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RESEARCH ARTICLE

Fasting C-peptide at type 2 diabetes diagnosis is an independent risk factor for total and cancer mortality

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Abstract

Aims: We assessed the association between insulin resistance and blood glucose concentrations at type 2 diabetes diagnosis and future development of diabetes-related complications and mortality.

Materials and Methods: This retrospective cohort study included 864 individuals with type 2 diabetes (median age 60 years) whose fasting C-peptide and HbA1c were measured at diabetes diagnosis. The median follow-up time until death or study end was 16.4 years (interquartile range 13.3–19.6). The association between C-peptide and mortality/complications was estimated by Cox regression adjusted for sex, age at diabetes diagnosis, smoking, hypertension, BMI, total cholesterol, and HbA1c. C-peptide and HbA1c were converted to Z scores before the Cox regression analysis.

Results: An increase by one standard deviation in fasting C-peptide at diabetes diagnosis was associated with all-cause (hazard ratio [HR] 1.33; 95% confidence intervals [CI] 1.12–1.58; $p = 0.001$) and cancer mortality (HR 1.51; 95% CI 1.13–2.01; $p = 0.005$) in the fully adjusted model. An increase by one standard deviation in HbA1c at diabetes diagnosis was associated with all-cause mortality (HR 1.24; 95% CI 1.07–1.44; $p = 0.005$), major cardiovascular events (HR 1.20; 95% CI 1.04–1.39; $p = 0.015$), stroke (HR 1.36; 95% CI 1.09–1.70; $p = 0.006$), and retinopathy (HR 1.54; 95% CI 1.34–1.76; $p < 0.0001$) in the fully adjusted model.

Conclusions: Fasting C-peptide at type 2 diabetes diagnosis is an independent risk factor for total and cancer-related mortality. Thus, treatment of type 2 diabetes should focus not only on normalising blood glucose levels but also on mitigating insulin resistance.

KEYWORDS

cancer mortality, diabetes mellitus type 2, insulin resistance, mortality

1 | INTRODUCTION

The prevalence of diabetes is increasing worldwide, and mortality is approximately doubled among individuals with type 2 diabetes compared to those without it.[1,2] Moreover, type 2 diabetes leads to a number of comorbidities, such as coronary heart disease, stroke, retinopathy, nephropathy, and neuropathies.

Type 2 diabetes is often clustered with other cardiovascular risk factors, including hypertension and dyslipidemia.[3] Therefore, treatment for this condition aims not only at reducing blood glucose but also at mitigating these risk factors. Treating hypertension and dyslipidemia undoubtedly decreases the risk for cardiovascular events and cardiovascular death in individuals with type 2 diabetes.[4-6] However, for blood glucose–lowering therapy, a positive treatment effect in terms of cardiovascular event and mortality prevention is not guaranteed. In those with newly diagnosed type 2 diabetes, glucose-lowering therapy may decrease myocardial infarction and death risk after 12 years of follow-up at the earliest, and many more years may be required to yield a positive effect.[7] In contrast, with a median diabetes duration of 10 years, strict glucose lowering is linked to increased mortality after a mean follow-up of 3.5 years.[8]

In the past decade, new drug classes for the treatment of type 2 diabetes have emerged. In large placebo-controlled randomised trials, sodium glucose cotransporter 2 inhibitors and glucagon-like peptide 1 analogues have been associated with decreased total and cardiovascular mortality.[9,10] However, the mean HbA1c improvement in those trials was less than 0.5% (5 mmol/mol). Thus, lowering blood glucose may not be the most promising point of attack for decreasing mortality in type 2 diabetes.

C-peptide is usually interpreted as a measure of beta cell function. However, fasting C-peptide is not a good estimate for this endpoint and should ideally be measured after a carbohydrate load.[11] In contrast, fasting C-peptide and fasting insulin are more suitable measurements of insulin resistance.[12] For these reasons, we interpret fasting C-peptide as a measure of insulin resistance.

