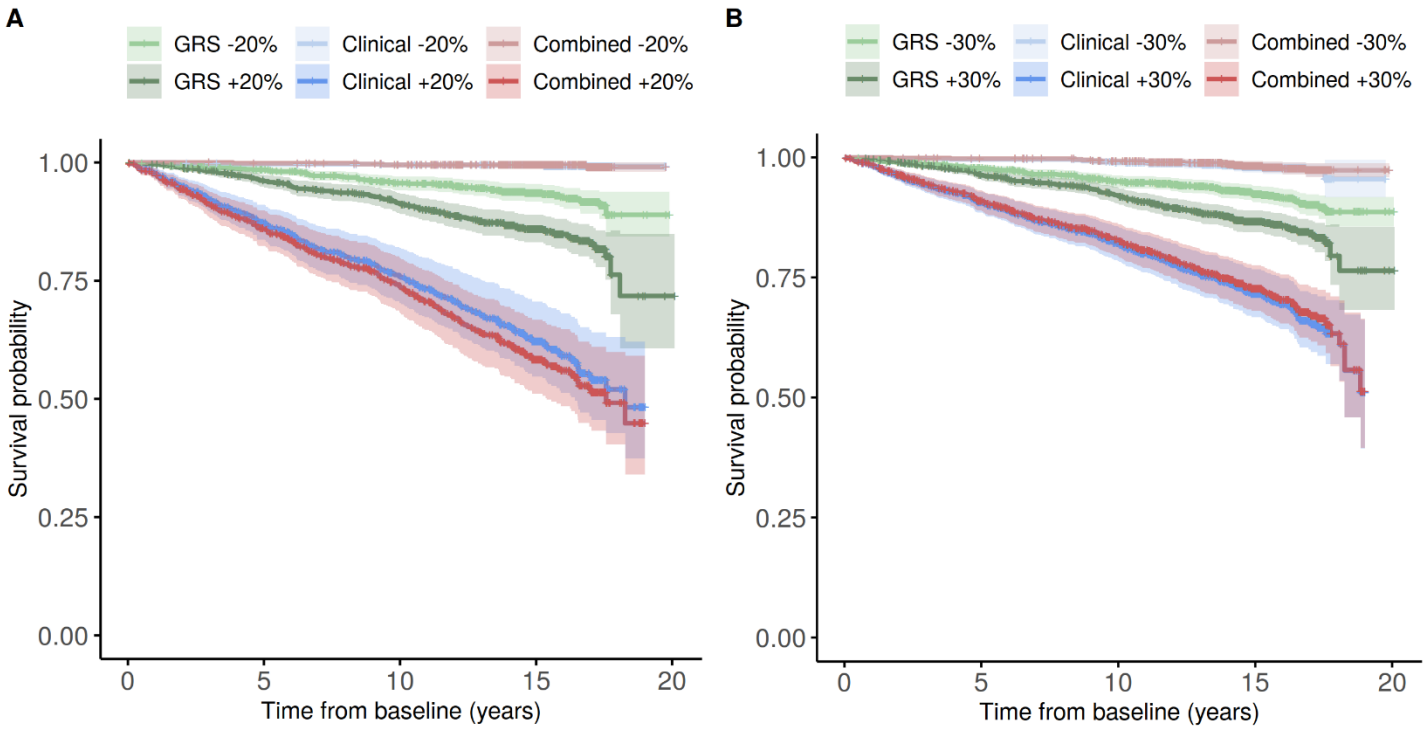
Supplemental Figure S3. Distributions of clinical variables. Systolic BP (**A**), diastolic BP (**B**), total cholesterol (**C**) HDL cholesterol (**D**) triglycerides (**E**), LDL cholesterol (**F**), HbA_{1c} (**G**), waist-to-height ratio (**H**) and diabetic nephropathy (DN) status (1. normal AER, 2. microalbuminuria, 