Prevalence, Risk Factors and Consequences of Chronic Polyneuropathy:
The Rotterdam Study

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Prevalentie, risicofactoren en gevolgen van chronische polyneuropathie
De Rotterdam Studie

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Chapter 1

General introduction

Worldwide, life-expectancy is increasing and populations are aging.[1] This will lead to an increased prevalence of age-related diseases. Peripheral neuropathy is one of such diseases. However, despite the high frequency of occurrence and the impact on the individual patient, epidemiological data on peripheral neuropathies in scarce and public awareness is limited.

Peripheral neuropathy encompasses a spectrum of clinical syndromes that result in injury to axons or the myelin sheath of nerves of the peripheral nervous system. In general, this peripheral nerve injury leads to sensory disturbances, such as numbness and tingling or prickling sensations, often accompanied by neuropathic pain and motor symptoms, such as cramps, muscle wasting and especially muscle weakness. Peripheral neuropathy comprises radiculopathies, mononeuropathies, multifocal neuropathies and polyneuropathies. The most prominent symptoms and signs depend on the type and location of the neuropathy (Figure 1).
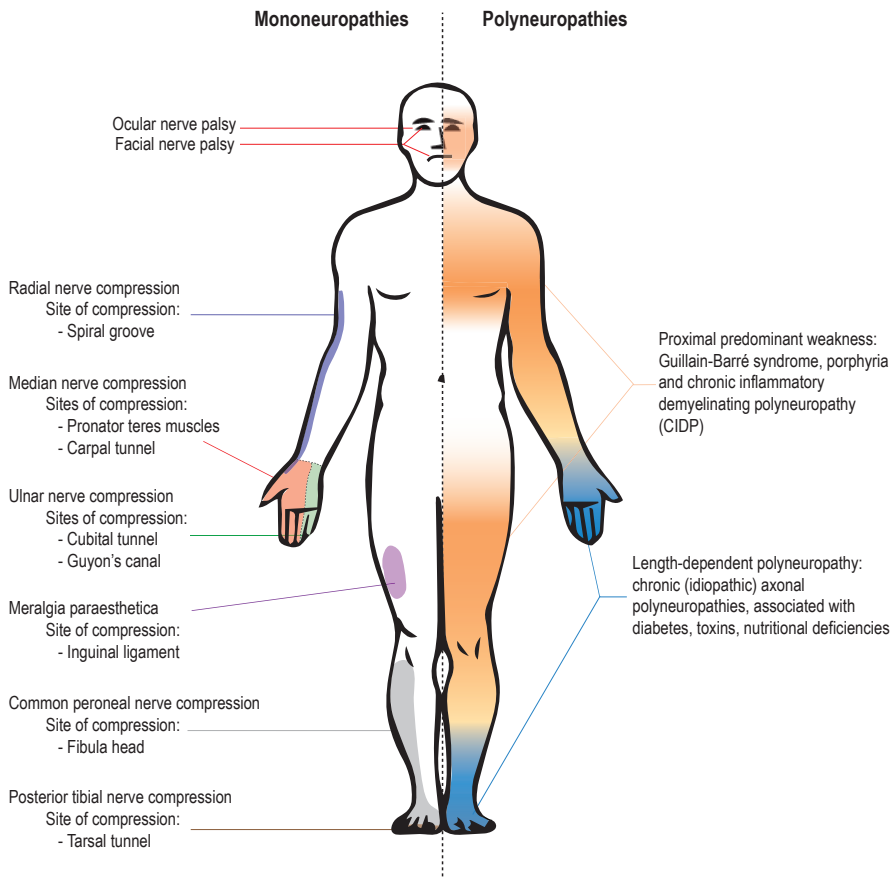

Figure 1. Overview of peripheral neuropathies
(Hanewinckel et al. Handbook of Clinical Neurology: Neuroepidemiology, 2016)

