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Impact of *TCF7L2* rs7903146 on clinical presentation and risk of complications in patients with type 2 diabetes

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Abstract

Aims: *TCF7L2* rs7903146 is the most impactful single genetic risk variant for type 2 diabetes. However, its role on disease progression, complications and mortality among people with type 2 diabetes at diagnosis remains unclear.

Materials and Methods: We assessed the per allele impact of the rs7903146 T-allele on clinical characteristics and complication risk in 9231 individuals with type 2 diabetes at diagnosis and over a 10-year follow-up period. Log-binomial and robust Poisson regression analyses were used to estimate prevalence ratios for clinical characteristics and macro- and microvascular complications at diabetes onset, while Cox regression was applied to estimate the risk of complications post-diagnosis. Analyses were adjusted for sex, calendar year at birth, age at enrollment and diabetes duration.

Results: The per T-allele impact was associated with 0.6 kg/m^2 (95% CI: 0.4, 0.8) lower BMI, 1.4 cm (95% CI: 1.0, 1.8) smaller waist circumference, 5.6% (95% CI: 4.2, 7.0) lower insulin secretion and 5.0% (95% CI: 3.3, 6.7) higher insulin sensitivity. Over 10 years, the per T-allele impact was associated with lower risks for major adverse

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cardiovascular events (0.87 [95% CI 0.79, 0.95]), myocardial infarction (0.82 [95% CI: 0.72, 0.93]) and heart failure (0.85 [95% CI 0.73, 1.00]), with no significant impact on microvascular complications.

Conclusions: The *TCF7L2* variant is associated with less obesity, lower insulin secretion and higher insulin action at diabetes onset, and decreased risk of cardiovascular events following type 2 diabetes onset.

KEYWORDS
cardiovascular disease, cohort study, diabetes complications, genetic predisposition, observational study, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is a multifactorial disease and a leading cause of death and disability worldwide.[1] Susceptibility to type 2 diabetes is influenced by genetic predispositions, an adverse foetal environment,[2,3] as well as with time- and age-dependent lifestyle behaviours (e.g., unhealthy diet, physical inactivity) leading to excess body weight gain, eventually precipitating overt type 2 diabetes.[4] Genome-wide association studies have identified over 1200 type 2 diabetes risk association signals.[5] rs7903146 (C/T) is a common variant in the transcription factor 7-like 2 (*TCF7L2*) gene, with the T-allele identified as the risk allele for type 2 diabetes.[6,7] This variant confers one of the largest single-gene population attributable risks for type 2 diabetes[7,8] and has been associated with impaired β-cell function, defective suppression of α-cell secretion by glucose and with reduced insulin secretion in people with and without diabetes.[9,10] Previous studies have further reported associations of the *TCF7L2* variant with decreased BMI, lower blood lipids and possibly increased risks of micro- and macrovascular complications in small cohorts of people both with and without type 2 diabetes.[9,11–18] However, the phenotypic impact of the *TCF7L2* variant may differ extensively in people with and without type 2 diabetes, particularly concerning the occurrence of complications. Givin its impact, understanding how this variant affects clinical presentation and disease progression is crucial for potential precision medicine approaches. We conducted a combined cross-sectional and prospective analysis of the *TCF7L2* rs7903146 variant's association with clinical characteristics, reflecting of disease severity, including insulin secretion and sensitivity, as well as complications and comorbidities, in a large cohort of individuals with type 2 diabetes from diagnosis and up to 10 years thereafter.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) is a Danish nationwide cohort of patients recently diagnosed with type 2 diabetes who have been enrolled by general practitioners and hospital outpatient clinics since 2010.[19] The enrollment process, implementation, logistics, biobanking and characteristics of the DD2 cohort have been described previously.[19,20] Briefly, clinical healthcare providers throughout Denmark identify individuals recently diagnosed with type 2 diabetes and complete an online questionnaire on lifestyle factors. Urine and fasting blood samples are collected for storage in a biobank. The unique civil personal registration number assigned to all Danish citizens links the DD2 cohort to a wide range of Danish health and administrative registries. Details on all data collected in DD2 are available in previous publications[19] and at www.dd2.dk. Information on baseline covariates, definitions and codes used in this study is provided in Tables 1 and S2.[21]

2.2 | Genotyping

A total of 10 162 individuals enrolled in the DD2 cohort 2010–2023 were genotyped using the Global Screening Array-24 v2.0 or v3.0 chip (Illumina, San Diego, CA, USA). Genotypes were called with the Illumina GenCall algorithm. Quality control excluded individuals based on sex mismatches, relatedness closer than 3rd degree, >5% missing genotypes, heterozygosity outliers and non-European ethnicity. The rs7903146 variant had a genotyping success rate >99.9%, and quality control left data for 9231 individuals. Our study marks the first instance of reporting associations for a genetic risk variant as primary exposure within a large majority of the DD2 cohort.