3. macroalbuminuria and 4. end-stage renal disease (**I**) for 467 CAD cases (red) and for 2,828 controls (grey) at the baseline



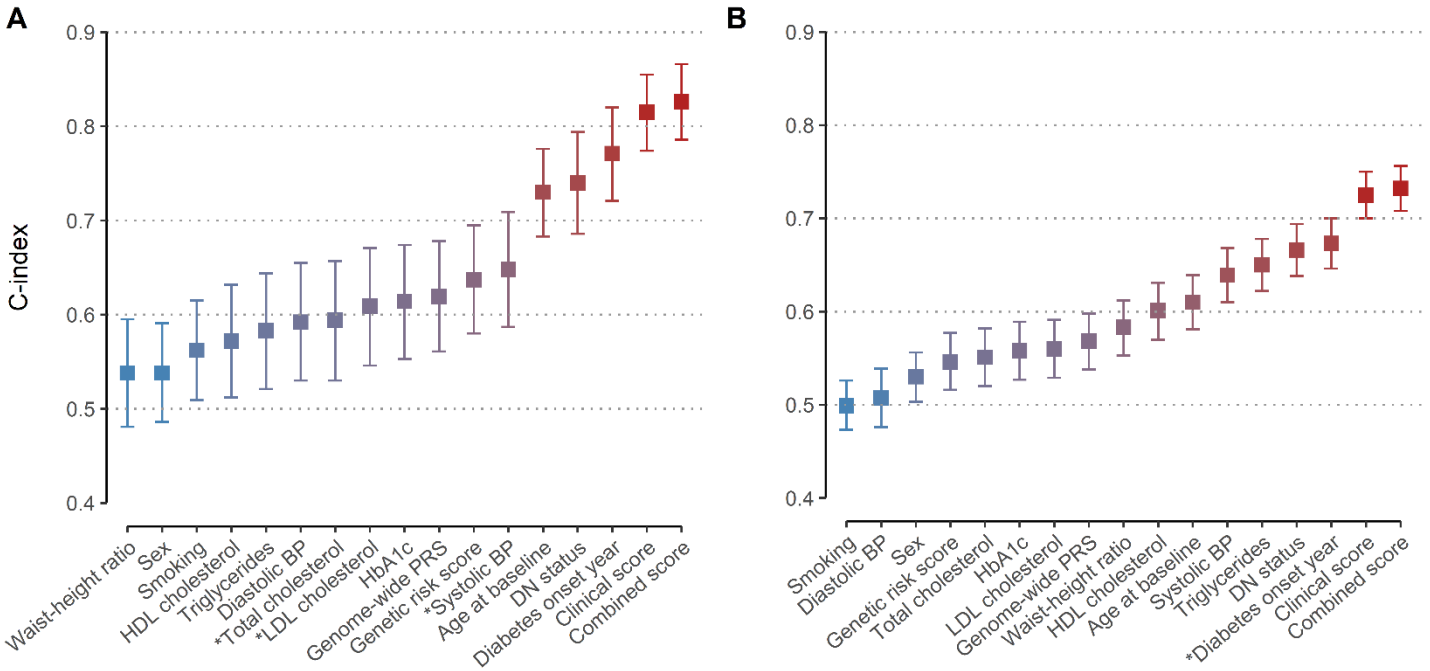
Supplemental Figure S4. Kernel density distribution of genetic (**A**), genome-wide polygenic (**B**), clinical (**C**) and combined (**D**) risk scores for 467 CAD cases (red) and for 2,828 controls (grey) at the baseline



