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Diet quality and chronic axonal polyneuropathy: a population-based study

Noor E. Taams[1,2], Trudy Voortman[1], Rens Hanewinckel[1,2], Judith Drenthen[2,3], Pieter A. van Doorn[2] & Mohammad A. Ikram[1]

[1]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands
[2]Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands
[3]Department of Clinical Neurophysiology, Erasmus University Medical Center, Rotterdam, the Netherlands

Correspondence
Mohammad A. Ikram, Department of Epidemiology, Erasmus University Medical Center, Room NA-2818, Dr. Molewaterplein 50, Rotterdam 3015 GE, The Netherlands.
Tel: +31107043488; Fax: +31107044657;
E-mail: m.a.ikram@erasmusmc.nl

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Abstract

Objective: To investigate the association between diet quality and chronic axonal polyneuropathy. **Methods**: Between June 2013 and January 2017, among 1650 participants of the Rotterdam Study (median age 69.1 years, 54.2% women), diet quality was quantified based on food frequency questionnaires as a sum score of adherence (yes/no) to 14 components of the Dutch dietary guidelines. Presence of polyneuropathy was determined based on a questionnaire, neurological examination of the legs, and nerve conduction studies. We used logistic regression to associate diet quality with the presence of chronic axonal polyneuropathy and linear regression to associate with sural sensory nerve action potential (SNAP) amplitude in participants without polyneuropathy. Results were adjusted for age, sex, time between measurements, body mass index, blood pressure, diabetes mellitus, smoking, kidney function, and education. **Results**: Overall diet quality was not associated with chronic axonal polyneuropathy (odds ratio [OR] = 0.99, 95% confidence interval [CI] 0.88; 1.12, $P = 0.842$), nor with sural SNAP amplitude in participants without polyneuropathy (difference = 0.01, 95% CI −0.14; 0.15, $P = 0.993$). Although not surviving multiple testing, a nominally significant association was found between salt intake ≤6 g/day and presence of chronic axonal polyneuropathy (OR = 0.55, 95% CI 0.35; 0.86, $P = 0.008$). **Interpretation**: We did not find an association between diet quality and chronic axonal polyneuropathy.

INTRODUCTION

Chronic axonal polyneuropathy is the most common form of polyneuropathy. It is characterized by symmetrical sensory symptoms and predominant distal weakness. Even before clinical symptoms or signs occur, peripheral nerve dysfunction can be quantified through nerve conduction studies (NCS).[1] The most common risk factors in high-income countries are diabetes mellitus, deficiencies of vitamins B1 and B12, alcohol overuse, and metabolic syndrome.[2–4] Yet, one-third of the patients suffer from chronic axonal polyneuropathy in the absence of known risk factors, usually referred to as chronic idiopathic axonal polyneuropathy (CIAP).[5] This suggests that additional risk factors remain to be identified.

Diet is an important determinant of health and has been recognized as modifiable risk factor for various chronic diseases, including cardiovascular disease, cancer, dementia and diabetes mellitus.[6–9] Diet has also been linked to several known risk factors of polyneuropathy,

including insulin resistance, obesity, and other components of metabolic syndrome.[10] However, data on the association between diet and polyneuropathy are scarce. The single study on this topic, a case–control design, failed to find a link between intake of specific nutrients and CIAP.[11] Moreover, given the complexities of studying individual nutrients, it may be more meaningful to study dietary patterns, especially since such patterns can be judged against existing guidelines and are potentially amenable.

Therefore, we investigated the association of diet quality, based on adherence to dietary guidelines, with the presence of chronic axonal polyneuropathy and with peripheral nerve damage as measured with sensory NCS in participants without polyneuropathy.