2.3 | Outcomes and covariates

Information on outcomes, covariates, definitions, ICD-10 and ATC codes is provided in Table 1.[21] This includes age at diagnosis, family history of type 2 diabetes, anthropometric measures (BMI and waist circumference), blood pressure, markers of glucose homeostasis, circulating lipid levels and macro- and microvascular complications (retinopathy, nephropathy and neuropathy). Complication outcomes, except chronic kidney disease (CKD) where laboratory tests were used, were collected from the Danish National Patient Registry, which covers diagnosis codes and procedures for all inpatient hospital contacts since 1977 and outpatient contacts since 1995.[22] For myocardial infarction (MI) and stroke, we considered only inpatient discharge

diagnoses due to their high predictive value.[23,24] For heart failure (HF), peripheral arterial disease (PAD), retinopathy and neuropathy, we also included diagnoses from hospital specialist outpatient clinics and emergency contacts without inpatient admission.[25] Dates of death were obtained from the Danish Civil Registration System, and information on death from CVD was from the Danish National Patient Registry and the Danish Registry of Causes of Death. CVD death was assigned if listed as either an immediate or underlying cause of death or if followed by death within 30 days of a CVD diagnosis. Major adverse cardiovascular event (MACE) was defined as the first occurrence of MI or coronary revascularization, stroke or CVD death. CKD was defined using the Kidney Disease Improving Global Outcomes (KDIGO) criteria, requiring either two eGFR <60 mL/min/1.73 m^2 or two urine albumin-creatinine ratios (UACR) >30 mg/g 90–365 days apart.[26–28] Measurements were from The Danish National Laboratory database,[29,30] excluding emergency and inpatient values that could reflect acute kidney dysfunction.

2.4 | Statistical analyses

Descriptive data are provided as medians and IQRs for continuous variables, and as counts and percentages for categorical variables, stratified by rs7903146 genotype (CC, CT, TT). To examine the additive impact of the *TCF7L2* rs7903146 T-allele at diagnosis, we used a cross-sectional design with multivariable linear regression for continuous variables (e.g., age at diagnosis, anthropometric measures, markers of glucose homeostasis, blood pressure, circulating plasma lipid levels and subclinical inflammation), and log-binomial or robust Poisson regression[31] for categorical variables (medication usage and complications) to estimate prevalence ratios (PRs). To examine the risk of complications following diagnosis, we used a prospective cohort design, using Cox proportional hazard models to estimate cause-specific hazard ratios (HRs) as a measure of the incidence rate ratio. The proportional hazards assumption was verified using Schoenfeld or Martingale residual plots. Our main models were adjusted for potential confounders, that is, sex, calendar year at birth, age at enrollment (except when focusing on age at diagnosis) and diabetes duration. We refrained from additional adjustments in our main model to prevent over adjustment of intermediates between the rs7903146 T-allele and type 2 diabetes. Exploratory analyses included further adjustments for birthweight, behavioural lifestyle factors (physical activity, smoking status, alcohol consumption), socio-economic markers (marital status and rural-urban residence), BMI, HbA1C and number of glucose-lowering medication used (treatment intensity). Logarithmic transformed variables are presented as the percentage change per T-allele. Missing data were imputed using multivariate imputations by chained equations (MICE) via the R package MICE,[32] with predictive mean matching for continuous variables, logistic regression for binary and polytomous regression for multilevel categorical variables. Missingness ranged between 0% and 56%, with the highest percentage missing for blood pressure and with a 12% median among all covariates with any missing values. The distribution of missingness was similar across rs7903146 genotype status, sex and age at enrollment. See Supplementary Methods: Multivariate imputations by chained equations (MICE) model specification[21] for further specification of the method and the missing-data pattern.

2.5 | Sensitivity analysis

We repeated Cox regression models excluding individuals with prior CVD history to assess the impact of the T-allele in CVD-naïve participants. Sub-distributional HRs were estimated using the Fine and Gray model, accounting for competing risk of death, and for CVD outcomes, non-CVD death. To investigate whether the effect of the *TCF7L2* risk variant changes over time, we performed a Cox regression analysis restricting follow-up to 0–5 years, 0–10 years and 0–10+ years.

