RESEARCH ARTICLE

Lipid Levels and Risk of Diabetic Polyneuropathy in 2 Danish Type 2 Diabetes Cohorts

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Abstract

Background and Objectives

Reduction of blood lipids may aid in preventing diabetic polyneuropathy (DPN), but evidence remains conflicting. We investigated the association between lipid parameters and DPN risk in individuals with type 2 diabetes mellitus (T2DM).

Methods

We conducted a population-based cohort study of individuals with newly diagnosed T2DM and a cross-sectional study using a clinically recruited T2DM cohort. Triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and non-HDL cholesterol were measured in routine diabetes care. Each lipid parameter was categorized according to the latest cutoffs in clinical guidelines on dyslipidemia. DPN was assessed with validated hospital diagnosis codes in the population-based cohort and with the Michigan Neuropathy Screening Instrument questionnaire in the clinical cohort. We calculated hazard ratios (HRs) using Cox regression and prevalence ratios (PRs) using Poisson regression.

Results

We included 61,853 individuals in the population-based cohort (median age 63 [quartiles 54–72] years) and 4,823 in the clinical cohort (median age 65 [quartiles 57–72] years). The incidence rate of hospital-diagnosed DPN in the population-based cohort was 3.6 per 1000 person-years during a median follow-up of 7.3 years. Achieving guideline targets for HDL, LDL, and non-HDL cholesterol showed no association with DPN risk. By contrast, adjusted HRs (95% CI) for DPN were 1.02 (0.89–1.18) for triglyceride levels between 150 and 204 mg/dL (1.7–2.3 mmol/L) and 1.28 (1.13–1.45) for levels >204 mg/dL (2.3 mmol/L). In the clinical cohort with a DPN prevalence of 18%, DPN associated strongly with triglycerides >204 mg/dL (2.3 mmol/L) with an adjusted PR (95% CI) of 1.40 (1.21–1.62). The prevalence of DPN was modestly elevated for individuals with HDL cholesterol <39 mg/dL (1.0/1.3 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women (PR 1.13 [0.99–1.28]) and for individuals with non-HDL cholesterol >131 mg/dL (3.4 mmol/L) (PR 1.27 [1.05–1.52]). In both cohorts, spline models showed an increasing risk of DPN starting from triglyceride levels >124 mg/dL (1.4 mmol/L). All results were similar among statin users.

Discussion

High triglyceride levels are a strong DPN risk factor. Future intervention studies shall determine whether triglyceride reduction is more important for DPN prevention than reduction of other lipids.

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Glossary

DD2 = Danish Centre for Strategic Research in Type 2 Diabetes; **DPN** = diabetic polyneuropathy; **HbA1c** = hemoglobin A1c; **HDL** = high-density lipoprotein; **HR** = hazard ratio; **LABKA** = Clinical Laboratory Information System Database; **LDL** = low-density lipoprotein; **MNSIq** = Michigan Neuropathy Screening Instrument questionnaire; **PR** = prevalence ratio; **T2DM** = type 2 diabetes mellitus.

Introduction

Diabetic polyneuropathy (DPN) is a chronic peripheral nerve complication affecting up to 30% of all individuals with type 2 diabetes mellitus (T2DM) and is a leading cause of foot ulcers, falls, and lower-limb amputations.[1-4] All metabolic syndrome components—central obesity, hypertension, hyperglycemia, and dyslipidemia—have been implicated as risk factors of DPN.[1] However, reported associations between dyslipidemia and DPN are less consistent and robust than for the other metabolic risk factors.[1]

Despite uncertainty about the causal relationship between dyslipidemia and DPN, clinical guidelines have suggested that lowering blood lipids may aid in DPN prevention.[5-7] However, dyslipidemia is an umbrella term covering a broad range of lipoprotein sizes, compositions, and functions, for example, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.[8-10] The evidence linking these specific lipid parameters with DPN is uncertain and conflicting.[11-27] Previous studies mostly relied on cross-sectional analyses of relatively small hospital-treated populations with and without diabetes (N < 2,500).[12-25,27] Few large longitudinal studies have examined the association between distinct lipid parameters and risk of subsequent DPN in T2DM-specific cohorts, while adjusting for other metabolic risk factors that could confound this relation, reporting inconsistent results.[11,26] An improved understanding of the impact of specific lipid parameters on DPN risk is needed to inform guidelines and preventive interventions.[1]

We, therefore, aimed to clarify the association between distinct lipid parameters (i.e., triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) and DPN, using 2 T2DM cohorts, each offering unique advantages: (1) a large population-based cohort of people with newly diagnosed T2DM, representing individuals seen in everyday clinical practice with long-term follow-up and (2) a clinically recruited T2DM cohort with detailed information on potentially confounding lifestyle behaviors and anthropometric measures.

Methods

Study Design

We sampled a population-based T2DM cohort to conduct a longitudinal study following individuals for DPN starting 1 year after their T2DM diagnosis. In addition, we used a clinically recruited T2DM cohort to conduct a cross-sectional study at the time of questionnaire-based DPN assessment. The setting and databases used for each cohort are described in the eAppendix.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Danish Data Protection Agency (No. 2016-051-000001/438/812/2514 and 2008-58-0035) and Danish Regional Ethical Committee on Health Research for Southern Denmark (record no. S-20100082). All participants in the clinically recruited cohort gave written informed consent.