METHODS

Setting and study population

This study was part of the Rotterdam Study, an on-going prospective population-based cohort study to investigate chronic diseases in the older population (age ≥45 years).[12] The cohort started in January 1990 (RS-I) and was extended in 2000 (RS-II) and 2006 (RS-III). Follow-up examinations took place every 3–5 years. Since June 2013 a polyneuropathy screening was implemented. From this moment until January 2017, 2069 participants of subcohorts RS-I, RS-II, and RS-III were screened for polyneuropathy. From this group, 151 persons were excluded due to insufficient screening. Of the 1918 remaining participants, dietary data were present for 1650 participants. Sural sensory nerve action potential (SNAP) amplitude and dietary data were available in 1272 participants of which 70 participants had definite polyneuropathy. We investigated subclinical nerve damage by analyzing the sural SNAP amplitude in participants without definite polyneuropathy (N = 1202).

Standard protocol approvals, registrations and patients consents

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register and into the WHO International Clinical Trials Registry Platform under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Assessment of diet quality and intake

Diet quality was assessed using a 389-item validated food frequency questionnaires (FFQ) as described elsewhere.[13] Nutrient data were calculated using the Dutch Food Composition Table. For the current analyses, we used dietary data collected in subcohort RS-I, RS-II, and RS-III at examination round 5, 3, and 1 respectively. Median time difference between assessment of dietary habits and polyneuropathy screening was 5.1 years (range 3.7–8.2 years), but dietary habits have been shown to be relatively stable over time.[14–16] Based on the 2015 Dutch Dietary guidelines and additional information from the Netherlands Nutrition Center and Dutch food consumptions surveys, adherence to 14 components was assessed, scored as yes (adherence) or no (no adherence): vegetables (≥200 g/day), fruit (≥200 g/day), whole grain products (≥90 g/day), ratio wholegrains:total grains (≥50%), legumes (≥135 g/week), nuts (≥15 g/day), dairy (≥350 g/day), fish (≥100 g/week), tea (≥450 mL/day), ratio unsaturated fats and oils:total fats (≥50%), red and processed meat (≤300 g/week), sugar-containing beverages (≤150 mL/day), alcohol (≤10 g/day) and salt (≤6 g/day). Diet quality score was calculated as sum-score of the adherence to the individual components (0–14), in which a higher score represents a healthier diet.[13,17]

Polyneuropathy screening

Polyneuropathy screening consisted of a symptoms questionnaire, neurological examination of the legs, NCS of the peroneal and sural nerves, and a review of medical records.[18] The questionnaire included questions concerning bilaterally tingling or burning sensations, cotton-wool feeling, muscle cramps, muscle pain not related to exercise, stabbing pain, weakness, numbness, tightness and allodynia of the feet or legs during the last 3 months. Answers could be never, sometimes or (almost) continuously. They were also asked if they were ever diagnosed with polyneuropathy. Neurological examination consisted of a bilateral examination of the legs including several sensory tests, assessment of tendon reflexes and muscle strength of the feet. Sensory tests included vibration sense using a Rydel–Seiffer tuning fork at the hallux of both feet, and superficial pain sensation using a disposable wooden pin starting with stimulation at the knee and ascending to the big toe. Ankle and knee tendon reflexes were assessed in sitting position. Muscle strength of the anterior tibial muscles was measured in lying position

and participants were also asked to stand on their heels, using balance support if needed. NCS were performed with a Nicolet™ Viking Quest (Natus Medical Incorporated, San Carlos, CA). The peroneal nerve was measured unilaterally and the sural nerve bilaterally, according to a predefined protocol.[18] Both sensory and motor action potential amplitudes were measured from baseline to peak. Distal peroneal nerve compound muscle action potential amplitude <1.1 mV and sural SNAP amplitude <4.0 μV were considered abnormal, in accordance with the cut-off values of our local hospital and literature.[19,20] The highest of both sural SNAP amplitudes was used for analyses.