3 | RESULTS

A total 963 (10.4%) carried the TT-genotype, 4070 (44.1%) the CT-genotype and 4198 (45.5%) the CC-genotype. The T-allele frequency was 0.32. The median age at enrollment was 62 years, median diabetes duration 0.8 years and 41% were women. Further details on covariates according to rs7903146 genotype can be found in Tables 1 and S2–S4.[21]

3.1 | Age at diagnosis and body composition

The per allele impact of the rs7903146 T-allele was 0.22 years (95% CI: −0.13, 0.57) younger age at diagnosis, a 0.63 kg/m^2 (95% CI: 0.42, 0.83) lower BMI and a 1.39 cm (95% CI: 0.99, 1.79) smaller waist circumference (Figure 1) Further explorative adjustments for birthweight, BMI at enrollment, lifestyle factors (alcohol consumption, smoking status and physical activity), socio-economic markers (marital status and rural-urban residence), HbA1c and number of glucose-lowering medication increased the effect of rs7903146 on age at diagnosis to 0.49 years (95% CI: 0.16, 0.82) per T-allele, while associations with BMI and waist circumference remained similar (Table S5[21]).

3.2 | Blood pressure and circulating lipid levels

Per T-allele, systolic blood pressure was 0.57 mmHg (95% CI: −0.08, 1.23) higher, while no association was observed for diastolic blood pressure (Figure 1). For lipids, the per T-allele impact was a 2.78% (95% CI: 0.74, 4.79) lower level of triglycerides, 1.14% (95% CI: 0.15, 2.16) higher HDL cholesterol and 1.48% (95% CI: −0.08, 3.06) higher LDL cholesterol, while no association was observed for total cholesterol (Figure 1). Further adjustments increased impact of T-allele on systolic blood pressure to 0.71 mmHg (95% CI: 0.05, 1.37) per T-allele. These further adjustments for lipids showed similar associations, except the impact on HDL cholesterol almost halved (Table S5[21]).

TABLE 1 Baseline characteristics in the DD2 according to *TCF7L2* rs7903146 genotype.

	TCF7L2 rs7903146 (CT)			
Enrollment characteristics	**CC ($n = 4198$)**	**CT ($n = 4070$)**	**TT ($n = 963$)**	**Total ($n = 9231$)**
Sex				
Female	1696 (40.4)	1662 (40.8)	397 (41.2)	3755 (40.6)
Age at enrollment (years)				
Median [iqr]	61.9 [53.2, 68.6]	61.9 [53.1, 68.9]	61.6 [52.7, 68.5]	61.9 [53.1, 68.7]
Age at diagnosis (years)				
Median [iqr]	60.2 [51.5, 67.0]	60.2 [51.5, 67.2]	59.1 [51.4, 66.8]	60.1 [51.5, 67.0]
Diabetes duration (years)				
Median [iqr]	0.8 [0.1, 2.5]	0.7 [0.1, 2.5]	1.0 [0.2, 2.7]	0.8 [0.1, 2.5]
Family History of type 2 diabetes (*n*)				
0	2079 (49.5)	2016 (49.5)	450 (46.7)	4545 (49.2)
1	1316 (31.4)	1263 (31.0)	290 (30.1)	2869 (31.1)
2	601 (14.3)	578 (14.2)	160 (16.6)	1339 (14.5)
3+	202 (4.8)	213 (5.2)	63 (6.5)	478 (5.2)
Birthweight (g)				
Median [iqr]	3400 [3000, 3700]	3400 [3000, 3700]	3400 [3050, 3700]	3400 [3000, 3700]
Missing	634	584	146	1364
Born-at-term				
Preterm	1040 (24.8)	1022 (25.1)	228 (23.7)	2290 (24.8)
BMI (kg/m^2)				
Median [iqr]	31.5 [27.8, 35.7]	30.5 [27.2, 35.2]	30.2 [27.0, 34.3]	30.9 [27.5, 35.4]
Missing	1830	1786	446	4062
Waist circumference (cm)				
Median [iqr]	109 [102, 118]	107 [101, 116]	107 [101, 114]	108 [101, 117]
Missing	60	38	6	104
Alcohol consumption (units pr week)				
≥21 units per week is for males and ≥14 is for females	269 (6.4)	243 (6.0)	54 (5.6)	566 (6.2)
Smoking status				
Never	912 (48.2)	891 (47.9)	237 (52.8)	2040 (48.5)
Former	627 (33.1)	614 (33.0)	144 (32.1)	1385 (33.0)
Current	355 (18.7)	355 (19.1)	68 (15.1)	778 (18.5)
Missing	2304	2210	514	5028
Physical activity (days pr week)				
0	657 (15.7)	570 (14.1)	130 (13.6)	1357 (14.8)
1–2	853 (20.4)	825 (20.3)	184 (19.2)	1862 (20.3)
3–4	928 (22.2)	983 (24.2)	239 (24.9)	2150 (23.4)
5–6	679 (16.2)	619 (15.3)	155 (16.2)	1453 (15.8)
7	1064 (25.5)	1060 (26.1)	251 (26.2)	2375 (25.8)