In the pathophysiology of type 2 diabetes, blood glucose rises because of insulin resistance and insufficient beta cell function.[13] Insulin resistance per se has been proposed as a marker of risk for diabetes complications and mortality. Ahlqvist and colleagues proposed a classification of adult-onset diabetes into five subgroups based on age at diagnosis, BMI, and insulin resistance estimated with the homoeostatic model assessment (HOMA).[14] After a follow-up of 11 years, they found that those with insulin resistance had the highest risk for diabetic kidney disease. Moreover, those with higher levels of insulin resistance had a higher risk of coronary events and stroke compared to those with lower levels of insulin resistance, although not in the fully adjusted model. Similarly, Pikkemaat et al. found that insulin resistance measured as fasting C-peptide levels at diabetes diagnosis was an independent risk factor for all-cause and cardiovascular mortality.[15] Moreover, in a study of people with insulin-treated type 2 diabetes, people with diabetic kidney disease had higher fasting C-peptide levels than those without this diabetes complication.[16] However, the results of the United Kingdom Prospective Diabetes Study (UKPDS) showed no association between insulin resistance at diabetes diagnosis and later cardiovascular disease.[17] A possible explanation for these mixed findings is that in UKPDS, blood samples for measuring insulin resistance were obtained after 3 months of dietary intervention, which may have affected the values. Overall, evidence is conflicting regarding the impact of insulin resistance at diabetes diagnosis on later diabetes complications and mortality.

To clarify the association, we conducted this retrospective population-based study, which to our knowledge is the largest such study addressing this question and measuring fasting C-peptide levels at type 2 diabetes diagnosis. We hypothesised that fasting C-peptide levels at type 2 diabetes diagnosis would be associated with total, cancer-related, and cardiovascular-related mortality and coronary heart disease independently of other risk factors.

2 | MATERIALS AND METHODS

2.1 | Study population

The diabetes registry DiabNorth includes inhabitants of the counties of Västerbotten and Norrbotten in Sweden who are diagnosed with diabetes and participate in either the Västerbotten Intervention Programme (VIP) or in the multinational MONitoring of trends and determinants in CArdiovascular disease (MONICA) study.[18] We carried out a retrospective cohort study of DiabNorth participants diagnosed with type 2 diabetes who had C-peptide measured at the time of diagnosis or up to 5 years prior.

DiabNorth was founded in 2002 and updated in 2007, 2008, and 2012. Patients were identified through searches of the computerised regional inpatient, outpatient, and National Board of Health and Welfare drug register initiated in 2005.

For the VIP, most individuals in Västerbotten county turning 40, 50, and 60 years of age were invited to their nearest health care centre for a health survey. The attendance rate was ~70%. Participants answered an extensive questionnaire related to health and lifestyle, and their BMI, blood pressure, total cholesterol, and fasting blood glucose were measured. In the MONICA study, random samples of the population in Västerbotten and Norrbotten counties were invited for a health survey with content similar to the VIP survey. Between 1986 and 2009, six surveys were performed with participants aged 25 to 74 years. By 2012, a total of 105,906 unique individuals had been included in the VIP and 10,792 in the MONICA study. Most participants in the VIP and MONICA studies had donated blood for research.

All identified patients with diabetes who were still alive were asked to participate in the DiabNorth registry, and 74% provided written informed consent.[18] All deceased individuals were included in DiabNorth because according to Swedish law, deceased individuals can be included in a registry without previous consent.

The DiabNorth cohort consisted of 4097 patients with diabetes in Northern Sweden. After clinical assessment according to World

Health Organisation guidelines and measurement of glutamic acid decarboxylase, isoform 65 (GAD65) antibodies, 3018 patients were considered to have type 2 diabetes (Figure 1). Individuals with positive GAD65 antibodies were considered to have type 1 diabetes or latent autoimmune diabetes in adults and were not included in this present study. A total of 918 patients had fasting blood samples available within 5 years prior to diagnosis for analysis of C-peptide. After exclusion of four patients with fasting blood glucose <3.5 mmol/L and 50 patients with myocardial infarction or stroke before their diagnosis, the study cohort consisted of 864 patients. Of these, 414 had blood samples available from the time of diabetes diagnosis, 125 had samples within 1 year prior to diagnosis, and 325 had samples from 1 to 5 years prior to diagnosis. HbA1c measurements were available from the year of diabetes diagnosis for 727 patients.