This thesis focusses on *chronic polyneuropathy*, which is the most common age-related disorder of the peripheral nervous system. Chronic polyneuropathy is typically characterized by a gradual onset (over more than six weeks) of mostly sensory symptoms that usually start distally in the feet. As the disease progresses, generally over the course of months to years, these symptoms often ascend into the legs and also appear in the hands, leading to a symmetrical stocking and glove-like distribution of symptoms (Figure 1). Besides numbness, pain and paresthesia, patients often experience foot drop due to distal muscle weakness, unsteadiness in walking due to sensory ataxia and sometimes also symptoms of autonomic dysfunction, such as impotence, constipation and orthostatic hypotension. These symptoms of peripheral nerve dysfunction can lead to severe mobility problems and a reduced quality of life.[2-4]

Neurological examination of a patient with polyneuropathy usually shows decreased or absent sensation of touch, pin prick and vibration, reduced proprioception, decreased or absent tendon reflexes, and mild to moderate muscle weakness, all with a proximal to distal gradient. In clinical practice, the diagnosis of chronic polyneuropathy is made based on the combination of symptoms and signs, which is often complemented with nerve conduction studies. In case of an axonal polyneuropathy (which is the most frequent form of polyneuropathy) these typically show a decline in nerve action potential amplitudes in both sensory and motor nerves, especially in distal parts of the limbs (Table 1 and Figure 2).[5, 6]

The described phenotype is that of the most common type of chronic polyneuropathy. This length-dependent polyneuropathy results from irreversible axonal degeneration of peripheral nerves. Polyneuropathy can also present more acutely with more prominent muscle weakness due to immune-mediated demyelination of peripheral nerves (Table 1

Table 1. Typical clinical and electrophysiological findings in axonal and demyelinating polyneuropathies

Type	Symptoms	Signs	Nerve conduction studies
Axonal polyneuropathy	Usually slowly progressive, distal symmetric sensory-predominant symptoms (numbness, tingling, pain). Muscle weakness occurs but often is relatively mild	Reduced or absent sensation of touch, vibration, pinprick, reduced or absent distal (Achilles) tendon reflexes, distal muscle weakness, sensory ataxia	Distal amplitudes: decreased Distal latency: normal Conduction velocity: normal Conduction block: absent Temporal dispersion: absent
Demyelinating polyneuropathy	More often proximal, primarily motor symptoms with mild to very severe muscle weakness. Usually mild sensory symptoms. Often a more acute onset and a more progressive or a relapsing course (in CIDP)	Proximal (or distal) muscle weakness, mild sensory deficits, absent tendon reflexes, sometimes cranial nerve deficits	Distal amplitudes: normal Distal latency: prolonged Conduction velocity: slowed Conduction block: present Temporal dispersion: present
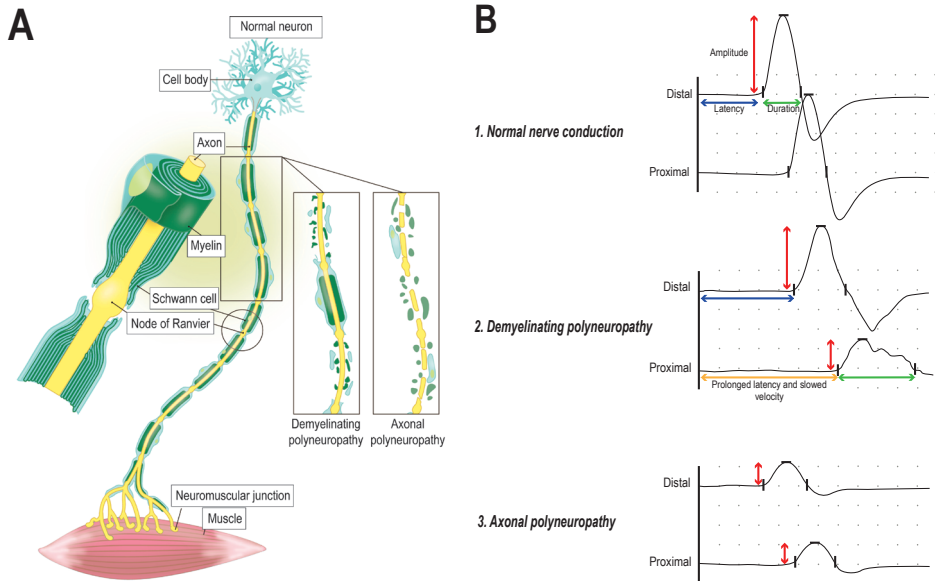
Figure 2. Demyelinating and axonal polyneuropathy (adapted from van Doorn et al.[9]). Panel A shows the two different types of polyneuropathy: demyelinating (destruction of the myelin sheath surrounding the axon) and axonal (degeneration of the axon itself) polyneuropathy. Panel B shows the typical nerve conduction findings in these neuropathies. B1 shows normal nerve conduction studies. B2 shows the characteristics in demyelinating neuropathy: prolonged distal latency, slowed conduction velocity, temporal dispersion (longer duration and lower amplitude of the action potential on proximal stimulation) and conduction block (drop in amplitude when comparing proximal to distal stimulation). B3 shows the characteristics in axonal polyneuropathy: reduced distal and proximal action potential amplitudes.