Note: Baseline characteristics according to *TCF7L2* rs7903146 genotype. Data are provided as medians (interquartile range) for continuous variables and as counts (percentages) for categorical variables.
Abbreviation: BMI, body mass index.

3.3 | Metabolic variables

For markers of glucose homeostasis, the per T-allele impact was a 0.94% (95% CI: 0.18, 1.71) higher level of plasma glucose, 4.97% (95% CI: 3.44, 6.46) lower level of plasma C-peptide, 5.63% (95% CI: 4.21, 7.03) lower HOMA2-insulin secretion and 4.98% (95% CI: 3.31, 6.68) higher HOMA2-insulin sensitivity (Figure 1). Further adjustments did not substantially change the associations though effects on C-peptide, HOMA2-insulin secretion and HOMA2-insulin sensitivity nearly halved (Table S5[21]). No associations were observed with HbA1c or hsCRP (Figure 1).

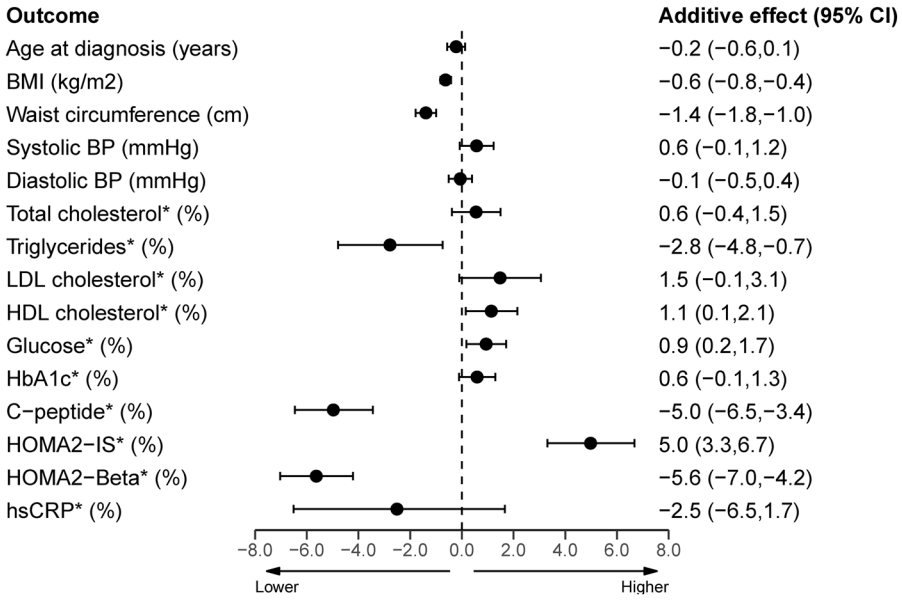

FIGURE 1 The impact of TCF7L2 rs7903146 on metabolic traits at time of diagnosisPer allele impact of the *TCF7L2* rs7903146 T-allele in linear regression models at diabetes onset. *Log transformed outcomes are presented as the percentage change per T-allele. All models are adjusted for sex, year at birth and age at enrollment (except age at diagnosis). BMI = body mass index, BP = blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein, HOMA = Homeostasis Model Assessment, IS = insulin sensitivity, hsCRP = high-sensitive C-reactive protein.