All participants were individually discussed in an expert panel. The panel was led by a neuromuscular specialist (P. D.) and included a neurophysiology specialist (J. D.) and two physicians trained in epidemiology (N. T. and R. H.) with a special interest in neuromuscular diseases. Information from the three components of the polyneuropathy screening was used to categorize participants into "no", "possible", "probable", or "definite" chronic axonal polyneuropathy, based on their level of abnormalities of the components of the screening. Each component of the screening was evaluated separately before establishing the overall conclusion. Participants were discussed until unanimity was reached. Afterwards, their medical records were reviewed for a diagnosis of polyneuropathy. A diagnosis by a neurologist after extensive neurological work-up, irrespective of the cause, was considered superior to our screening and participants were, if needed, (re)classified. Participants with missing data in more than one component were exluded.[18] For this study, participants were divided in two groups: those having definite chronic axonal polyneuropathy or not (no, possible and probable combined).

Assessment of covariates

Covariates were measured during the home interviews by trained interviewers or during the following visit to the research center. Covariate assessment from the same examination round as the dietary data was used. Blood pressure was measured at the research center in sitting position on the right arm and the average of two measurements was used. Body mass index was calculated as [(body weight in kilograms)/(length in meters)^2]. Serum cholesterol (mmol/L) was acquired by an automated enzymatic procedure (Roche Hitachi 917 and Roche Modular P800, Roche Diagnostics, Indianapolis, USA). Serum creatinine levels were determined using an enzymatic assay method,[21] and used to calculated the estimated glomerular filtration rate (eGFR).[22] Diabetes mellitus type 2 was diagnosed if fasting blood glucose ≥7.0 mmol/L and/or use of antidiabetic drugs and/or previous diagnosis after review of the medical records. Information about the use of antidiabetic and/or antihypertensive drugs were obtained by interview and pharmacy records.[23] Smoking was categorized as never, past, or current smoking. Education level was categorized according to the UNESCO classification in four groups ranging from low (primary education) to high (higher vocational education or university). To maximize our statistical power, missing data on covariates was imputed using fivefold multiple imputation, based on determinant, outcome, and covariates. The percentages of missing values in covariates ranged from 0.3% to 1.9%.

Data analysis

Logistic regression was used to investigate the association between diet quality and chronic axonal polyneuropathy. Next, we used linear regression to determine the association between diet quality and sural SNAP amplitude in participants without definite polyneuropathy to investigate a possible relation with subclinical nerve damage. Additionally, logistic and linear regressions were also performed with dietary intake data on a continuous (g/day) instead of dichotomized scale (adherence yes/no). Sensitivity analysis was performed comparing participants with no versus definite polyneuropathy to rule out any possible misclassification into either group of persons with probable polyneuropathy. Furthermore, we stratified by sex, diabetes mellitus and alcohol intake (≤10 g/day), chosen based on literature and biological plausibility, to explore effect modification. All models were adjusted for age, sex, time between determinant assessment and polyneuropathy screening, body mass index, smoking status, blood pressure, use of anti-hypertensive drugs, total cholesterol, education level, eGFR, and diabetes mellitus.

Analyses were performed with IBM SPSS Statistics, version 25. To correct for multiple testing we used the Sidàk correction that is based on the correlations between the investigated food components.[24] Using R statistical software version 3.6.0, we computed the number of effective tests (Meff = 13.61) and set the new alpha level for two-tailed tests on $P < 0.004$.

Data availability

Data can be obtained on request. Requests should be directed toward the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

Table 1. Characteristics of the overall study population, and stratified for participants with definite and without polyneuropathy (no, possible and probable polyneuropathy).