and Figure 2). The clinical features of a demyelinating polyneuropathy can range from a very acute, potentially life-threatening disorder with severe muscle weakness as occurs in Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy or AIDP), to a more chronic relapsing-remitting or slowly progressive neuropathy with also prominent proximal weakness as is observed in chronic inflammatory demyelinating polyneuropathy or CIDP (see also Figure 1).[7, 8] The prevalence and incidence of demyelinating polyneuropathies is much lower than chronic axonal polyneuropathies. In contrast to axonal degeneration, demyelination however can be reversible, and patients with a demyelinating polyneuropathy usually respond to treatment. Unfortunately, treatment of chronic axonal polyneuropathy currently is mainly symptomatic, with a focus on physiotherapy, rehabilitation and treatment of neuropathic pain.

Chronic axonal polyneuropathy is one of the most commonly encountered diseases in neurological practice and is associated with significant morbidity, and even mortality.[10] Yet, the exact prevalence and incidence is unknown. Based on general practitioner and hospital registries, it is estimated that approximately 4% of elderly people suffer from

polyneuropathy, with an estimated 77 new cases per 100 000 persons per year.[11, 12] However, due to underreporting and underdetection, the true burden of polyneuropathy is likely underestimated in these studies.

Chronic polyneuropathy is a heterogeneous disease with over a hundred putative causes or risk factors.[13] These causes and risk factors have emerged from hospital-based studies and include diabetes mellitus, vitamin deficiencies, toxic factors (alcohol, chemotherapy and other drugs), end-stage kidney disease, hereditary factors, and immune-mediated factors, among others. Aside from symptomatic treatment, removing any toxic factors and treating vitamin deficiencies or underlying diseases if these are present is appropriate. However, despite an extensive diagnostic work-up the cause of chronic polyneuropathy remains unexplained in 25-30% of cases.[14] These patients are generally diagnosed with chronic idiopathic axonal polyneuropathy (CIAP).[15, 16]

Diabetes mellitus is considered to be the most important known risk factor for polyneuropathy. About one third of all chronic polyneuropathy cases is attributed to diabetes.[14] However, it is remarkable that only half of all diabetics develop polyneuropathy, suggesting that additional factors must be involved.[17] Accumulating evidence suggests that dyslipidemia, obesity, hypertension and other cardiovascular risk factors play an important role in the pathophysiology of micro- and macrovascular complications of diabetes, such as polyneuropathy.[17-20] Similarly, these factors have increasingly been associated with CIAP in recent uncontrolled and case-controlled studies.[14, 15, 21, 22] Axonal degeneration currently is irreversible and therefore curative options do not (yet) exists. This underlines the relevance to identify modifiable risk factors that can serve as a target for therapeutic and potential preventive strategies. If vascular or metabolic factors indeed increase the risk of polyneuropathy, optimal treatment of these factors may, in part, prevent the occurrence or progression of polyneuropathy. Along with a more comprehensive investigation of these vascular and metabolic factors, the search for other potential risk factors must also continue, to further elucidate the etiology of chronic polyneuropathy and especially CIAP. Ideally, potential risk factors need to be investigated in population-based settings to overcome methodological limitations of hospital-based studies, the most important being selection bias.