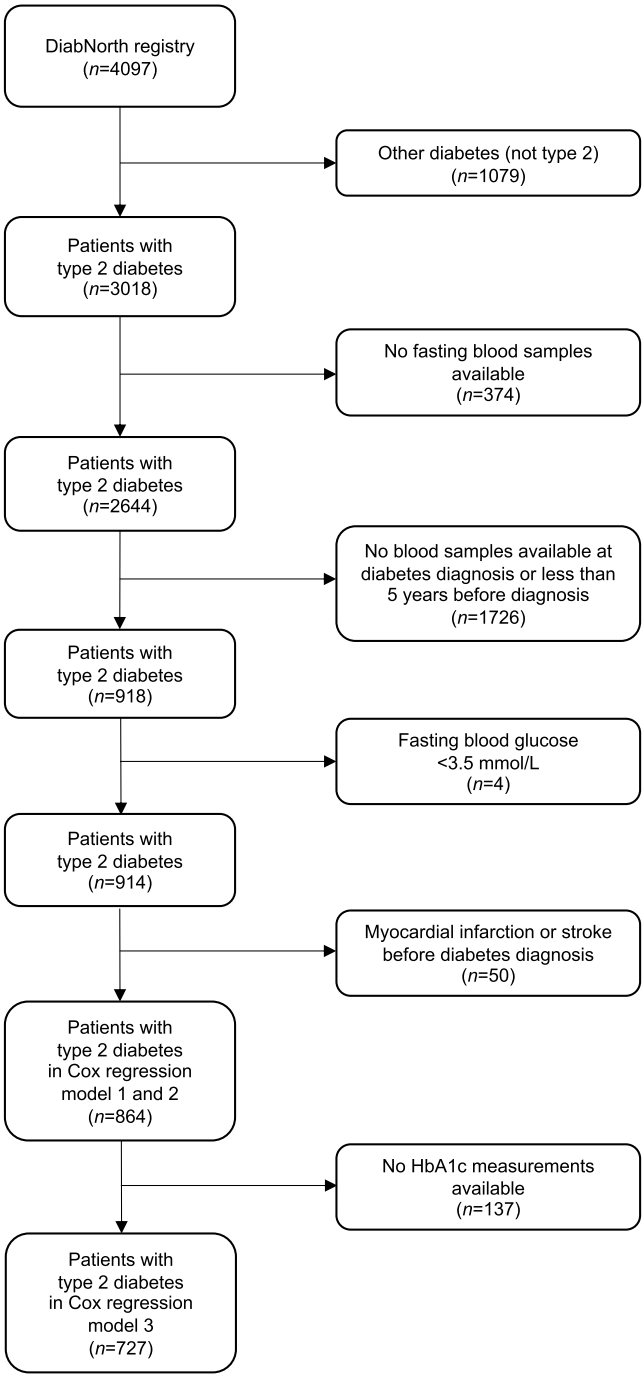

FIGURE 1 Flow chart

2.2 | Measurements

Systolic and diastolic blood pressure were measured with the patient either in the sitting position or lying down. Measurements obtained with the patient lying down were adjusted using sex- and age-specific formulae.[19] Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication.

In the VIP, capillary plasma glucose was analysed using a benchtop analyser (Reflotron®, Roche Diagnostics, Basel, Switzerland or HemocCue®, Radiometer Medical Aps, Brønshøj, Denmark). In MONICA, venous plasma glucose was analysed at the clinical chemistry laboratory of the nearest hospital up to 2004 and then with a benchtop analyser (HemocCue®, Radiometer Medical Aps, Brønshøj, Denmark) thereafter.

In the VIP, frozen fasting plasma samples were sent to the Department of Clinical Chemistry, Umeå University Hospital (Umeå, Sweden; $n = 525$) or to the Department of Clinical Chemistry, Östersund's Hospital (Östersund, Sweden; $n = 307$) for C-peptide analysis. In both laboratories, C-peptide was analysed using a Cobas 8000 analyser (Roche Diagnostics, Basel, Switzerland). For the MONICA study, frozen plasma/serum samples (≥4 h fasting) were analysed for C-peptide using an Abbott Architect i2000 (Abbott Laboratories, Chicago, Illinois, USA) as a part of the BiomarCare project in Hamburg, Germany ($n = 58$). We also included previous measurements from the clinical routine at the Department of Clinical Chemistry, Umeå University Hospital ($n = 24$). In our study cohort, C-peptide levels measured with the Abbott Architect i2000 were lower than the C-peptide levels measured with the Cobas 8000 analyser, and we adjusted the analyses for method.

Total cholesterol was analysed using a benchtop analyser (Reflotron®, Roche Diagnostics, Risch, Switzerland) or by an enzymatic method in the clinical chemistry laboratory at the nearest hospital. Reflotron®-measured total cholesterol was adjusted using a formula for comparability with measurements made at the clinical chemistry laboratory.