	Total population *N* = 1650	Definite polyneuropathy *N* = 99	Without polyneuropathy *N* = 1551
Female	894 (54.2)	46 (46.5)	848 (54.7)
Age, years, median (IQR)	69.1 (58.8–73.8)	73.7 (68.8–77.4)	68.8 (58.4–73.5)
Education			
Primary	92 (5.6)	5 (5.1)	87 (5.6)
Low-intermediate	576 (34.8)	46 (46.5)	529 (34.1)
Intermediate	557 (33.8)	28 (28.3)	529 (34.1)
High	426 (25.8)	20 (20.2)	406 (26.2)
Smoking status			
Never	532 (32.3)	34 (34.3)	499 (32.2)
Past	881 (53.4)	61 (61.6)	820 (52.9)
Current	236 (14.3)	4 (4.0)	232 (15.0)
Systolic blood pressure, mmHg	144.0 (21.8)	146.8 (17.2)	143.8 (22.0)
Diastolic blood pressure, mmHg	84.7 (10.9)	83.9 (10.2)	84.7 (10.9)
Use of anti-hypertensive drugs	620 (37.6)	56 (56.6)	564 (36.4)
Diabetes mellitus	215 (13.0)	30 (30.3)	185 (11.9)
Body mass index, kg/m^2	27.1 (3.9)	28.0 (4.2)	27.1 (3.8)
Cholesterol, mmol/L	5.4 (1.1)	5.2 (1.1)	5.5 (1.1)
eGFR, ml/min per 1.73 m^2	78.7 (14.9)	76.4 (13.6)	78.8 (13.9)
Diet quality score	7.0 (1.9)	6.9 (1.6)	7.0 (1.9)
1	1 (0.1)	0	1 (0.1)
2	10 (0.6)	0	10 (0.6)
3	30 (1.8)	0	30 (1.9)
4	106 (6.4)	6 (6.1)	100 (6.4)
5	218 (13.2)	12 (12.1)	206 (13.3)
6	306 (18.5)	23 (23.2)	283 (18.2)
7	343 (20.8)	24 (24.2)	319 (20.6)
8	298 (18.1)	19 (19.2)	279 (18.0)
9	189 (11.5)	10 (10.1)	179 (11.5)
10	108 (6.5)	3 (3.0)	105 (6.8)
11	30 (1.8)	1 (1.0)	29 (1.9)
12	8 (0.5)	1 (1.0)	7 (0.5)
13	3 (0.2)	0	3 (0.2)
Sural SNAP amplitude, μV, median (IQR)[1]	7.0 (4.0–11.0)	0.0 (0.0–3.0)	8.0 (5.0–11.0)

Continuous data are in mean (SD) unless otherwise specified in the table. Categorical data are in number (%). Percentages do not all add up to 100% due to rounding. Diet quality score is a sum score of adherence (yes/no) to the components of the 2015 Dutch dietary guideline, ranging from 0 to 14. IQR, interquartile range; eGFR, estimated glomerular filtration rate; SNAP, sensory nerve action potential.
[1]Available in 1272 participants.

RESULTS

We included 1650 participants of which 99 had definite polyneuropathy (Table 1). Median age was 69.1 years (interquartile range 58.8–73.8). Diabetes mellitus was present in 30.3% of the participants with polyneuropathy and in only 11.9% of the participants without polyneuropathy. Participants without polyneuropathy were more often current smokers (15.0%) compared to participants with definite polyneuropathy (4.0%) while participants with definite polyneuropathy were more often past smokers (61.6% vs. 52.9%). Systolic and diastolic blood pressures were comparable between groups, but the participants with definite polyneuropathy more often used antihypertensive drugs (56.6% vs. 36.4%).

Overall diet quality was not associated with the presence of chronic axonal polyneuropathy (odds ratio [OR] 0.99, 95% confidence interval [CI] 0.88; 1.12, $P = 0.842$), and also not with the sural SNAP amplitude in participants without definite polyneuropathy ($\beta = 0.01$, 95% CI −0.14; 0.15, $P = 0.993$) (Table 2). Although not surviving multiple testing, investigating individual components of the dietary guidelines showed an association between adhering to the advised amount of salt intake (≤6 g/day) and a lower risk of having polyneuropathy (OR 0.55, 95% CI 0.35; 0.86, $P = 0.008$) (Table 2). Although not

Table 2. Association between diet quality and presence of chronic axonal polyneuropathy in all participants (A) and between diet quality and sural SNAP amplitude in participants without polyneuropathy (B).