Population-Based T2DM Cohort

We used the Danish National Patient Registry and the Danish National Prescription Registry to identify a population-based cohort of individuals residing in the Central and Northern Danish Regions (one-third of the total Danish population, 1.9 million inhabitants) with T2DM diagnosed between January 1, 2005, and December 31, 2017.[28] We defined newly diagnosed T2DM as either a first-time hospital inpatient or outpatient diagnosis of diabetes or a first-time redemption of a glucose-lowering drug prescription issued by a hospital-based or primary care physician in individuals older than 30 years. Eligible individuals had to have a prior registration in the laboratory database (Figure 1A). We excluded individuals who had likely gestational diabetes (i.e., gave birth within 9 months after a T2DM diagnosis); individuals who died or emigrated or lacked triglyceride, LDL, HDL, and total cholesterol measurements within 1 year after their T2DM diagnosis; and those with any prior neuropathy. Follow-up started 1 year after the T2DM diagnosis (index date) to allow time for initial diagnostic workup for prevalent neuropathy, lipid assessment, lifestyle modifications, and potential early lipid-lowering therapy.

Clinically Recruited T2DM Cohort

The clinically recruited T2DM cohort was nested in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project.[29] The ongoing DD2 project prospectively enrolls individuals with newly diagnosed T2DM from hospital departments and general practitioners' offices. Upon enrollment, participants complete a short baseline questionnaire on lifestyle behaviors, undergo a short physical examination, and provide urine and blood samples for a biobank.[29] The DD2 data are linked to Danish population-based registries and the Danish Diabetes Database for Adults, which supply additional information on anthropometric measurements, lifestyle

behaviors, and routine clinic biochemistry test results.[29] In 2016, DD2 researchers sent a questionnaire to participants enrolled in the DD2 cohort (median of 3.0 years after DD2 enrollment).[29,30] The questionnaire included the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) and items such as height, weight, and lifestyle behaviors. The response rate was 86%.[30] In this study, we included individuals with a valid answer on the MNSIq and a registration in the laboratory database. We excluded individuals without an available lipid measurement (Figure 1B).

Lipid Levels

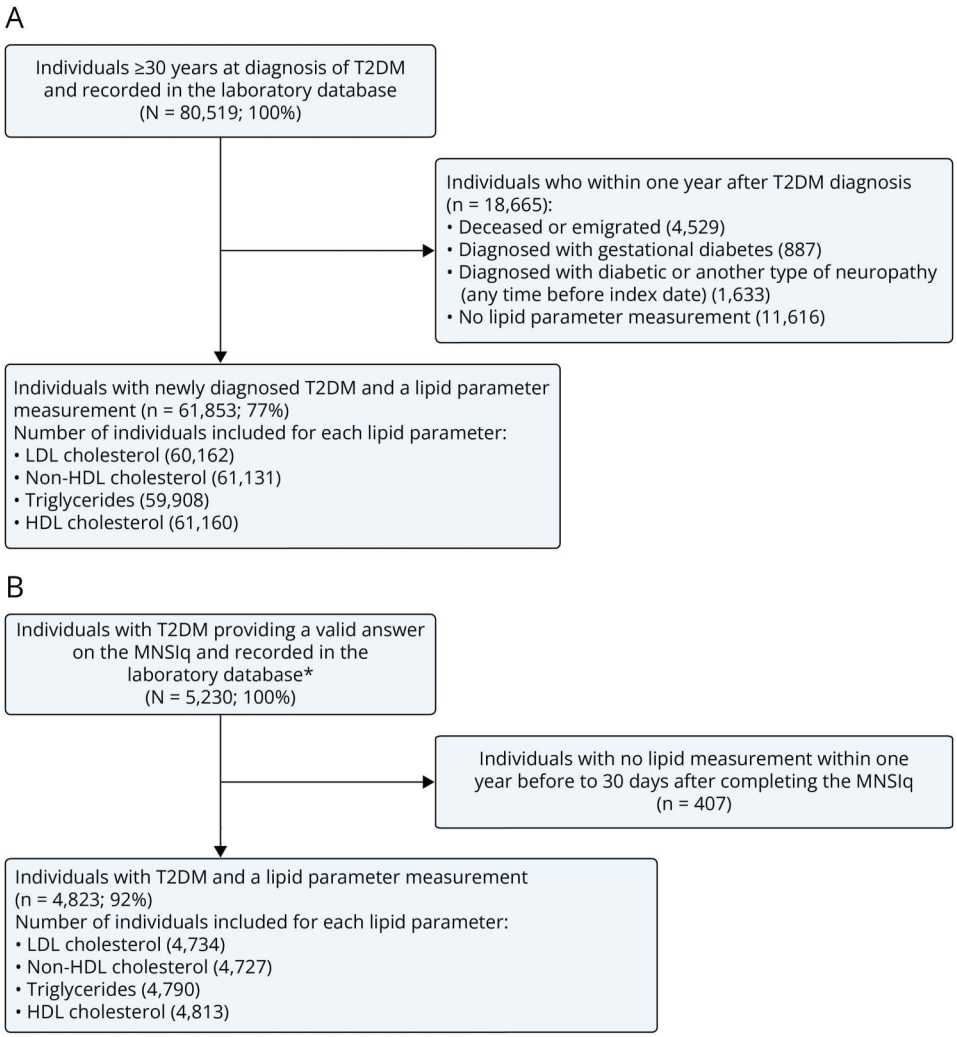
Lipid levels were measured in both primary and secondary care using standard hospital laboratory assays, and the results were recorded in the Clinical Laboratory Information System (LABKA)/Register of Laboratory Results for Research.[31] In the population-based T2DM cohort, we assessed the latest measured lipid value within 1 year after the first diabetes record. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Each individual lipid parameter was categorized according to the latest cutoffs in clinical guidelines on dyslipidemia,[6,10] as follows: triglycerides <150 mg/dL (1.7 mmol/L), 150–204 mg/dL (1.7–2.3 mmol/L), and ≥204 mg/dL (2.3 mmol/L); HDL cholesterol <39/50 mg/dL or ≥39/50 mg/dL (1.0/1.3 mmol/L for men/women); LDL cholesterol <70 mg/dL (1.8 mmol/L), 70–100 mg/dL (1.8–2.6 mmol/L), and ≥100 mg/dL (2.6 mmol/L); and non-HDL cholesterol <85 mg/dL (2.2 mmol/L), 85–131 mg/dL (2.2–3.4 mmol/L), and ≥131 mg/dL (3.4 mmol/L).