HbA1c was analysed (TOSOH G5, Tosoh, Tokyo, Japan) at the nearest hospital.

2.3 | Data on mortality and diabetes complications

Information on mortality and diabetes complications were retrieved from the Swedish Cause of Death Register and the Swedish National Patient Register. Both registers were started in the 1960s and have nationwide coverage. Mortality data were available until 11 March

2018, and diabetes complications and cause of death data were available until 31 December 2016. The median follow-up time until death or study end was 16.4 years (interquartile range [IQR] 13.3–19.6).

Death from cardiovascular causes was defined as a main diagnosis according to the International Classification of Diseases (ICD) using specific diagnostic codes from ICD-10 (I21-I25, I46.1, I46.9, I47.2, I49.0, I60, I61, I63, I64.9, R96, and R99) or ICD-9 (410, 412, 413, 414, 427E, 427F, 430X, 431, 434, 436X, 798, 799W, and 799X).

Death from cancer was defined as underlying cause of death coded with 'C' after 1997 (ICD-10) or coded 140–209 before 1997 (ICD-9).

For diabetes complications, main or secondary ICD codes were used, as follows: myocardial infarction and unstable angina (ICD10: I20.0, I20.1, I21, I22; ICD9: 410, 411A, 411B), stroke (ICD10: I61, I63, I64, I679; ICD9: 431, 434, 436), end-stage renal disease (ICD10: Z49, Z99, Z94, DR016; ICD9: V56A, V56W, V45B, V42A), and retinopathy (ICD10: H350, H352, H356, H359, H360, E103, E113, E143; ICD9: 362A). For end-stage renal disease, we had only seven events in total during our follow-up and could not conduct a survival analysis. We created a composite of major cardiovascular events (MACE), which was defined as the first coronary heart disease event, stroke, or death from cardiovascular causes.

2.4 | Statistical analysis

Data are presented as medians with IQRs. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated by Cox regression. Time from diabetes diagnosis was used as the survival time. Values for C-peptide, HbA1c, and fasting glucose were transformed into Z-scores before analysis. In model 1, the analysis was adjusted for sex and age at diabetes diagnosis as continuous variables and for C-peptide laboratory measurements as two categories. In model 2, the analysis was

TABLE 1 Characteristics of the study participants at type 2 diabetes diagnosis

N	864
Male sex, *N* (%)	520 (60.2)
Smokers and ex-smokers, *N* (%)	475 (55.0)
Age at diabetes diagnosis (years)	60 (50–60)
BMI (kg/m^2)	29.7 (27.1–33.1)
Systolic blood pressure (mmHg)	140 (131–153)
Diastolic blood pressure (mmHg)	88 (83–94)
Total cholesterol (mmol/L)	6.0 (5.3–6.7)
Fasting glucose (mmol/L)	7.4 (6.6–8.6)
Fasting C-peptide (nmol/L)	1.1 (0.9–1.4)
Date blood samples for C-peptide were taken in relation to date of diabetes diagnosis (years)	0.0 (−2.6; 0.0)
HbA1c (mmol/mol)	51 (44–68)
HbA1c (%)	6.8 (6.2–8.4)
Treatment[a]	
Metformin (%)[b]	63
Sulfonylureas (%)[b]	26
Alpha glucosidase inhibitors (%)[b]	1
Glitazones (%)[b]	2
Other oral diabetes medication (%)[b]	6
Insulin (%)[b]	16
Lipid lowering treatment (%)[c]	62
Hypertension treatment (%)[c]	74

Note: Data are displayed as median (IQR), except where indicated.

[a]Patients were treated with the medication during 5 years after diabetes diagnosis.

[b]Information available for 44 % of the study population only (*N* = 381).