A

	Chronic axonal polyneuropathy		
N = 1650	Odds ratio	95% CI	*P*-value*
Diet quality score, per point increase	0.99	0.88; 1.12	0.842
Adherence to dietary guideline, yes versus no			
Vegetables (≥200 g/day)	1.23	0.79; 1.91	0.354
Fruit (≥200 g/day)	0.95	0.61; 1.49	0.832
Whole grains (≥90 g/day)	1.15	0.73; 1.80	0.552
Whole grains (as 50% of total grains)	1.76	0.92; 3.34	0.086
Legumes (≥135 g/week)	0.87	0.54; 1.41	0.580
Nuts (≥15 g/day)	1.34	0.81; 2.21	0.261
Dairy products (≥350 g/day)	1.02	0.66; 1.58	0.918
Fish (≥100 g/week)	1.18	0.77; 1.81	0.459
Tea (≥450 mL/day)	1.19	0.43; 2.63	0.673
Healthy fat (as 50% of total fats)	0.77	0.49; 1.19	0.238
Red meat (<300 g/week)	0.78	0.45; 1.34	0.364
Sugar containing beverage (≤150 mL/day)	0.84	0.49; 1.46	0.543
Alcohol (≤10 g/day)	1.00	0.63; 1.57	0.985
Salt (≤6 g/day)	0.55	0.35; 0.86	0.008

B

	Sural SNAP amplitude (μV)		
N = 1202	Difference[1]	95% CI	*P*-value*
Diet quality score, per point increase	0.01	−0.14; 0.15	0.993
Adherence to dietary guideline, yes versus no			
Vegetables (≥200 g/day)	0.30	−0.24; 0.84	0.279
Fruit (≥200 g/day)	−0.16	−0.72; 0.40	0.573
Whole grains (≥90 g/day)	−0.29	−0.85; 0.28	0.321
Whole grains (as 50% of total grains)	0.31	−0.37; 0.99	0.379
Legumes (≥135 g/week)	−0.29	−0.88; 0.30	0.333
Nuts (≥15 g/day)	0.56	−0.08; 1.20	0.085
Dairy products (≥350 g/day)	−0.17	−0.71; 0.37	0.531
Fish (≥100 g/week)	0.39	−0.15; 0.92	0.158
Tea (≥450 mL/day)	0.32	−0.73; 1.37	0.548
Healthy fat (as 50% of total fats)	0.18	−0.39; 0.75	0.532
Red meat (<300 g/week)	−0.22	−0.86; 0.42	0.508
Sugar containing beverage (≤150 mL/day)	−0.16	−0.85; 0.52	0.641
Alcohol (≤10 g/day)	−0.59	−1.15; −0.03	0.038
Salt (≤6 g/day)	0.13	−0.44; 0.70	0.659

Results are adjusted for age, sex, time between covariate assessment and polyneuropathy screening, body mass index, smoking status, systolic and diastolic blood pressure, use of antihypertensive drugs, total cholesterol, education level, eGFR and diabetes mellitus. Diet quality score (range 0–14) is a sum score of adherence (yes/no) to the components of the 2015 Dutch dietary guideline. SNAP, sensory nerve action potential; CI, confidence interval.

[1]Adjusted mean difference for 1 unit increase.

*Significance level of $P < 0.004$ due to Sidak correction for multiple testing.

statistically significant, a similar trend was present on the continuous scale where each g/day increase of salt was associated with a higher risk of chronic axonal polyneuropathy (OR 1.10, 95% CI 0.99; 1.22, $P = 0.071$) (Table 3). No significant association between salt intake and sural SNAP amplitude was found. Other individual components of the dietary guidelines, both dichotomized and continuously, also did not show an association with diet quality (Tables 2 and 3).

The sensitivity analysis in participants with no or definite polyneuropathy showed similar results for diet quality (OR 0.99, 95% CI 0.88–1.13, $P = 0.916$) and the individual components of the dietary guidelines (data not shown). The results for the association between salt intake and polyneuropathy were slightly strengthened (OR 0.51, 95% CI 0.32–0.82, $P = 0.005$). There was no effect modification by sex, diabetes mellitus, or alcohol use (data not shown).