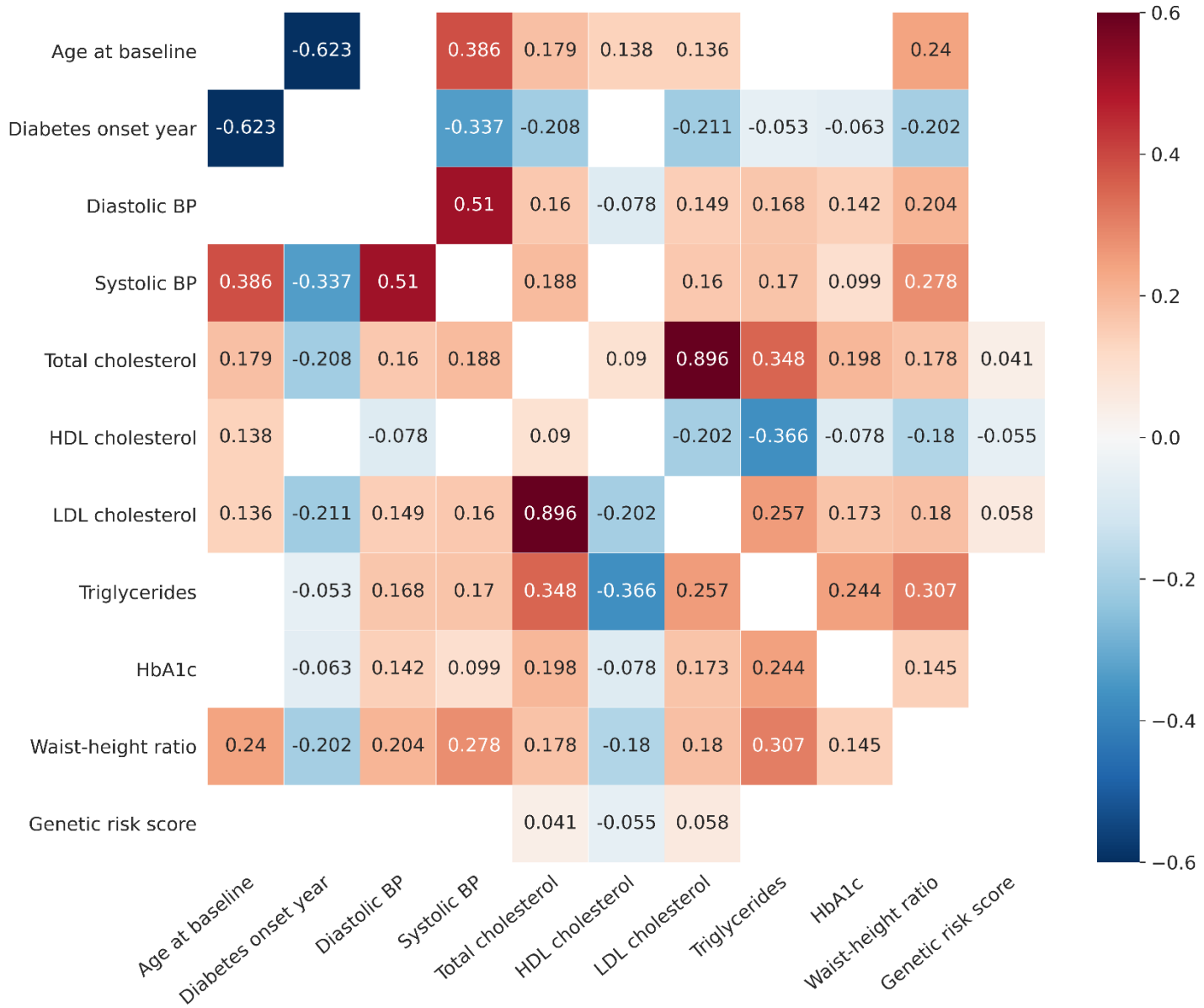
Supplemental Figure S5. Predicted survival functions of Cox proportional hazards models according to 20th percentiles of genetic (GRS), clinical- and combined scores (**A**), and 30th percentiles of GRS, clinical and combined risk scores (**B**). Models are adjusted for sex and type 1 diabetes onset year.