Unfortunately, the absence of a simple gold standard test for the diagnosis of polyneuropathy makes it a quite challenging disease to investigate in population-based research settings. Preferably, the diagnosis should be based on medical history, full neurological examination and nerve conduction studies, similar to clinical neurological practice.[5] This complex diagnostic procedure however is costly and time-consuming, and difficult to implement in large cohort studies utilizing an in-person screening. This probably explains why large population-based cohort studies focused on polyneuropathy are lacking. Other, simplified methods have been developed to screen for

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polyneuropathy in high-risk patients, but there are several downsides of these simplified methods, which are discussed extensively in the next chapter.

Despite these complexities, we were able to implement an extensive in-person screening for polyneuropathy in a population-based study. This screening consists of an assessment of symptoms using a questionnaire, an assessment of signs with a short neurological examination of the legs, and also a short non-invasive nerve conduction protocol. The results of all individual participants are subsequently discussed by an expert panel. This screening provides information about important clinical and electrophysiological parameters to be able to diagnose chronic axonal polyneuropathy. The development and usage of this screening protocol in a population-based study is further detailed throughout this thesis.

SCOPE AND OUTLINE OF THESIS

The overall aim of this thesis is to extend the epidemiological knowledge on chronic axonal polyneuropathy and on chronic idiopathic axonal polyneuropathy (CIAP) in particular. More specifically, the aims of the studies described in this thesis are:

1. To develop a sensitive screening protocol for chronic polyneuropathy that can be utilized in the general population.
2. To describe the prevalence of chronic polyneuropathy and especially CIAP in the general population.
3. To investigate the association of prediabetes, metabolic syndrome and its separate components with polyneuropathy and peripheral nerve function.
4. To investigate the effects of age, height, weight, and several metabolic factors on peripheral nerve function in persons yet without polyneuropathy.
5. To investigate to what extent polyneuropathy affects daily functioning, gait patterns and the risk of falls.

The research of most studies in this thesis is embedded within the epidemiological framework of the Rotterdam Study, a large prospective population-based cohort study that aims to investigate prevalence, incidence and determinants of various chronic diseases in the elderly.[23] Until the work described in this thesis, the main neurological focus of the study has been on cerebrovascular and neurodegenerative diseases, like stroke, dementia and Parkinson's disease. In 2013, an extensive in-person screening protocol for polyneuropathy has been added to the core protocol of the Rotterdam Study. Details of this screening procedure are described in chapter 3.2.

In **Chapter 2** of this thesis, polyneuropathy screening methods that can be applied in research settings are described. In **Chapter 2.1** several questionnaires and scoring systems that have previously been developed with the aim to identify patients with polyneuropathy in high-risk populations, such as diabetics or patients receiving chemotherapy, are summarized. **Chapter 2.2** delineates which neuropathic symptoms are most informative for the diagnosis of polyneuropathy. The development of new, simple questionnaire that can help to distinguish persons with polyneuropathy from persons without polyneuropathy is also described in this chapter.

Chapter 3 comprises studies that describe the prevalence of polyneuropathy in the general population. In **Chapter 3.1** data are reviewed from previous studies that estimated the prevalence of polyneuropathy in the general population. Limitations of these studies are also discussed in this chapter. Next, the overall and age- and sex-specific prevalence of polyneuropathy in the population-based Rotterdam Study are presented in **Chapter 3.2**. Putative causes and the proportion of idiopathic cases, as well as the underreported nature of polyneuropathy are also addressed in this chapter.

In **Chapter 4** potential risk factors for polyneuropathy are explored. In **Chapter 4.1** the association of prediabetes and metabolic syndrome with polyneuropathy and peripheral nerve function is examined. Early effects of age, height and several metabolic factors, like obesity, kidney disease, and liver dysfunction on peripheral nerve function in persons yet without polyneuropathy are discussed in **Chapter 4.2**.

Chapter 5 is dedicated to the impact of polyneuropathy and related disorders on daily life. **Chapter 5.1** focusses on the association between polyneuropathy and impairment in activities of daily living, gait and falls. In **Chapter 5.2** gait patterns of persons with diabetes are investigated.

Finally, in **Chapter 6** the main findings of this thesis are summarized. Additionally, methodological considerations concerning the performed studies and the clinical implications of the main findings are discussed in this chapter.