In the clinically recruited T2DM cohort, we assessed lipid values within 365 days before to 30 days after completion of the MNSIq and applied similar clinical cutoffs.

Definition of DPN

For the population-based T2DM cohort, we used a validated algorithm to identify hospital-diagnosed DPN recorded in the Danish National Patient Registry during an inpatient or outpatient hospital contact.[32] Validation of the DPN algorithm has previously been described in detail, yielding a positive

Figure 1 Sampling of Individuals in the Population-Based T2DM Cohort (A) and in the Clinically Recruited T2DM Cohort (B)



*Eligible individuals in the clinically recruited T2DM cohort: individuals with MNSIq data. We excluded individuals who completed the questionnaire twice (N = 15), returned a blank questionnaire (N = 212), or provided an invalid answer (N = 151). DD2 = Danish Centre for Strategic Research in Type 2 Diabetes; HDL = high-density lipoprotein; LABKA = Clinical Laboratory Information System Database; LDL = low-density lipoprotein; MNSIq = Michigan Neuropathy Screening Instrument Questionnaire; T2DM = type 2 diabetes mellitus.

Table Selected Characteristics of Individuals in the Population-Based T2DM Cohort and in the Clinically Recruited T2DM Cohort

Cohort	Population based	Clinically recruited
N	61,853	4,823
Men	35,220 (57)	2,765 (57)
Age	63 (54–72)	65 (57–72)
Diabetes duration, y	1.0 (1.0–1.0)	4.6 (3.4–5.7)
Current smokers	NA	944 (20)
Alcohol units >14/21 per week (M/F)	NA	311 (6)
BMI, kg/m^2 (quartiles)	NA	30.0 (26–34)
Waist circumference, cm (quartiles)	NA	106 (97–116)
Hospital-diagnosed obesity	6,208 (10)	730 (15)
Hypertension	31,747 (51)	3,289 (68)
HbA1c, % (quartiles)	6.4 (6.0–6.8)	6.5 (6.2–7.1)
HbA1c, mmol/mol (quartiles)	46 (42–51)	48 (44–54)
Total cholesterol, mg/dL (quartiles)	166 (143–193)	158 (139–181)
Total cholesterol, mmol/L (quartiles)	4.3 (3.7–5.0)	4.1 (3.6–4.7)
LDL cholesterol, mg/dL (quartiles)	85 (66–112)	77 (62–97)
LDL cholesterol, mmol/L (quartiles)	2.2 (1.7–2.9)	2.0 (1.6–2.5)
HDL cholesterol, mg/dL (quartiles)	46 (39–58)	46 (39–58)
HDL cholesterol, mmol/L (quartiles)	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Non-HDL cholesterol, mg/dL (quartiles)	116 (93–143)	108 (89–131)
Non-HDL cholesterol, mmol/L (quartiles)	3.0 (2.4–3.7)	2.8 (2.3–3.4)
Triglycerides, mg/dL (quartiles)	133 (97–195)	150 (106–212)
Triglycerides, mmol/L (quartiles)	1.5 (1.1–2.2)	1.7 (1.2–2.4)
eGFR, mL/min/1.73m2 (quartiles)	88 (73–99)	86 (72–96)
Cardiovascular disease	14,740 (24)	1,058 (22)
Peripheral vascular disease	2,472 (4)	264 (5)
Foot ulcers	2,732 (4)	288 (6)
Chronic liver disease	1,028 (2)	83 (2)
Alcohol abuse	2,388 (4)	149 (3)
Cancer	4,610 (7)	405 (8)
Chemotherapy	2,087 (3)	199 (4)
Vitamin deficiencies	3,351 (5)	290 (6)
Intensity of GLD treatment		
No therapy	5,955 (10)	607 (13)
Monotherapy	43,876 (71)	2,699 (56)
Insulin or GLD polytherapy	12,022 (19)	1,517 (31)
Insulin	4,352 (7)	465 (10)
Statins	42,407 (69)	3,745 (78)

Continued

Table Selected Characteristics of Individuals in the Population-Based T2DM Cohort and in the Clinically Recruited T2DM Cohort *(continued)*

Cohort	Population based	Clinically recruited
Antihypertensives	45,141 (73)	3,750 (78)
Loop diuretics	9,409 (15)	526 (11)
Antipsychotics and anticonvulsants	5,748 (9)	212 (4)
Antidepressants	11,000 (18)	683 (14)

Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; F = female; HbA1c = hemoglobin A1c; GLD = glucose-lowering drug; HDL = high-density lipoprotein; LDL = low-density lipoprotein; M = male; NA = not applicable.
Categorial data are presented as n (%) and continuous data are presented as median (interquartile range), unless otherwise specified. Definition and missingness of each covariate are described in eTable 1. Multiply by 0.0259 to convert cholesterol levels in mg/dL to mmol/L. Multiply by 0.0113 to convert triglyceride levels in mg/dL to mmol/L.

predictive value of 74% for DPN (see eMethods for further information).

In the clinically recruited T2DM cohort, we defined DPN as an MNSIq score ≥4 points.[2,33] While hospital-based diagnosis codes are likely to capture more severe patients with DPN, the MNSIq may also identify milder patients with DPN who are previously undiagnosed or diagnosed in primary care only.[2,33]

Covariates

In the population-based cohort, we defined each covariate according to hospital diagnoses, procedure codes, and drug use by linking the cohort to the Danish National Patient Registry and the Danish National Prescription Registry. Covariates were assessed prior to or on the index date. In the clinically recruited cohort, we used both information from the above registries (with covariates assessed prior to or on the MNSIq completion date) and exact information on smoking status, alcohol consumption, physical activity, blood pressure, body mass index, and waist circumference recorded at DD2 enrollment and in the Danish Diabetes Database for Adults. In both cohorts, hemoglobin A1c (HbA1c) and creatinine measurements were assessed in the LABKA/Register of Laboratory Results for Research database. eTable 1 provides the definitions of covariates used for each cohort.