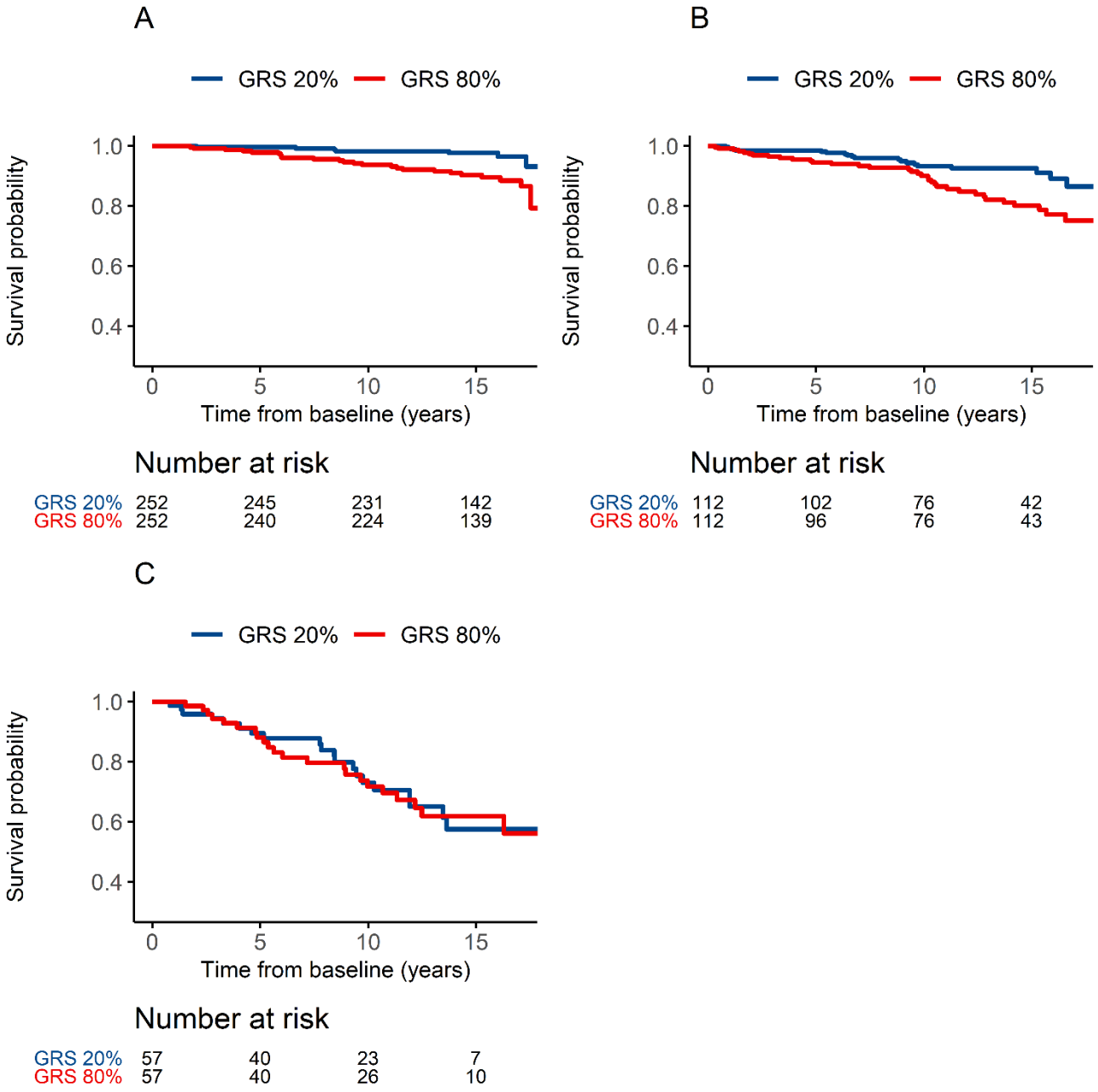
Supplemental Figure S6. C-indexes for clinical covariates, as well as genetic, clinical and combined risk scores according to the younger (i.e. median age at baseline <38.6 years) (**A**) and the older (i.e. median age at baseline ≥38.6 years) (**B**) age groups**.** Variables marked with an * violated the Cox proportional hazard assumption. Following the method from Zhang et al. (16) the follow-up time was split into three distinct periods as required for the model not to violate the assumption, however C-indexes were similar to ones reported. Notably, no differences were observed in C-indexes between the genetic risk score and the genome-wide polygenic risk score (PRS) neither in the younger (p-value 0.34) nor in the older (p-value 0.12) age groups.