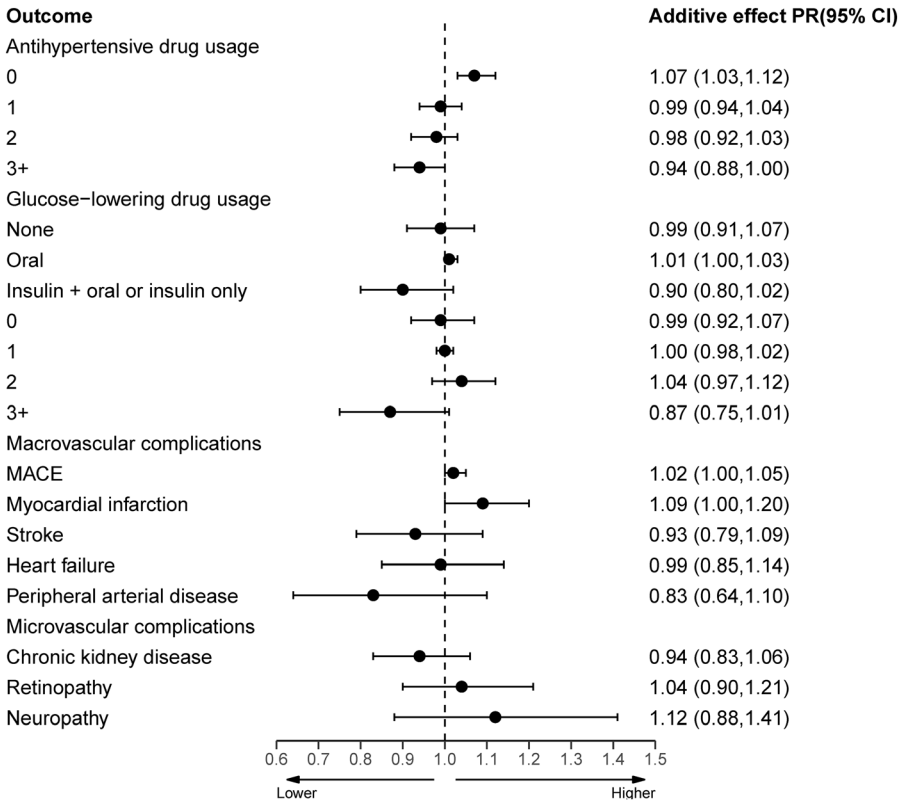

FIGURE 2 The impact of *TCF7L2* rs7903146 on complications and medication usage at time of diagnosis Per allele impact of the *TCF7L2* rs7903146 T-allele in categorical models. All models are adjusted for sex, year at birth and age at enrollment. PR = prevalence ratio, MACE = major adverse cardiovascular event.

3.4 | Prevalent complications and medication usage

The rs7903146 T-allele was associated with a slightly greater likelihood of having a history of myocardial infarction prior to type 2 diabetes diagnosis (PR 1.09 [95% CI: 1.00, 1.20]), and lower use of antihypertensive medication (PR for using no antihypertensive medication = 1.07 [95% CI: 1.03, 1.12]) (Figure 2). Associations were consistent after further adjustment. No association was observed for prevalent MACE, stroke, HF, PAD, CKD, retinopathy, neuropathy and use of glucose-lowering medication at time of type 2 diabetes diagnosis (Table S6[21]).

3.5 | Hazard ratios of macro- and microvascular complications

During a median follow-up of 9.0 years (IQR 5.4, 10.8 years; May 5, 2024), 1114 MACE, 1407 CKD diagnosis, 406 retinopathy diagnosis, 384 neuropathy diagnosis and 1379 deaths occurred (Table S4).

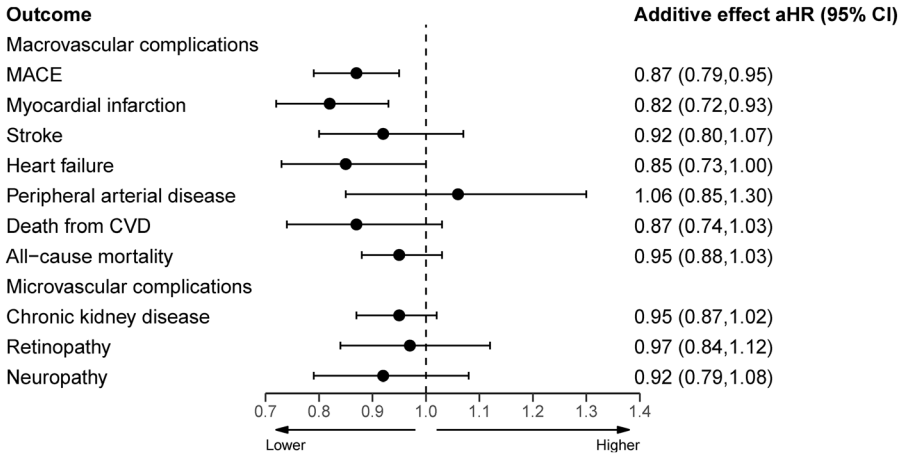

FIGURE 3 Hazard ratios (HRs) for the additive impact of rs7903146 T-allele on macro- and microvascular complications following type 2 diabetes diagnosis. Per allele impact of the *TCF7L2* rs7903146 T-allele in Cox regression models. All models are adjusted for sex, year at birth, age at enrollment and diabetes duration. HR = hazard ratio, CI = confidence interval, MACE = major adverse cardiovascular event, CVD = cardiovascular disease.