DISCUSSION

We found no association between diet quality and the presence of chronic axonal polyneuropathy. Furthermore, no association was found between diet quality and sural SNAP amplitude in participants without polyneuropathy.

Diet is known to be an important modifiable risk factor for chronic diseases, such as diabetes and cardiovascular diseases, and for vitamin deficiencies and metabolic syndrome.[7,9,10,25] Metabolic syndrome is in turn linked with chronic axonal polyneuropathy.[26] Therefore, we hypothesized that diet would be associated with chronic

Table 3. Association of individual diet components and presence of chronic axonal polyneuropathy in all participants (A) and amplitude of the sural SNAP amplitude in participants without polyneuropathy (B).

A

	Chronic axonal polyneuropathy		
N = 1650	Odds ratio	95% CI	*P*-value*
Vegetables (per 100 g/day)	1.03	0.91; 1.16	0.677
Fruit (per 100 g/day)	0.96	0.89; 1.03	0.959
Whole grains (per 10 g/day)	1.01	0.98; 1.04	0.757
Whole grains (per 10% of total grain)	1.04	0.95; 1.14	0.377
Legumes (per 10 g/week)	0.98	0.89; 1.09	0.750
Nuts (per 10 g/day)	1.09	0.98; 1.23	0.096
Dairy products (per 100 g/day)	1.06	0.97; 1.15	0.232
Fish (per 10 g/week)	1.03	0.94; 1.14	0.534
Tea (per 50 g/day)	1.05	1.00; 1.10	0.065
Healthy fat (per 10% of total fats)	0.95	0.87; 1.04	0.257
Red meat (per 10 g/week)	1.04	0.99; 1.09	0.141
Sugar containing beverages (per 100 mL/day)	1.16	0.94; 1.43	0.157
Alcohol (per 10 g/day)	1.04	0.88; 1.23	0.661
Salt (per 1 g/day)	1.10	0.99; 1.22	0.071

B

	Sural SNAP amplitude (μV)		
N = 1202	Difference[1]	95% CI	*P*-value*
Vegetables (per 100 g/day)	0.02	−0.13; 0.17	0.790
Fruit (per 100 g/day)	−0.08	−0.17; 0.01	0.075
Whole grains (per 10 g/day)	−0.01	−0.04; 0.03	0.749
Whole grains (per 10% of total grain)	−0.03	−0.14; 0.08	0.603
Legumes (per 10 g/week)	−0.07	−0.20; 0.06	0.290
Nuts (per 10 g/day)	0.08	−0.09; 0.24	0.375
Dairy products (per 100 g/day)	−0.05	−0.16; 0.06	0.368
Fish (per 10 g/week)	0.06	−0.06; 0.19	0.322
Tea (per 50 g/day)	0.06	−0.01; 0.13	0.071
Healthy fat (per 10% of total fats)	0.05	−0.06; 0.16	0.402
Red meat (per 10 g/week)	−0.05	−0.11; 0.01	0.112
Sugar containing beverages (per 100 mL/day)	0.16	−0.12; 0.44	0.257
Alcohol (per 10 g/day)	0.15	−0.06; 0.36	0.173
Salt (per 1 g/day)	−0.07	−0.20; 0.06	0.309

Results are adjusted for age, sex, time between covariate assessment and polyneuropathy screening, body mass index, smoking status, systolic and diastolic blood pressure, use of antihypertensive drugs, total cholesterol, education level, eGFR and diabetes mellitus. Diet quality score (range 0–14) is a sum score of adherence (yes/no) to the components of the 2015 Dutch dietary guideline. SNAP, sensory nerve action potential; CI, confidence interval.

[1]Adjusted mean difference for 1 unit increase.

*Significance level of $P < 0.004$ due to Sidak correction for multiple testing.

axonal polyneuropathy, but we could not confirm this in our study. In line with our findings, a previous study on intake of nutrients and CIAP also failed to show an association.[11]

Despite the strong hypothesis there are a few explanations why diet was not associated with chronic axonal polyneuropathy in our study. First, it is possible that polyneuropathy shares a strong genetic link with diabetes and metabolic syndrome, which consequently clouds any association with more subtle nongenetic influences, such as diet. Second, we might have inadvertently attenuated any effect by adjustment for factors that are affected by metabolic syndrome and such factor might be mediators of the association between diet and polyneuropathy. However, a model without such adjustment also did not show any association, rendering this explanation less likely. Finally, given the small effect size, a lack of power cannot be ruled out.