Supplemental Figure S7. Correlation heatmap of clinical variables and genetic risk score (GRS). GRS correlates significantly only with HDL, LDL, and total cholesterol. Most of the clinical variables are inter-correlated with each other. These variables correlate at least with four other parameters (baseline age correlated with five other parameters, while the rest with more than five parameters).



Supplemental Figure S8. Predicted survival functions of Cox models according to the low and the high genetic risk score quintiles at each medication group. Models adjusted for sex and type 1 diabetes onset calendar year. A=no antihypertensive or lipid-lowering drugs, B=antihypertensive drug only, C=both antihypertensive and lipid-lowering drugs.



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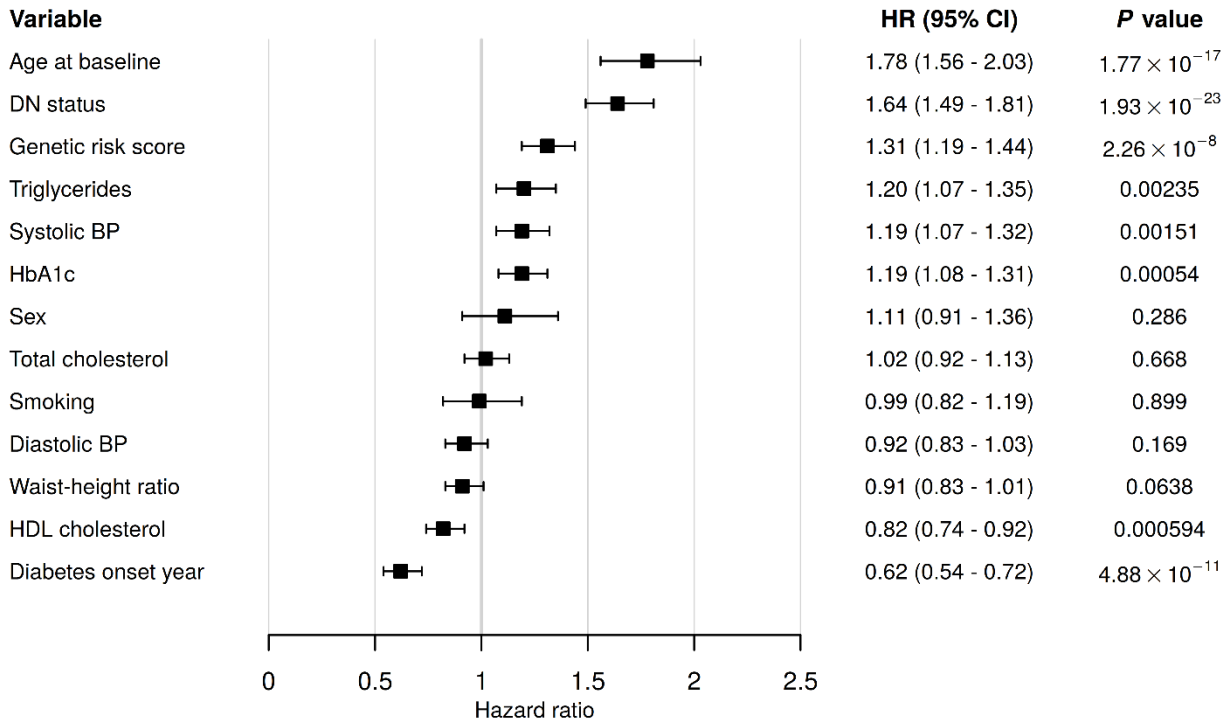

Figure 2. Forest plot for clinical variables and genetic risk score as separate covariates in one multivariable Cox regression model. All covariates were standardized.