The rs7903146 T-allele was associated with a lower risk of MACE (aHR of 0.87 [95% CI 0.79, 0.95]), MI (aHR 0.82 [95% CI: 0.72, 0.93]), HF (aHR 0.85 [95% CI: 0.73, 1.00]), stroke (aHR 0.92 [95% CI: 0.80, 1.07]) and death from CVD (aHR 0.87 [95% CI: 0.74, 1.03]) (Figure 3), although all with limited precision. Further adjustments did not alter the associations with MACE or MI, however it attenuated to some degree the association with HF. The T-allele was also associated with a slightly lower risk of death from all causes (aHR 0.95 [95% CI: 0.88, 1.03]). No strong associations were found with risk of PAD, CKD, retinopathy or neuropathy, though HRs were all slightly below 1.0 for all microvascular complications (Table S7).

3.6 | Sensitivity analysis

Sub-distributional hazards using Fine and Gray models were consistent with Cox regression models (Table S8[21]). When excluding pre-existing CVD, the lower risk of MACE, MI, HF, stroke, death from CVD and death from all-causes was slightly attenuated (MACE: aHR 0.92 [95% CI: 0.80, 1.04]; MI: aHR 0.84 [95% CI: 0.70, 1.01]; HF: aHR 0.97 [95% CI: 0.77, 1.22]); stroke: aHR 0.97 [95% CI: 0.79, 1.19]; death from CVD: aHR 1.00 [95% CI: 0.76, 1.23]; all-cause mortality: aHR 0.99 [95% CI: 0.89, 1.11] although with less precision (Table S9). However, an increased risk of PAD was observed (aHR 1.51 [95% CI 1.05, 2.17]) (Table S9). Restricting follow-up to 0–5 years and 0–10 years gave similar estimates as the 0–10+ years (main analysis), although with a lower impact per T-allele for the 0–5 years of follow-up compared with the 0–10+ years (Table S10).

4 | DISCUSSION

In this large cohort of persons recently diagnosed with type 2 diabetes, the *TCF7L2* rs7903146 T-allele was associated with younger age at diabetes onset, lower BMI, smaller waist circumference, higher insulin sensitivity and lower insulin secretion. The rs7903146 T-allele was associated with slightly lower use of antihypertensive medications, potentially explaining a higher systolic blood pressure. The T-allele was also associated with lower plasma levels of triglycerides, higher HDL and LDL cholesterol levels. Importantly, compared with type 2 diabetes patients carrying the C-allele, the T-allele was associated with a lower risk of MACE, particularly MI, HF, death from CVD and with a slightly decreased risk of microvascular complications up to 10 years following a type 2 diabetes diagnosis. Restricting to a shorter follow-up time indicated a lower impact per T-allele, suggesting a consistent pattern of an increasing impact over time.

TCF7L2 operates as a transcription factor with β-catenin, regulating WNT-signalling target genes involved in cell differentiation, including pancreatic β-cell as well as α-cell development and function[10,33] Indeed, *TCF7L2* is highly expressed in pancreatic-islet cells, and prior studies have demonstrated reduced insulin secretion among healthy subjects of all ages carrying the rs7903146 variant.[13,14,34] The current study revealed that, even within a group of persons recently diagnosed with type 2 diabetes—all of whom exhibit some degree of absolute or relative insulin resistance and impaired insulin secretion—the rs7903146 variant was associated with lower estimated insulin secretion, consistent with Bonetti et al.'s[12] findings in a smaller cohort. Our novel finding of a quantitatively major impact of the T-allele on HOMA2-insulin sensitivity contrasts with Bonetti et al.'s results indicating a worse insulin action in carriers of the risk T variant.[12] This, however, may be explained by different methodologies. HOMA2 estimates favour hepatic insulin sensitivity, while Bonetti et al. used the hyper insulinemic clamp to measure peripheral (muscle and adipose tissue) insulin sensitivity. Indeed, hepatic versus peripheral insulin sensitivity is regulated by different mechanisms[35] and can even move in opposite directions under certain conditions, such as prolonged fasting.[36] Notably, sustained hyperinsulinemia is an established risk factor of insulin resistance,[37] and a higher degree of insulin sensitivity among carriers of the *TCF7L2* risk T-allele could therefore be explained by reduced long-term exposure to hyperinsulinemia. Although the *TCF7L2* risk variant markedly influenced insulin secretion in the DD2 cohort of people with type 2 diabetes, we observed no substantial effects on glycaemic control or insulin use. Additionally, the *TCF7L2* variant had only a minor impact on body composition, which is somewhat unexpected given that low insulin secretion is often associated with less obesity in people with type 2 diabetes.