Statistical Analyses

We described baseline characteristics of individuals in each study cohort both overall and according to the lipid parameters. In the population-based T2DM cohort, we followed all individuals from their index date until occurrence of DPN, death, emigration, or study end (April 30, 2021), whichever occurred first. We calculated crude incidence rates and crude and adjusted hazard ratios (HRs) using a Cox proportional regression model. Based on prior research and guided by a directed acyclic graph (eFigure 1),[1,5,34,35] we adjusted for the following potential confounders: age, sex, calendar year of index date, smoking-related disorders (hospital diagnoses or use of respiratory inhalants), alcohol abuse (hospital diagnoses or use of drugs to treat alcohol abuse), obesity (hospital diagnoses or use of antiobesity drugs), hypertension (hospital diagnoses or use of at least 2 antihypertensive drugs), and HbA1c level. Log-minus-log plots showed no violation of the proportional hazard assumption.

For the clinically recruited T2DM cohort, we used a Poisson regression model (with robust variance estimation) to calculate crude and adjusted prevalence ratios. Because more detailed information on potential confounders was available for this cohort,[29] the model was adjusted for age, sex, calendar year of enrollment, diabetes duration, exact smoking status, alcohol consumption, physical activity level, waist circumference, hypertension (blood pressure ≥130 systolic or ≥85 mm Hg diastolic, hospital diagnoses or use of at least 2 antihypertensives), and HbA1c level.

In both cohorts, we applied restricted cubic spline models with 5 degrees of freedom (knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th quantiles) to examine the patterns of association between the individual baseline lipid parameters and DPN. Splines were adjusted for the covariates listed above. Although all individuals with available data were included in the regression models, the graphs were limited to the 2.5th and 97.5th percentile of the individual lipid distribution because of the underlying linearity assumption for extreme values when using spline models.[36]

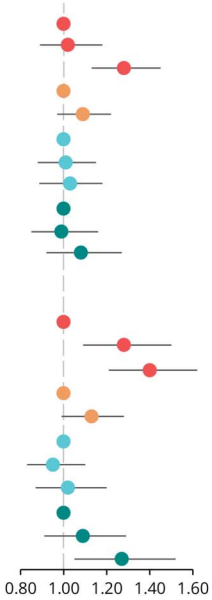
Because missingness for covariates was low, that is, below 5% (except for exact blood pressure in the clinical cohort with 52% missing values; instead, we added information on hypertension diagnoses and drugs) (eTable 1), all analyses were conducted in individuals with complete information.

Additional and Sensitivity Analyses

We performed 4 additional analyses in both cohorts. First, to examine the effect of baseline statin treatment on the lipid-DPN association, we stratified by statin use (yes, no) before the lipid measurement. Second, because increasing triglyceride levels may affect the cholesterol parameters,[8] we reran our analyses of cholesterol exposures while also adjusting for triglyceride levels (we did not attempt to conversely adjust the triglyceride exposure for the cholesterol parameters because these may be considered mediators on the

Figure 2 Absolute and Relative Associations Between DPN and Lipid Parameters in the Population-Based Cohort (Longitudinal Design) and the Clinically Recruited T2DM Cohort (Cross-Sectional Design)

Cohort	Lipid parameter	Lipid level (mg/dL)	N	DPN events	DPN incidence rates per 1,000 PYs (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Population-based cohort	Triglycerides	<150	33,120	789	3.2 (3.0–3.4)	Reference	Reference
		150–204	12,573	309	3.4 (3.1–3.8)	1.07 (0.94–1.22)	1.02 (0.89–1.18)
		≥204	14,215	460	4.6 (4.2–5.0)	1.45 (1.29–1.62)	1.28 (1.13–1.45)
	HDL cholesterol	≥39/50 (M/F)	41,321	1,084	3.5 (3.3–3.8)	Reference	Reference
		<39/50 (M/F)	19,839	505	3.6 (3.3–3.9)	1.02 (0.92–1.14)	1.09 (0.97–1.22)
	LDL cholesterol	<70	15,186	368	3.5 (3.2–3.9)	Reference	Reference
		70–100	22,953	607	3.5 (3.3–3.8)	0.99 (0.87–1.13)	1.01 (0.88–1.15)
		≥100	22,023	572	3.5 (3.2–3.8)	0.98 (0.86–1.11)	1.03 (0.89–1.18)
	Non–HDL cholesterol	<85	9,218	219	3.5 (3.0–4.0)	Reference	Reference
		85–131	29,516	740	3.4 (3.2–3.6)	0.96 (0.82–1.11)	0.99 (0.85–1.16)
		≥131	22,397	629	3.8 (3.5–4.1)	1.07 (0.92–1.25)	1.08 (0.92–1.27)
	Lipid parameter	Lipid level (mg/dL)	N	DPN events	DPN prevalence (%)	Crude PR (95% CI)	Adjusted PR (95% CI)
Clinically recruited cohort	Triglycerides	<150	2,327	326	14	Reference	Reference
		150–204	1,075	216	20	1.43 (1.23–1.68)	1.28 (1.09–1.50)
		≥204	1,388	325	23	1.67 (1.46–1.92)	1.40 (1.21–1.62)
	HDL cholesterol	≥39/50 (M/F)	3,230	518	16	Reference	Reference
		<39/50 (M/F)	1,583	350	22	1.38 (1.22–1.56)	1.13 (0.99–1.28)
	LDL cholesterol	<70	1,645	292	18	Reference	Reference
		70–100	1,911	329	17	0.97 (0.84–1.12)	0.95 (0.83–1.10)
		≥100	1,178	224	19	1.07 (0.92–1.25)	1.02 (0.87–1.20)
	Non–HDL cholesterol	<85	953	142	15	Reference	Reference
		85–131	2,463	429	17	1.17 (0.98–1.39)	1.09 (0.91–1.29)
		≥131	1,311	285	22	1.46 (1.21–1.75)	1.27 (1.05–1.52)