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Chapter 2

Screening methods for polyneuropathy

Chapter 2.1

Assessment scales for the diagnosis of polyneuropathy

Rens Hanewinckel, M. Arfan Ikram, Pieter A. van Doorn

ABSTRACT

Epidemiological studies that investigate the occurrence and determinants of chronic length-dependent polyneuropathy are scarce. Population-based studies on polyneuropathy require a valid and reliable screening protocol with both good sensitivity and specificity. Several questionnaires and scoring scales have been developed for the detection of polyneuropathy, grading the severity of the disease or evaluating the clinical course during follow-up. This review summarizes the aims and content of existing diagnostic polyneuropathy screening tools in order to help future studies decide which scale to use for screening in specific situations. We searched the PubMed database and identified 27 scales, 13 are based on symptoms alone, 8 on neurological signs alone, and 6 on a combination of symptoms and signs. Scales that combine questions concerning symptoms and a neurological examination with a focus on sensory alterations seem to have the best discriminatory power. However, all scoring scales were developed for and investigated in pre-specified patient populations. Therefore, the generalizability of specific findings to the general population may be limited. We also discuss other limitations of existing scales. Future studies are required to determine which clinimetrically well-developed scales are preferred for use in population-based studies.

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INTRODUCTION

Polyneuropathy is a common disorder in the general population and is even more common in diabetics and in elderly.[1, 2] Patients with polyneuropathy present with tingling sensations or pins and needles, numbness, weakness and pain, often starting in the lower legs and feet. Much research is being performed to identify pathways that can contribute to the development of polyneuropathy. As these pathways become more apparent, early detection of symptoms of the disease becomes even more crucial. Avoiding special products, drugs or environmental situations, but also intervening early in the pathological process may decrease progression of symptoms and associated morbidity. Polyneuropathy may be difficult to diagnose early on, since onset is insidious. Validated assessment scales may aid in diagnosis. Therefore, sensitive, specific and preferably also easy to perform assessment scales would be very helpful.

To detect chronic, length-dependent and often mild forms of polyneuropathy, several scoring systems for neurological symptoms and signs have been developed. Some investigators report reasonable sensitivity and specificity for screening questionnaires[3, 4], while others conclude that the identification of neuropathic symptoms alone has little diagnostic value.[5, 6] Diagnosing polyneuropathy at an early stage requires an assessment tool that is able to detect mild polyneuropathy in low-risk populations with a high sensitivity. Such a tool would also be useful for epidemiological studies into polyneuropathy. A recent review article concluded that there is a paucity of up-to-date epidemiological data on polyneuropathy.[2] Further field studies are required to obtain more data on epidemiological characteristics of polyneuropathy. For future studies an overview of existing scoring systems that can be used to diagnose chronic polyneuropathy can be very helpful. This article provides such an overview.

METHODS

On November 12, 2015, we searched the PubMed database for studies in which scoring scales or questionnaires were used to detect or follow the course of polyneuropathy symptoms and/or signs. We searched using the terms 'polyneuropathy' and 'neuropathy', in combination with the terms 'questionnaire', 'scoring scale', 'score', 'scored symptoms', or 'screening tool', and limited the search to publication about humans in the English language. The search yielded 2951 publications. Titles and abstracts were scanned to identify articles in which scales were used suitable for the detection of chronic polyneuropathy, herewith referring to length-dependent, predominantly distal, symmetrical polyneuropathy, which is the most common subtype. Acute, small-fiber or predominantly autonomic polyneuropathies do not fall under the scope of this review. We subse-

quently searched for the publication that first described the specific scales, if these were not already included in the search. We selected scales that combined symptoms and/or signs into a screening tool for the detection of polyneuropathy, but also tools primarily used for the follow-up of symptoms and severity of polyneuropathy, since these may also be useful for epidemiological studies. Studies that only investigated the correlation between a single examination or apparatus and a reference test and studies that only used advanced techniques to detect polyneuropathy (e.g. only nerve conduction studies, biothesiometer, confocal microscopy) were not considered. Additionally, we did not include single tests (e.g. monofilament or vibration sense) into this review. Scales that were primarily developed to detect or characterize neuropathic pain (e.g. McGill Pain questionnaire, Douleur Neuropathique (DN4), Leeds assessment of Neuropathic Symptoms and Signs) were not included, nor were scales assessing the consequences of polyneuropathy, such as quality of life scales and disability scales (like the Overall Neuropathy Limitation Scale and the Rasch-built Overall Disability Scale), since we were primarily interested in methods that can be used to diagnose polyneuropathy.