These findings suggest that *TCF7L2* alleles may influence the set point of the inverse relationship between insulin secretion and action in type 2 diabetes, functioning partly independently of obesity. This could explain the limited impact on glycaemic control and insulin usage observed in this cohort. From a clinical perspective, the previously reported differences in frequency of the *TCF7L2* variant between the severe insulin-deficient (SIDD) and severe insulin-resistant (SIRD) ANDIS type 2 diabetes clusters[38] might be explained by the fact that these groups were á priori defined based on HOMA insulin secretion and resistance.[39]

While prior studies in people with and without diabetes suggested increased risk of nephropathy, retinopathy, neuropathy and even CVD in carriers of the *TCF7L2* diabetes risk variant,[15–17,40,41] we in sharp contrast found indications of lower risk of MACE, including MI, HF and death from CVD, in the years following type 2 diabetes diagnosis. This finding remained after adjustment for conventional clinical CVD risk factors including glycaemia (HBA1c), and glucose-lowering medication usage, as well as after restricting the analyses to individuals without any history of CVD prior to enrollment. The explanation for this important finding most likely relates to the inherent limitation of previous studies that all included mixed cohorts of people with and without diabetes,[9,11–18] raising the likelihood that hyperglycaemia rather than the *TCF7L2* variant drove these associations. The *TCF7L2* variant has been consistently associated with reduced insulin secretion across all ages,[13,42] and prolonged periods of undiagnosed mildly or periodically elevated plasma glucose levels may explain the increased prevalent MI at type 2 diabetes diagnosis. Indeed, similar reasoning may apply to findings of increased coronary artery disease prevalence in a non-diabetes population,[43] as well as the finding of relatively increased MI prevalence in carriers of the T risk allele at the time of diagnosis in this study.

Type 2 diabetes is a multifactorial disease developing due to different admixtures of genetic, pre- as well as postnatal risk factors, with the risk of type 2 diabetes complications also likely to differ according to the individual contribution and composition of each of these risk factors. In a cohort where all individuals are included at the time of diabetes onset, each person must exhibit a particular burden of these risk factors to develop overt type 2 diabetes. For those with a high burden of one specific factor, such as a strong genetic predisposition, the remaining population without such a predisposition likely are characterized by greater burdens of alternative risk factors, such as an adverse foetal environment, or postnatal (e.g., lifestyle) influences. Consequently, individuals without a strong genetic predisposition may require more severe lifestyle-related risk factors, such as obesity, to develop type 2 diabetes. Indeed, we in the DD2 cohort recently reported an elevated risk of CVD up to 10 years post-diagnosis in individuals with low birthweight, who also presented with less family history of diabetes as well as less obesity at diabetes onset.[2,44] Accordingly, when stratifying based on the most impactful common genetic variant for type 2 diabetes, the observed reduction in CVD risk may be explained by a dilution of other risk factors linked to a higher CVD risk, including an adverse foetal environment, postnatal lifestyle or potentially competing genetic factors.

The reduced CVD risk observed after a type 2 diabetes diagnosis in carriers of the *TCF7L2* variant could also be explained by its direct influence on intermediate CVD risk factors. Previous studies have reported an impact of the *TCF7L2* variant on body composition, age at diabetes onset, blood pressure, plasma lipids, insulin secretion, inflammation and markers of micro- and macrovascular complications, even in relatively small cohorts of people both with and without type 2 diabetes.[9,11] In this study, carriers of the rs7903146 T-allele at diabetes onset were relatively younger, had lower BMI, smaller waist circumference, higher HDL cholesterol, lower triglycerides, higher insulin sensitivity and lower insulin secretion. Hyperinsulinemia and insulin resistance are increasingly recognized as independent CVD risk factors,[45] suggesting that reduced insulin levels and resistance may contribute to the reduced CVD risk. However, carriers also displayed higher systolic blood pressure and LDL cholesterol, which are associated with increased CVD risk.[46] While the higher systolic blood pressure may be explained by slightly lower use of antihypertensive medications, further research is needed to determine how these intermediary factors, particularly reduced hyperinsulinemia, may contribute to reduced CVD risk among carriers of the *TCF7L2* variant.