Multiply by 0.0259 to convert cholesterol levels in mg/dL to mmol/L. Multiply by 0.0113 to convert triglyceride levels in mg/dL to mmol/L. In the population-based T2DM cohort, the analysis was conducted among individuals with complete data on all covariates in the adjusted model (total n = 61,853; triglycerides: n = 56,831; HDL cholesterol: n = 57,841; LDL cholesterol: n = 56,887; non-HDL cholesterol: n = 57,815). The model was adjusted for age, sex, calendar year of index date, smoking-related disorders (hospital diagnoses or use of respiratory inhalants), alcohol abuse (hospital diagnoses or use of drugs to treat alcohol abuse), obesity (hospital diagnoses or use of antiobesity drugs), hypertension (hospital diagnoses or use of at least 2 antihypertensives), and HbA1c level. In the clinically recruited T2DM cohort, analyses were conducted among individuals with complete data on all covariates in the adjusted model (total n = 4,823; triglycerides: n = 4,702; HDL cholesterol: n = 4,724; LDL cholesterol: n = 4,648; non-HDL cholesterol: n = 4,638). The model was adjusted for age, sex, calendar year of enrollment, diabetes duration, exact smoking status, alcohol consumption, physical activity level, waist circumference, hypertension (blood pressure ≥130 systolic or ≥85 mm Hg diastolic, hospital diagnoses or use of at least 2 antihypertensives), and HbA1c level. DPN = diabetic polyneuropathy; F = female; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein; M = male; PR = prevalence ratio; PY = person-years.

pathway to DPN; see eFigure 2).[8] Third, because heavy alcohol use may lead to neuropathy[37] and at the same time is associated with elevated triglycerides and HDL cholesterol levels,[38] we repeated the main analysis while excluding all individuals with any alcohol abuse or chronic liver disease diagnosis (eTable 1). Finally, to maximize the likelihood of excluding causes of neuropathy other than diabetes, we reran analyses while excluding those with a hospital history of cancer, chemotherapy, alcohol abuse, chronic liver disease, and vitamin deficiencies.

In the population-based cohort, we further performed 4 sensitivity analyses. First, we started follow-up at 180 days instead of 365 days after the T2DM diagnosis to capture possible early DPN events at the expense of less time for initial diagnostic workup (N = 52,529, eFigure 3). Second, we used a more restrictive DPN outcome algorithm with a positive predictive value of 86% (eTable 1).[32] Third, we used a Fine-Gray model to account for the competing risk of death.[39] Finally, to test the robustness of our methodology, we examined acute myocardial infarction risk as a positive control outcome associated with all the lipid parameters under study.[8,10,40] Analyses were conducted using Stata, version 18.0 (StataCorp., College Station, TX).

Data Availability

The data are available for research upon request to the Danish Health Data Authority and within the framework of the Danish data protection legislation and any required permissions from authorities.

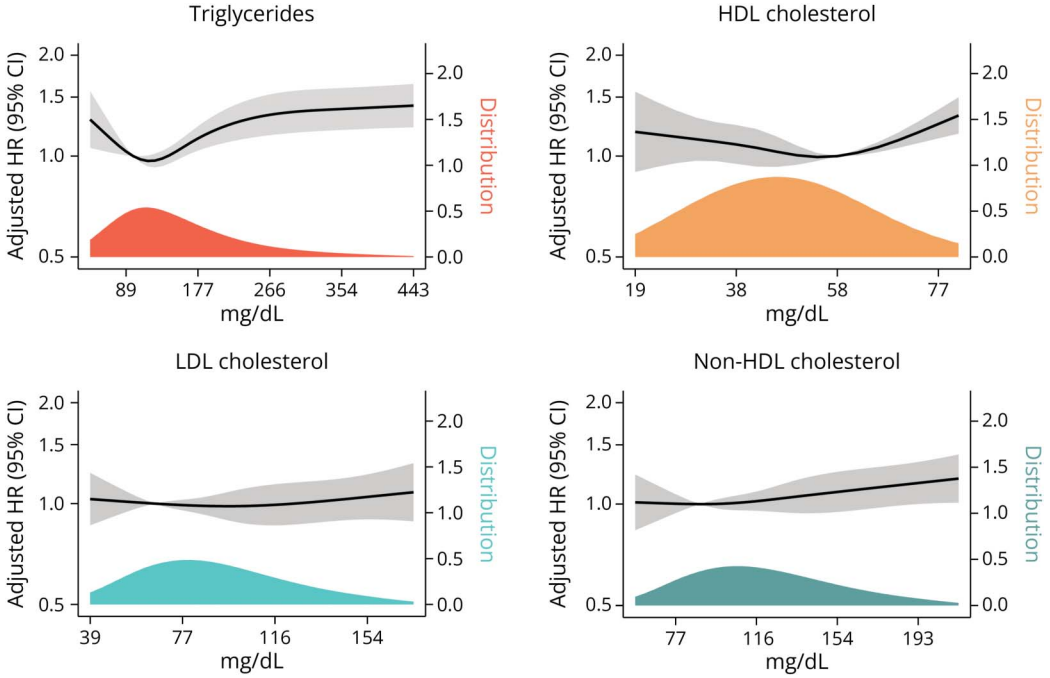
Results

The Population-Based T2DM Cohort

Among 80,519 eligible individuals, 61,853 (77%) had at least 1 triglyceride, HDL cholesterol, LDL cholesterol, or total cholesterol measurement (Figure 1A). Overall characteristics of the population-based cohort are presented in Table 1, whereas characteristics according to lipid levels are shown in eTables 2 and 3. Individuals with dyslipidemia were younger and more obese than those without dyslipidemia. They also had higher HbA1c levels, more hypertension, smoking-related disorders, and alcohol abuse (mainly associated with high rather than low HDL cholesterol) (eTables 2 and 3).