[c]Information available for 40 % of the study population only (*N* = 346).

additionally adjusted for smoking (present or past/never), hypertension (yes/no), and the continuous variables BMI and total cholesterol. For smoking and hypertension, missing values were treated as a separate category ($n = 42$ and $n = 28$, respectively). For BMI and total cholesterol, missing values were imputed from another time point (before or after diabetes diagnosis) if available ($n = 23$ and $n = 25$, respectively). For model 3, the analysis was additionally adjusted for HbA1c. For model 4, the following variables were included: fasting C-peptide, sex, age at diabetes diagnosis, C-peptide laboratory, smoking, hypertension, BMI, total cholesterol, HbA1c, and treatment with either insulin or sulonylurea. For model 5, the following variables were included: fasting C-peptide, sex, age at diabetes diagnosis, C-peptide laboratory, smoking, hypertension, BMI, total cholesterol, and fasting glucose. We conducted three univariate Cox regression analyses to analyse the association between (a) fasting C-peptide and total mortality, (b) fasting C-peptide and cancer mortality and (c) treatment with insulin/sulfonylurea and total mortality.

IBM SPSS Statistics for Macintosh, Version 25.0 (Armonk, New York, USA) was used for all statistical analyses.

3 | RESULTS

A total of 864 individuals had fasting C-peptide available at their type 2 diabetes diagnosis and were included in this study (Figure 1). Their baseline characteristics are presented in Table 1. The median follow-up time until death or study end was 16.4 years (IQR 13.3–19.6). The number of outcome events is depicted in Table 2. During the follow-up, 191 died: 59 from cancer (31%), 56 from cardiovascular causes (29%), and 76 from other causes (40%). A coronary heart disease event occurred in 118 (14%) and a stroke in 81 (9%). MACE occurred in 190 (22%). Retinopathy was diagnosed in 170 patients (20%).

In the univariate Cox regression, an increase by one standard deviation in fasting C-peptide at diabetes diagnosis was associated with all-cause mortality (HR 1.16; 95% CI 1.02–1.32; $p = 0.022$). In the fully adjusted model, this association was also significant (Table 3). The association between C-peptide levels and all-cause mortality was independent of HbA1c levels at diabetes diagnosis (model 3, Table 3). Moreover, HbA1c levels were associated with all-cause mortality.

Fasting C-peptide levels at diabetes diagnosis also were associated with cancer mortality in the fully adjusted model and independent of HbA1c levels (Table 3). However, in the univariate model, the association between fasting C-peptide and cancer mortality was not significant (HR 1.20; 95% CI 0.96–1.49; $p = 0.110$). HbA1c levels at diabetes diagnosis were not associated with cancer mortality (Table 3).

We found no association between fasting C-peptide levels at diabetes diagnosis and cardiovascular mortality, MACE, coronary heart disease events, stroke, or retinopathy (Table 3). However, HbA1c at diabetes diagnosis was associated with later development of retinopathy, stroke, and MACE in the fully adjusted model (Table 3).

We measured C-peptide at diabetes diagnosis and up to 5 years prior to this diagnosis. We therefore conducted a sensitivity analysis including only individuals who had C-peptide analysed no longer than one year before their diabetes diagnosis ($n = 539$). We still found an independent association between fasting C-peptide and all-cause mortality (HR 1.39; 95% CI 1.13–1.72; $p = 0.002$, $n = 539$) and cancer mortality (HR 1.87; 95% CI 1.38–2.53; $p < 0.0001$; $n = 539$).

Hypoglyemica is a risk factor for mortality. Diabetes medication causing hypoglyemia may therefore increase mortality. In an univariate model, treatment with insulin/sulfonylurea was associated with all-cause mortality (HR1.66; 95% CI 1.09–2.55; $p = 0.019$, $N = 381$). In the fully adjusted, model 4, both fasting C-peptide levels (HR 1.40; 95% CI 1.08–1.82; $p = 0.012$) and treatment with insulin/sulfonylurea (HR 1.98; 95% CI 1.21–3.26; $p = 0.007$) were associated with all-cause mortality.

To compare the effect of HbA1c versus glucose at diabetes diagnosis on later total mortality and cancer mortality, we conducted Cox regression model 5 and included fasting glucose (instead of HbA1c). We found that with this model, the association between fasting C-peptide at diabetes diagnosis and total mortality (HR 1.29; 95% CI 1.11–1.49; $p = 0.001$) was comparable to results with model 3. However, fasting glucose at diabetes diagnosis was not associated with total mortality in model 5 (HR 1.07; 95% CI 0.93–1.24; $p = 0.343$). We did find an association between C-peptide and cancer

TABLE 2 Number of outcome events

	Number of events	% of all-cause death
All-cause death	191	100
Cancer death	59	31
Lung cancer	9	5
Colon cancer	6	3
Prostate cancer	6	3
Pancreas cancer	5	3
Breast cancer	3	2
Liver cancer	3	2
Bile duct cancer	3	2
Stomach cancer	3	2
Bladder cancer	3	2
Kidney cancer	2	1
Lymphoma	2	1
Other cancers of the digestive tract	6	3
Other cancers	8	4
Cardiovascular death	56	29
MACE	190	-
Coronary heart disease events	118	-
Stroke	81	-
Retinopathy	170	-

Abbreviation: MACE, major cardiovascular events.