RESULTS

We identified 27 different questionnaires or composite scores that were used to screen for polyneuropathy. Of these 27 scales, 13 were solely based on symptoms, 6 on a combination of symptoms and signs, and 8 on signs alone (some in combination with additional tests, see Table 1). Most scales were primarily designed for the detection and grading of polyneuropathy, the remaining scales were constructed to longitudinally evaluate the severity of neuropathy. However, since the original development of the scales, several diagnostic scales have also been used for longitudinal assessment and vice versa. An overview of scoring systems and questionnaires with their specific purpose is listed in Table 1. More specific information about the contents of each questionnaire and the test characteristics is shown in Table 2. The components of the neurological examination included in different scales are shown in Table 3.

Polyneuropathy scales using only symptoms

One of the first and most frequently used scales for the assessment of peripheral nerve disorders is the Neuropathy Symptom Score (NSS). This scale was developed to detect and grade the severity of peripheral neuropathy in diabetic patients.[7] The NSS includes weakness of bulbar and limb muscles, negative sensory symptoms, positive sensory symptoms and autonomic symptoms. Each item is scored with 1 point if present. In the original scale 1 or more points was considered abnormal, but multiple adaptations of the scoring system have been published.[8-11] NSS significantly associated with neuro-

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Table 1. Overview of available scoring systems

Article	Score	Symptoms/Exam	Administered by	Time required[a]	Developed for	Aim
Dyck, et al., 1980[7]	NSS	Symptoms	Neurologist	++	Diabetes	Detection and grading of neuropathy
Freeman, et al., 1985[27]	-	Symptoms	Self-administered	+	Peripheral neuropathy	Distinguish patients with peripheral neuropathy from those without
Dyck, et al., 1986[16]	NSP	Symptoms	Self-administered	+++	Diabetes	Characterization and grading of symptoms
Beghi, et al., 1988[3]	-	Symptoms	Physician	+	Polyneuropathy	Diagnosis of polyneuropathy
Grootenhuis, et al., 1994[22]	DSC-Type 2	Symptoms	Self-administered	++	Diabetes	Detect and monitor diabetes complications
Ziegler, et al., 1995[26]	TSS	Symptoms	Physician/nurse	+	Diabetes	Evaluate treatment effects on symptoms
Dyck, et al., 1997[14]	NSC	Symptoms	Neurologist	+++	Diabetes	Monitor change in symptoms over time
McArthur, 1998[24]	SPNS	Symptoms	Self-administered	+	HIV	Screen for neuropathy in HIV patients
Meijer, et al., 2002[19]	DNS	Symptoms	Physician	+	Diabetes	Screen for diabetic polyneuropathy
Bastyr, et el., 2005[23]	NTSS-6	Symptoms	Physician	++	Diabetes	Evaluate frequency and intensity of symptoms
Leonard, et al., 2005[34]	-	Symptoms	Self-administered	++	Chemotherapy	Document incidence and type of neurotoxicity
Postma, et al., 2005[31]	CIPN20	Symptoms	Self-administered	+	Chemotherapy	Assessment of chemotherapy-induced neuropathy
Tofthagen, et al., 2011[30]	CIPNAT	Symptoms	Self-administered	+	Chemotherapy	Evaluate occurrence and distress of chemotherapy-induced neuropathy
Franklin, et al., 1990[28]	-	Symptoms + signs	Physician/nurse	++	Diabetes	Screen for polyneuropathy in patients with diabetes
Feldman, et al., 1994[35]	MNSI	Symptoms + signs	Physician/nurse	++	Diabetes	Detection of diabetic neuropathy
Chaudhry, et al., 1994[42]	TNS	Symptoms + signs + tests	Physician	+++	Chemotherapy/ Diabetes	Detecting and quantifying peripheral neuropathy

Table 1. (continued)