During a median follow-up time of 7.3 years (interquartile range 4.2–10.0), 1,610 hospital-diagnosed DPN events occurred, corresponding to a rate of 3.6 (95% CI 3.4–3.7) events per 1,000 person-years.

Figure 3 Associations Between Lipid Parameters and Risk of DPN in the Population-Based T2DM Cohort, Based on Spline Models



Multiply by 0.0259 to convert cholesterol levels in mg/dL to mmol/L. Multiply by 0.0113 to convert triglyceride levels in mg/dL to mmol/L. The analysis was conducted among individuals with complete data on all covariates in the adjusted model (total n = 61,853; triglycerides: n = 56,831; HDL cholesterol: n = 57,841; LDL cholesterol: n = 56,887; non-HDL cholesterol: n = 57,815). The model was adjusted for age, sex, calendar year, smoking-related disorders (hospital diagnoses or a drug prescription for respiratory inhalants), alcohol abuse (hospital diagnoses of alcohol-related conditions or a drug prescription to treat alcohol abuse), obesity (hospital diagnoses or a drug prescription for weight loss), hypertension (hospital diagnoses or at least 2 drug prescriptions for antihypertensives), and HbA1c level. The reference point was the 25th percentile of the given lipid parameter distribution, as follows: triglycerides = 97 mg/dL (1.1 mmol/L), LDL cholesterol = 66 md/dL (1.7 mmol/L), and non-HDL cholesterol = 89 mg/dL (2.3 mmol/L). The 75th percentile was used for HDL cholesterol (58 mg/dL [1.5 mmol/L]). The analysis was limited to the 2.5th–97.5th percentile of the individual lipid distribution. DPN = diabetic polyneuropathy; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HR = hazard ratio; LDL = low-density lipoprotein.

Using guideline-specific cutoff levels, the adjusted HRs for DPN were 1.02 (95% CI 0.89–1.18) for individuals with triglyceride levels between 150 and 204 mg/dL and 1.28 (95% CI 1.13–1.45) for individuals with triglyceride levels ≥204 mg/dL, compared with levels <150 mg/dL (Figure 2). HDL, LDL, and non-HDL cholesterol showed no clear association with DPN (HDL cholesterol levels <39/50 mg/dL in men/women: 1.09 [95% CI 0.97–1.22]; LDL cholesterol levels ≥100 mg/dL: 1.03 [95% CI 0.89–1.18]; non-HDL cholesterol levels ≥131 mg/dL: 1.08 [95% CI 0.92–1.27]) (Figure 2).

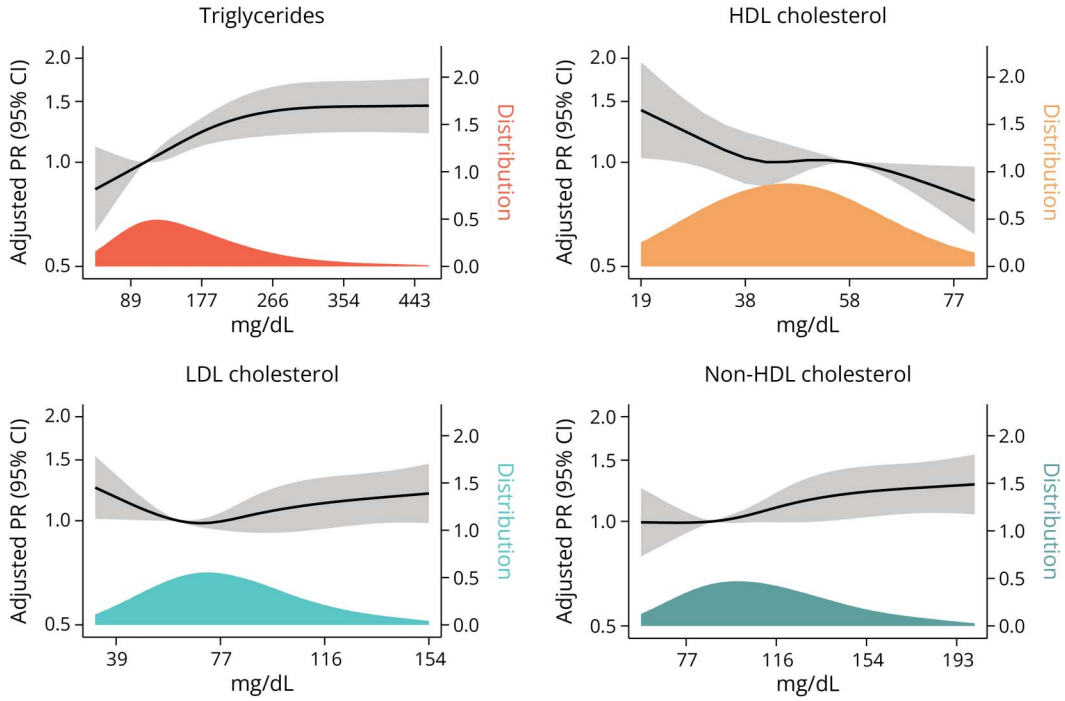
In spline analyses, the adjusted HRs for DPN increased markedly for individuals with triglyceride levels above 124 mg/dL (1.4 mmol/L), reaching a plateau at approximately 310 mg/dL (3.5 mmol/L). The adjusted HRs increased for HDL cholesterol levels above 66 mg/dL (1.7 mmol/L) and for levels below 50 mg/dL (1.3 mmol/L). In comparison, spline curves of adjusted HRs were almost flat and close to 1.0 for LDL and non-HDL cholesterol, although with a slight increase in HRs for non-HDL cholesterol levels above 135 mg/dL (3.5 mmol/L) (Figure 3).