TABLE 3 Mortality and diabetes complications and their association with fasting C-peptide at type 2 diabetes diagnosis

		Model 1[a]		Model 2[b]		Model 3[b]	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
All-cause death	C-peptide	1.30 (1.14–1.49)	0.0001	1.28 (1.11–1.49)	0.001	1.33 (1.12–1.58)	0.001
	HbA1c	-	-	-	-	1.24 (1.07–1.44)	0.005
Cancer death	C-peptide	1.31 (1.04–1.67)	0.024	1.42 (1.09–1.84)	0.009	1.51 (1.13–2.01)	0.005
	HbA1c	-	-	-	-	1.18 (0.89–1.56)	0.248
Cardiovascular death	C-peptide	1.18 (0.90–1.53)	0.230	1.13 (0.83–1.52)	0.438	1.12 (0.77–1.63)	0.539
	HbA1c	-	-	-	-	1.17 (0.86–1.61)	0.322
MACE	C-peptide	1.09 (0.95–1.26)	0.226	1.04 (0.89–1.22)	0.620	1.12 (0.93–1.34)	0.245
	HbA1c	-	-	-	-	1.20 (1.04–1.39)	0.015
Coronary heart disease events	C-peptide	1.08 (0.90–1.30)	0.399	1.03 (0.84–1.27)	0.782	1.09 (0.86–1.38)	0.483
	HbA1c	-	-	-	-	1.10 (0.91–1.34)	0.333
Stroke	C-peptide	1.07 (0.85–1.34)	0.592	1.03 (0.80–1.33)	0.791	1.12 (0.83–1.51)	0.456
	HbA1c	-	-	-	-	1.36 (1.09–1.70)	0.006
Retinopathy	C-peptide	0.92 (0.79–1.07)	0.286	0.86 (0.72–1.02)	0.861	0.85 (0.70–1.04)	0.107
	HbA1c	-	-	-	-	1.54 (1.34–1.76)	<0.0001

Note: The continuous variables C-peptide and HbA1c were converted to Z scores before the cox regression analyses were conducted.

Abbreviations: CI, confidence intervals; HR, Hazard ratios; MACE, major cardiovascular events.

[a]For model 1, Cox regression is adjusted for sex, age at diabetes diagnosis and measuring method of C-peptide.

[b]For model 2 and 3, Cox regression is adjusted for sex, age at diabetes diagnosis, measuring method of C-peptide, smoking, hypertension, BMI and total cholesterol. In model 3, Cox regression is additionally adjusted for HbA1c.

mortality (HR 1.42; 95% CI 1.09–1.84; $p = 0.009$) in model 5. Fasting glucose at diabetes diagnosis was not associated with cancer mortality (HR 1.01; 95% CI 0.76–1.34; $p = 0.945$) in model 5.

4 | DISCUSSION

In this large retrospective cohort study, a high fasting C-peptide concentration at the time of type 2 diabetes diagnosis was associated with total and cancer-related mortality independently of HbA1c and fasting blood glucose levels.

We conclude that insulin resistance at diabetes diagnosis is important for later mortality risk independent of HbA1c levels at diabetes diagnosis. Our results are in line with a recent mediation analysis showing that insulin resistance is responsible for 15% of the increased mortality risk in type 2 diabetes.[20] In other studies, insulin resistance had no impact on mortality or even was associated with decreased mortality.[21,22] In those studies, insulin resistance was measured as fasting C-peptide or HOMA at 9 and 4 years after diabetes diagnosis, respectively. Long-standing diabetes may lead to beta cell failure and lower fasting insulin levels, resulting in lower fasting C-peptide and HOMA measures despite or regardless of high insulin resistance. Thus, our study makes an important contribution because C-peptide levels were measured at diabetes diagnosis and before initiation of any diabetes medication. In line with our results, another smaller study found that individuals with high insulin resistance, based on fasting C-peptide at diabetes diagnosis, had higher total mortality than those with lower C-peptide levels.[15]