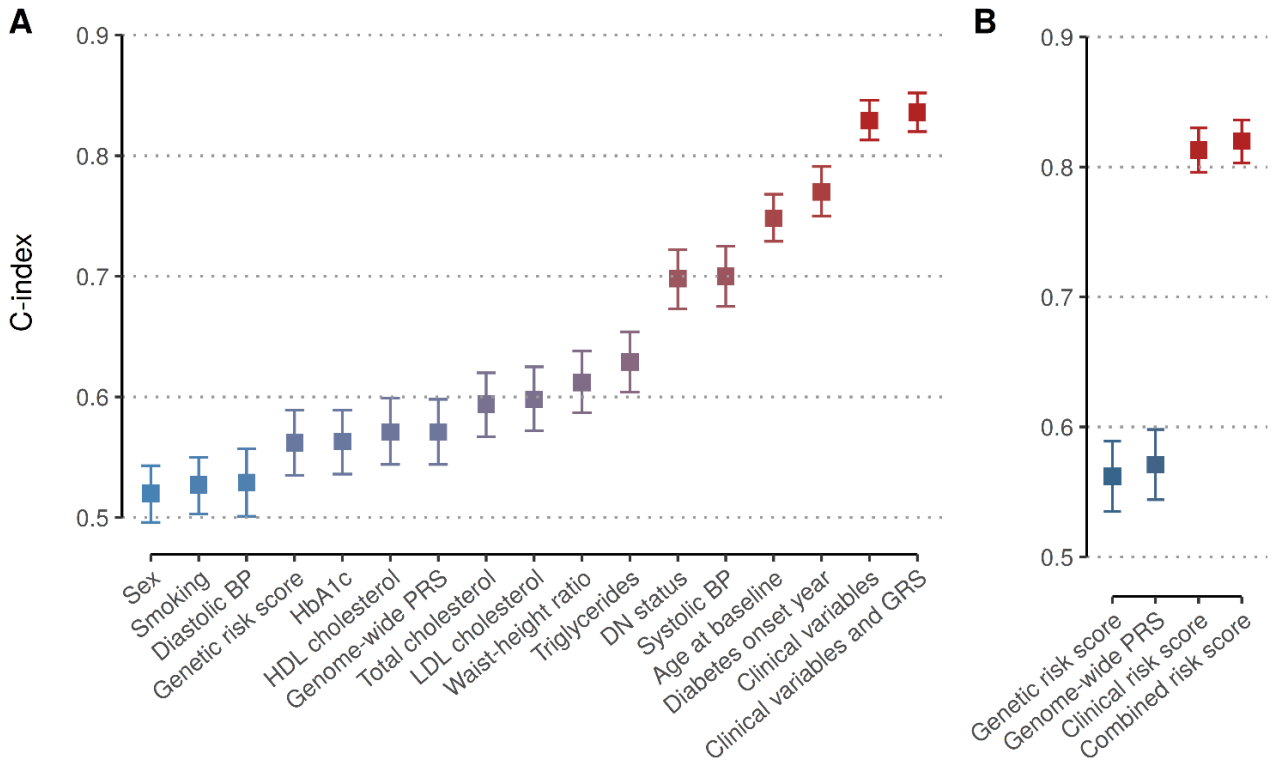

Figure 1. C-indexes with 95% CI for clinical covariates, as well as for the genetic, clinical and combined risk scores. PRS, polygenic risk score


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