Another question remains, why we did not find an association with alcohol intake, an established risk factor for polyneuropathy.[27,28] Misclassification of alcohol intake due to underreporting is expected to be more severe than of diet in general. Moreover, most data on the link with polyneuropathy come from studies on alcohol abuse, whereas in our study most people had moderate alcohol intake. Furthermore, the group abstainers is known to be a difficult group to categorize in observational studies, as both former and never drinkers together form this group and might differ systematically from drinkers in ways that are also related to disease but may be difficult to measure and adjust for.[29]

We observed a nominal association for salt intake, which points toward a role for a single nutrient as opposed to overall diet. This association between adherence to the advised amount of salt intake and the prevalence of chronic axonal polyneuropathy was present irrespective of other risk factors. Even though this association requires further replication, we speculate on possible mechanisms. An obvious link is hypertension, which may damage the nerves via two ways. First, by damaging the walls of small epi- and endoneural blood vessels and second, by aggravating other components of the metabolic syndrome.[30–32]

The major strength of this study is the use of comprehensive, validated FFQ that were converted into diet quality based on adherence to the dietary guidelines. By using diet quality, instead of studying individual nutrients, it is easy to translate findings to the general public. Moreover, it takes potential interactions between nutrients into account and it is less prone to measurement error than an approach with single nutrients. Other strengths of this study are the cohort design because these studies are less prone to bias since the exposure is prospectively collected

independent of the outcome of interest. Furthermore, we adjusted for several important possible confounders and investigated whether effect modification was present by stratification. Additionally, as persons that adherence to one component of the dietary guidelines are more likely to adhere to other components, we used the Sidàk correction to correct for multiple testing and to account for correlations between the food components.[14–16,24] A limitation of our study is the time difference between measurements that might have led to misclassification and selective survival, which can both lead to dilution of the effect. Yet, these methodological influences are likely minimal, as the time difference was relatively short and dietary patterns and other lifestyle factors are expected to remain relatively constant over time.[14–16] Furthermore, we have to take into account that assessment of dietary intake using questionnaires is prone to measurement error. Especially dietary sodium intake is hard to estimate and further studies are warranted before conclusions can be drawn on a role for salt intake in polyneuropathy.

In conclusion, we showed in this population-based study that diet quality is not associated with the presence of chronic axonal polyneuropathy.

Conflict of Interest

N. E. Taams, T. Voortman, R. Hanewinckel, J. Drenthen and M. A. Ikram report no disclosures relevant to the manuscript. P. A. van Doorn received a grant from the Prinses Beatrix Spierfonds for neuromuscular diseases (grant number W.OR17-10) to conduct this study.