Insulin resistance has previously been described as an independent risk factor for cancer incidence and cancer mortality.[23,24] The associated increase in plasma insulin levels may promote carcinogenesis by inducing tumour cell proliferation and through anti-apoptotic and angiogenetic effects.[25] However, other epidemiological studies have suggested that the hyperglycemia itself increases cancer risk and cancer mortality.[26,27] In these study cohorts, no measurements for insulin resistance were available, precluding investigation of the influence of hyperglycemia independent of insulin resistance. The effect attributed to hyperglycemia in these studies may trace in part to insulin resistance. When we controlled for insulin resistance in our study, HbA1c level at diabetes diagnosis was not an independent risk factor for cancer mortality. Based on our results, insulin resistance at diabetes diagnosis, not hyperglycemia, seems to be linked to the increased risk for cancer death.

In our study, fasting C-peptide at diabetes diagnosis was not associated with cardiovascular mortality. In line with these results, Bo and colleagues did not find increased cardiovascular mortality with higher fasting C-peptide in patients with type 2 diabetes after adjustment for hypertension and other risk factors.[21] In contrast to our results, however, Pikkemaat et al. reported an increased risk of cardiovascular death with increasing C-peptide levels in patients newly diagnosed with type 2 diabetes, independent of other cardiovascular risk factors, such as hypertension.[15] The lack of a similar

association in our study may trace to the older age of our cohort compared with the population in Pikemaat et al.

Microvascular diabetes complications are directly related to hyperglycemia, that is, the magnitude and duration of blood glucose elevation.[28,29] We found that HbA1c levels at diabetes diagnosis were independently associated with retinopathy, which is in line with current evidence. Ahlqvist et al. reported comparable results when stratifying diabetes patients into five subgroups: Across the subgroups, the cluster with the highest HbA1c levels had the highest risk of retinopathy.[14]

The present study has some limitations. First, C-peptide was not estimated exactly at the time of diabetes diagnosis for all individuals, but up to 5 years before diagnosis. However, according to our sensitivity analysis, this variability did not seem to influence the results. Second, only study participants who were still alive could give informed consent, which led to a proportionally greater inclusion of deceased individuals. This imbalance may have introduced a selection bias towards patients with more cardiovascular complications. Third, we could not control for kidney function in our analysis which is important since it is known that impaired kidney function might increase in C-peptide levels.

This study also has some important strengths. To the best of our knowledge, it is the largest retrospective population-based study measuring C-peptide at or before diabetes diagnosis. Furthermore, we adjusted for important confounders, such as sex, age, smoking, hypertension, BMI, and total cholesterol. The long follow-up of 16 years and the complete follow-up of all participants and high participation rates (~70%) in both the VIP and MONICA studies are also notable.[30]

In conclusion, insulin resistance measured as fasting C-peptide at type 2 diabetes diagnosis was found to be an independent risk factor for total mortality and cancer mortality. Thus, treatment of type 2 diabetes should focus not only on normalising blood glucose levels but also on mitigating insulin resistance.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The study protocol was in accordance with the Helsinki Declaration and approved by the Regional Ethical Review Board, Umeå, Sweden (Dnr 2016-429-32M).

PRIOR PRESENTATION

Elements of this study were presented in abstract form at the 80th Scientific Sessions of the American Diabetes Association (virtual conference), 12–16 June 2020, and at the 56th European Association for the Study of Diabetes Annual Meeting (virtual conference) 21–25 September 2020.

AUTHOR CONTRIBUTIONS

Olov Rolandsson is the principal investigator of DiabNorth, and Stefan Söderberg is the principal investigator of the MONICA project. Julia Otten, Björn Tavelin, and Olov Rolandsson designed the study. Björn Tavelin and Olov Rolandsson retrieved the data from the DiabNorth register, the Swedish Cause of Death Register, and the Swedish National Patient Register. Julia Otten performed the statistical analyses. All authors interpreted the data. Julia Otten and Olov Rolandsson wrote the manuscript. All authors critically revised the manuscript and approved the final version. Olov Rolandsson is the guarantor of this work, as such had full access to all of the study data, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study cannot be shared publicly because of the European General Data Protection Regulation. Data are available from the University Director of Umeå University (contact hans.wiklund@umu.se) for researchers who meet the criteria for access to confidential data.

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TRANSPARENT PEER REVIEW

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