Clinically Recruited T2DM Cohort

Among 5,230 eligible individuals, 4,823 (92%) had at least 1 triglyceride, HDL cholesterol, LDL cholesterol, or total cholesterol measurement (Figure 1B). Overall characteristics of the clinically recruited cohort are presented in Table 1, whereas characteristics according to lipid levels are shown in eTables 2 and 3. The median diabetes duration in the cohort was 4.6 years (interquartile range 3.4–5.7) at the time of DPN assessment. As in the population-based cohort, individuals with dyslipidemia were younger and more obese. They also had more hypertension, higher HbA1c levels, and unhealthier lifestyle behaviors (eTables 2 and 3).

The DPN prevalence was 18%. Using guideline-specific cutoff levels, the adjusted prevalence ratio for DPN was 1.28 (95% CI 1.09–1.50) for individuals with triglyceride levels between 150 and 204 mg/dL and 1.40 (95% CI 1.21–1.62) for individuals with triglyceride levels ≥204 mg/dL. Prevalence ratios were also modestly elevated for HDL cholesterol levels <39/50 mg/dL in men/women (1.13 [95% CI 0.99–1.28]) and non-HDL cholesterol ≥131 mg/dL (1.27 [95% CI 1.05–1.52]), however, not for elevated LDL cholesterol ≥100 mg/dL (1.02 [95% CI 0.87–1.20]) (Figure 2).

Figure 4 Associations Between Lipid Parameters and Risk of DPN in the Clinically Recruited T2DM Cohort, Based on Spline Models



Multiply by 0.0259 to convert cholesterol levels in mg/dL to mmol/L. Multiply by 0.0113 to convert triglyceride levels in mg/dL to mmol/L. The analyses were conducted among those with complete data on all covariates in the adjusted model (total n = 4,823; triglycerides: n = 4,702; HDL cholesterol: n = 4,724; LDL cholesterol: n = 4,648; non-HDL cholesterol: n = 4,638). The model was adjusted for age, sex, calendar year of enrollment, diabetes duration, exact smoking status, alcohol consumption, physical activity level, waist circumference, hypertension (blood pressure ≥130 systolic or ≥85 mm Hg diastolic, hospital diagnoses or use of at least 2 antihypertensives), and HbA1c level. The reference point was the 25th percentile of the given lipid parameter distribution, as follows: triglycerides = 106 mg/dL (1.2 mmol/L), LDL cholesterol = 62 mg/dL (1.6 mmol/L), and non-HDL cholesterol = 89 mg/dL (2.3 mmol/L). The 75th percentile was used for HDL cholesterol (58 mg/dL [1.5 mmol/L]). The analysis was limited to the 2.5th–97.5th percentile of the individual lipid distribution. DPN = diabetic polyneuropathy; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PR = prevalence ratio.

In spline analyses, the prevalence ratios increased substantially for triglyceride levels from approximately 124 mg/dL (1.4 mmol/L) reaching a plateau at approximately 310 mg/dL (3.5 mmol/L), similar to what was observed in the population-based cohort. In contrast to the population-based cohort, we observed more clearly increasing prevalence ratios with decreasing HDL cholesterol levels and no increase in the prevalence ratios with increasing HDL cholesterol levels. Spline curves for DPN showed slightly increasing prevalence ratios with elevated LDL and non-HDL cholesterol levels (Figure 4).

Additional Analyses

We observed no statistical interaction of statin use with triglycerides or cholesterol parameter associations in either of the 2 cohorts. Although we found that high triglyceride levels were associated with increased DPN risk among individuals who were statin users in the population-based cohort, this analysis had limited statistical precision (eTables 4–8). Further adjustment of the cholesterol associations for triglyceride levels attenuated the results toward the null in both cohorts (e.g., from a prevalence ratio of 1.27 [95% CI 1.05–1.52] to 1.15 [95% CI 0.94–1.41] for non-HDL cholesterol ≥131 mg/dL) (eTables 4–8). Additional adjustment for glucose-lowering drugs showed results consistent with the main analysis (data not shown). Excluding individuals with alcohol abuse or a chronic liver disease diagnosis left the DPN associations for all lipid parameters virtually unchanged in both cohorts (eTables 4–8). When excluding all other potential causes of neuropathy, we observed similar HRs as in the main analysis of the population-based cohort, except for an increase in the association for HDL cholesterol levels below 39/50 mg/dL for men/women (adjusted HR of 1.17 [1.03–1.32]). Associations were virtually unchanged in the clinically recruited cohort (eTables 4–8).

In the population-based cohort, we found consistent results when follow-up started 180 days after the T2DM diagnosis, when a more restrictive outcome algorithm was adapted, and when a Fine-Gray model was applied (eTables 4–8). As a positive control, we observed that increasing triglycerides, LDL cholesterol, and non-HDL cholesterol, as well as decreasing HDL cholesterol levels all had a clear dose-response association with increased risk of acute myocardial infarction (eTables 4–8).

Discussion

We found that elevated triglyceride levels were consistently associated with an increased risk of DPN. This association

remained strong after accounting for the effect of lifestyle behaviors, central obesity, HbA1c level, and other metabolic syndrome components. The results were less clear for low HDL cholesterol, and the evidence was weak for any effect of elevated LDL and non-HDL cholesterol levels on DPN risk.