References

1. Hanewinckel R, Ikram MA, Franco OH, et al. High body mass and kidney dysfunction relate to worse nerve function, even in adults without neuropathy. J Peripher Nerv Syst 2017;22:112–120.
2. Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol 2016;31:5–20.
3. Visser NA, Vrancken AF, van der Schouw YT, et al. Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. Diabetes Care 2013;36:817–822.
4. Callaghan BC, Gao L, Li Y, et al. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann Clin Transl Neurol 2018;5:397–405.
5. Notermans NC, Wokke JH, van der Graaf Y, et al. Chronic idiopathic axonal polyneuropathy: a five year follow up. J Neurol Neurosurg Psychiatry 1994;57:1525–1527.
6. Balder HF, Goldbohm RA, van den Brandt PA. Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. Cancer Epidemiol Biomarkers Prev 2005;14:483–490.
7. Montonen J, Knekt P, Harkanen T, et al. Dietary patterns and the incidence of type 2 diabetes. Am J Epidemiol 2005;161:219–227.
8. Shakersain B, Rizzuto D, Larsson SC, et al. The Nordic prudent diet reduces risk of cognitive decline in the Swedish older adults: a population-based cohort study. Nutrients 2018;10:E229.
9. Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. Educ Health (Abingdon) 2003;16:230.
10. Drake I, Sonestedt E, Ericson U, et al. A Western dietary pattern is prospectively associated with cardio-metabolic traits and incidence of the metabolic syndrome. Br J Nutr 2018;119:1168–1176.
11. Visser NA, Notermans NC, de Vries JHM, et al. The role of nutrition as risk factor for polyneuropathy: a case-control study. J Peripher Nerv Syst 2017;22:455–459.
12. Ikram MA, Brusselle GGO, Murad SD, et al. The Rotterdam Study: 2018 update on objectives, design and main results. Eur J Epidemiol 2017;32:807–850.
13. Voortman T, Kiefte-de Jong JC, Ikram MA, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol 2017;32:993–1005.
14. Arabshahi S, Lahmann PH, Williams GM, et al. Longitudinal change in diet quality in Australian adults varies by demographic, socio-economic, and lifestyle characteristics. J Nutr 2011;141:1871–1879.
15. Helldan A, Lallukka T, Rahkonen O, Lahelma E. Changes in healthy food habits after transition to old age retirement. Eur J Public Health 2012;22:582–586.
16. Marques-Vidal P, Quinteiros Fidalgo AS, Schneid Schuh D, et al. Lessons learned? Changes in dietary behavior after a coronary event. Clin Nutr ESPEN 2019;29:112–118.
17. Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr 2016;70:869–878.
18. Hanewinckel R, Drenthen J, van Oijen M, et al. Prevalence of polyneuropathy in the general middle-aged and elderly population. Neurology 2016;87:1892–1898.
19. Buschbacher RM. Peroneal nerve motor conduction to the extensor digitorum brevis. Am J Phys Med Rehabil 1999;78(6 Suppl):S26–S31.
20. Buschbacher RM. Sural and saphenous 14-cm antidromic sensory nerve conduction studies. Am J Phys Med Rehabil 2003;82:421–426.
21. Sedaghat S, Hoorn EJ, van Rooij FJ, et al. Serum uric acid and chronic kidney disease: the role of hypertension. PLoS ONE 2013;8:e76827.
22. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.
23. Alberti KG, Zimmet PZ. Definition diagnosis and classification of diabetes mellitus and its complications.

Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553.
24. Galwey NW. A new measure of the effective number of tests, a practical tool for comparing families of non-independent significance tests. Genet Epidemiol 2009;33:559–568.
25. Schupbach R, Wegmuller R, Berguerand C, et al. Micronutrient status and intake in omnivores, vegetarians and vegans in Switzerland. Eur J Nutr 2017;56:283–293.
26. Hanewinckel R, Drenthen J, Ligthart S, et al. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: a prospective population-based cohort study. J Neurol Neurosurg Psychiatry 2016;87:1336–1342.
27. Koike H, Sobue G. Alcoholic neuropathy. Curr Opin Neurol 2006;19:481–486.
28. Mellion M, Gilchrist JM, de la Monte S. Alcohol-related peripheral neuropathy: nutritional, toxic, or both? Muscle Nerve 2011;43:309–316.
29. Wood AM, Kaptoge S, Butterworth AS, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 2018;391:1513–1523.
30. Samuelsson K, Press R. Microangiopathy-a potential contributing factor to idiopathic polyneuropathy: a mini review. Front Neurol 2018;9:43.
31. Zarrelli MM, Amoruso L, Beghi E, et al. Arterial hypertension as a risk factor for chronic symmetric polyneuropathy. J Epidemiol Biostat 2001;6:409–413.
32. Teunissen LL, Notermans NC, Jansen GH, et al. Thickness of endoneurial vessel basal lamina area in chronic idiopathic axonal polyneuropathy. Acta Neuropathol 2000;100:445–450.