When restricting our analyses to participants without pre-existing CVD, we found that the rs7903146 T-allele was associated with an increased risk of developing PAD following type 2 diabetes diagnosis. To our knowledge this has previously only been reported by Ku et al.[47] in Korean patients with type 2 diabetes. However, due to the low numbers of PAD events, further data are needed to substantiate this finding.

The strengths of this large nationwide study include the use of a well-characterized cohort of persons recently diagnosed with type 2 diabetes, recruited from both primary and secondary healthcare sectors, with data linked to high-quality population-based health registries with a median follow-up of 9 years.

Our study carries certain limitations. The cross-sectional design comes with inherent drawbacks, such as a risk of selection bias. However, the population was nationwide and included only those with new-onset type 2 diabetes from general practice and outpatient hospital clinics. In addition, genes inherently precede the identification of clinical characteristics of type 2 diabetes. Although some covariates had missing data, the median percentage of missing across all used variables was low, and multiple imputations were used. Complications assessed exclusively through hospital contact diagnosis may lead to underestimation, particularly for microvascular complications. However, the validity of CVD diagnoses and procedures in Danish registries is very high,[24,25] and validity of laboratory measures such as eGFR and UACR for CKD are also generally high[48] and aligns with the KDIGO[27] criteria. Most participants had relevant treatments initiated at DD2 enrollment, resulting in nearly normalized blood pressure, lipids and glucose levels. Further, we lacked data on post-diagnosis changes, such as weight loss, physical activity, diet or medication.[49] Future research in diverse ethnicities will be important to validate our findings. Finally, we acknowledge the absence of information on education, income and maternal/paternal risk factors related to type 2 diabetes.

5 | CONCLUSION

The *TCF7L2* rs7903146 variant was associated with a slightly younger age at onset, lower BMI, lower insulin secretion and higher insulin sensitivity in persons recently diagnosed with type 2 diabetes. The *TCF7L2* variant was also associated with a lower risk of MACE, particularly MI, with no large impact on microvascular complications over 10 years following type 2 diabetes diagnosis. This study provides proof-of-concept of how a single high-impact diabetes risk variant can influence several key clinical characteristics in patients with newly diagnosed type 2 diabetes, and most importantly a hitherto unrecognized relatively lower risk of macrovascular complications up to 10 years after the diagnosis of type 2 diabetes.

AUTHOR CONTRIBUTIONS

AAV conceived and designed the study and is the guarantor of the study. JSN is the principal manager of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2). ALH performed the statistical analysis, prepared the first draft manuscript and revised the draft. All authors contributed to the interpretation of data and critically revised the content of the draft. AAV and RWT supervised the study. All authors gave final approval of the version to be published. As such, they had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

All authors have read and approved the manuscript. CB and TH owns stock in Novo Nordisk. MHO has received payments or honoraria for lectures, presentations or educational events from AstraZeneca, Novo Nordic A/S and Teva A/S, and has an unpaid position as chair of the Danish Hypertension Society. The Department of Clinical Epidemiology, Aarhus University and NNF Center for Basic Metabolic Research receives funding for other studies in the form of institutional research grants to (and administered by) Aarhus University and University of Copenhagen, respectively. None of these studies have any relation to the present study. No other potential conflicts of interest relevant to this article are reported.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16193.

DATA AVAILABILITY STATEMENT

Danish data protection legislation does not allow the authors to share individual-level patient data used for this study. However, the Danish health registry data used in this study are accessible to researchers at authorized research institutions after application to the Danish Health Data Authority, by e-mail to forskerservice@sundhedsdata.dk. Requests to use data from the DD2 cohort can be made on the DD2 website, https://dd2.dk/forskning/ansoeg-om-data.

ETHICS STATEMENT

This DD2 study was approved by the Danish Data Protection Agency (record number 2008-58-0035), the Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082) and the Danish National Center for Ethics (record number 2308518). All cohort participants provided written informed consent to participate in the DD2 study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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