Prior studies have focused mainly on the relation of DPN with high triglycerides and low HDL cholesterol as components of the metabolic syndrome.[11-26] Some observational studies of individuals with elevated triglycerides have reported a 1.2- to 2.0-fold increased risk of DPN,[15,18-20,23,26] while others have found no clear association.[11-14,21,22,25] Similarly inconsistent findings have been reported in studies focusing on low HDL cholesterol and DPN.[11-15,17,20,23,25,26] However, only a few of these studies have examined lipid-DPN associations in T2DM-specific cohorts in a longitudinal manner, while also adjusting for other metabolic risk factors.[11,26] A Danish longitudinal T2DM study suggested an increased DPN rate with low HDL, LDL, and total cholesterol levels, but not with high triglyceride levels.[11] This study had a high loss to follow-up (>40%) and may have been affected by uncontrolled confounding from lifestyle behaviors, hyperglycemia, central obesity, and hypertension.[11] Consistent with our findings, a UK biobank study of patients with T2DM reported that both high triglycerides and low HDL cholesterol levels were associated with DPN after adjusting for confounding factors.[26] However, as observed in our study, the association between low HDL cholesterol and DPN seemed to be confounded by high triglyceride levels, and a mediation analysis showed that triglycerides had the strongest effect on the risk of DPN compared with other lipid parameters.[26]

Prior cross-sectional studies examining LDL and non-HDL (or total) cholesterol have reported either a slight increase in DPN prevalence with low cholesterol levels[16,22,26,27] or no association.[11,17,21,23-25] Consistent with these findings, we previously reported that statin therapy, which mainly lowers LDL cholesterol, does not mitigate DPN risk in individuals with T2DM.[41] In addition, we found that the association between non-HDL cholesterol and DPN disappeared after adjusting for triglycerides, suggesting that triglyceride levels may be a confounder of the effect between non-HDL cholesterol and DPN. Supporting our conclusion, a recent systematic review found that neither LDL nor non-HDL cholesterol seems to be associated with DPN risk.[42]

Although our observational study cannot elucidate causal mechanisms, our results indicate that elevated triglycerides are associated with DPN independently of other metabolic risk factors. This is supported by preclinical studies of neuropathy development suggesting that elevated cholesterols may have a less harmful effect,[1,42] while elevated triglycerides may have specific nerve-damaging effects. The potential underlying mechanisms may be related to energy substrate overload of triglycerides and glucose, which impairs nerve metabolism and facilitates low-grade inflammation and bioenergetic failure causing mitochondrial dysfunction in peripheral neurons.[1,5,42] The effect on neuronal mitochondrial function may depend on chain length and saturation of the free fatty acids (stored and transported as triglycerides) because long-chain saturated fatty acids impair mitochondrial trafficking and are more detrimental to neuronal mitochondria than their unsaturated counterparts.[1,42]

Current clinical guidelines emphasize that lipid control may decrease DPN risk.[5-7] However, the optimal lipid parameter to target and the level to aim for is unclear from these guidelines. While fenofibrate—a triglyceride-lowering drug—has shown to reduce the risk of amputations in patients with T2DM,[43] no clinical trial has examined the effect of lipid-lowering therapy on risk of DPN among individuals with T2DM. Our results suggest that elevated triglycerides, rather than cholesterol, could be a target for DPN prevention in future clinical trials. Furthermore, our observations indicate that the optimal target level for triglycerides might be lower than the metabolic syndrome cutoff of 150 mg/dL (1.7 mmol/L). American and European scientific statements recommend that the optimal triglyceride level for cardiovascular disease prevention may be below 106 mg/dL (1.2 mmol/L) in the general population.[8,40,44] Our data support that such low triglyceride level may be relevant for identifying individuals at increased risk of DPN as well, which would have implications for current T2DM management.

The following limitations of our study are important to note. First, our reliance on hospital diagnosis codes and glucose-lowering drug prescriptions to identify individuals with T2DM may have led us to misclassify late-onset type 1 diabetes or latent autoimmune diabetes after the age of 30 years as T2DM. Second, to be included in our population-based cohort, individuals had to survive 1 year after their T2DM diagnosis and also have a lipid measurement that may affect the generalizability of our results.[45] Yet, our results are generalizable to individuals with T2DM who attend regular follow-up visits in primary care and outpatient clinics. Third, we did not assess repeated information on lipid measurements, confounders, or treatments during follow-up that could be important to capture time-varying DPN risk. Individuals with higher lipid values are more likely to initiate lipid-lowering therapy during follow-up, which potentially may have led to an underestimation of the DPN associations. Fourth, although cholesterol levels are relatively stable over time, nonfasting triglyceride measurements may have pronounced day-to-day fluctuations.[44] However, nonfasting blood samples may be clinically relevant because the postprandial state provides an average lipid profile during a 24-hour period.[44,46] Fifth, because of the heterogeneity in DPN presentation and the lack of clear-cut diagnostic criteria,[1] we may have misclassified some patients with DPN, both when relying on hospital diagnosis codes and when examining MNSIq-defined DPN.[47] Confirmation of the DPN diagnosis requires electrophysiologic examinations. However,

electrophysiologic tests are not recommended for standard clinical diabetes practice (i.e., the data used in our population-based cohort), and it was not feasible to conduct electrophysiologic tests in our large clinically recruited cohort. Accordingly, we were only able to categorize patients with DPN into diagnosis of possible or probable DPN based on the Toronto Consensus Panel definition.[48] However, our 2 outcome definitions complement each other, and may complement results from clinical research using electrophysiologic tests. Although the algorithm to identify hospital-diagnosed DPN likely identifies more severe patients with DPN, the MNSIq may also include patients with milder DPN who are previously undiagnosed or diagnosed in primary care only. Sixth, our study is unable to determine whether the association between lipid parameters and DPN is causal. Intervention studies or observational studies that emulate target trials could be used to determine whether a reduction in triglycerides is more important for preventing neuropathy outcomes than other lipid parameters. Finally, we cannot exclude the possibility of some residual confounding from socioeconomic factors or from imperfectly measured lifestyle behaviors including alcohol consumption and smoking.

We found that elevated triglyceride levels rather than LDL and non-HDL cholesterol are associated with increased DPN risk after adjustment for important confounding factors. The results were less clear for HDL cholesterol. Future intervention studies are needed to determine whether triglyceride reduction is more important for preventing neuropathy outcomes than reduction of other lipid parameters.

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Disclosure

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Appendix *(continued)*

Name	Location	Contribution
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