Article	Score	Symptoms/Exam	Administered by	Time required[a]	Developed for	Aim
Gentile, et al., 1995[4]	–	Symptoms + signs	Physician	++	Diabetes	Screening for polyneuropathy
Bril, 2002[40]	TCSS	Symptoms + signs	Neurologist	++	Diabetes	Detection and grading of neuropathy
Cherry, et al., 2005[25]	BPNS	Symptoms + signs	Physician	++	HIV	Screen for neuropathy in HIV patients
Dyck, et al., 1980[7]	NDS	Signs	Neurologist	++	Diabetes	Evaluation of neurological deficit
Valk, et al., 1992[68]	CNE	Signs	Physician	+	Diabetes	Diagnosis of diabetic neuropathy
Dyck, et al., 1997[14]	NIS(LL)(+)	Signs (+ tests)	Neurologist	+++	Diabetes	Quantification of neuropathic impairment
Feldman, et al., 1994[35]	MDNS	Signs + tests	Neurologist	+++	Diabetes	Diagnosis of diabetic neuropathy
Meijer, et al., 2000[20]	DNE	Signs	Physician	+	Diabetes	Diagnosis of diabetic neuropathy
Merkies, et al., 2000[52]	ISS	Signs	Neurologist	+	Inflammatory neuropathies	Assessing sensory deficits in polyneuropathies
Singleton, et al., 2008[53]	UENS	Signs	Neurologist	+	Diabetes	Detect early sensory predominant polyneuropathy
Zilliox, et al., 2015[54]	ENS	Signs	Neurologist	+	Diabetes	Assess abnormalities of early neuropathy

NSS: Neurological Symptom Score; NSP: Neuropathy Symptom Profile; DSC-Type 2: Type 2 Diabetes Symptom Checklist; TSS: Total Symptoms Score; NSC: Neuropathy Symptoms and Change; SPNS: Subjective Peripheral Neuropathy Screen; DNS: Diabetic Neuropathy Symptom score; NTSS-6: Neuropathy Total Symptoms Score-6; CIPN20: Chemotherapy-Induced Peripheral Neuropathy 20; CIPNAT: Chemotherapy-Induced Peripheral Neuropathy Assessment Tool; MNSI: Michigan Neuropathy Screening Instrument; TNS: Total Neuropathy Score; TCSS: Toronto Clinical Scoring System; BPNS: Brief Peripheral Neuropathy Screen; NDS: Neuropathy Disability Score; CNE: Clinical Neurological Examination; NIS(-LL): Neuropathy Impairment Score (Lower Limbs); MDNS: Michigan Diabetes Neuropathy Scale; CNE: Clinical Neurological Examination; DNE: Diabetic Neuropathy Examination; ISS: Inflammatory neuropathy cause and treatment group Sensory Sumscore; UENS: Utah Early Neuropathy Score; ENS: Early Neuropathy Score

[a] Estimated time required to complete the questionnaire or assessment. +: quite fast, estimated time approximately 5-10 minutes; ++: estimated time approximately 10-20 minutes; +++: estimated time probably more than 20 minutes

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logical examination scores, neuropathological abnormality of the sural nerve and with multiple parameters of nerve conduction.[12, 13] NSS is often used in combination with a scored neurological examination, the Neurological Disability Score (NDS, later named the Neurological Impairment Score, NIS).[7, 14] Administration is time-consuming, should preferentially be done by neurologists, and is therefore less useful for screening large amounts of patients in a primary care setting. Moreover, reproducibility is not optimal.[15]

The same research group also developed the Neuropathy Symptom Profile (NSP), a self-administered questionnaire that can be used for the characterization of neuropathy[16], and the Neuropathy Symptoms and Change score (NSC), which is performed by a neurologist to measure the number, the severity and the change in neuropathic symptoms since a previous time point.[14] An advantage of these extensive scales is that the questionnaires can be read by a computer that converts the responses into specific scores.[17, 18] These questionnaires are quite long and can take up to 45 minutes to finish. These scales are probably better suited to monitor progression of polyneuropathy, especially the NSC, rather than contribute to make the diagnosis of polyneuropathy.

In order to provide a faster screening tool for diabetic polyneuropathy, the Diabetic Neuropathy Symptom score (DNS) was developed.[19] This four-item questionnaire was developed by an expert panel consisting of a neurologist, a diabetologist, a vascular internist and a rehabilitation physician and includes symptoms of unsteadiness in walking, neuropathic pain, paresthesia and numbness. The DNS was validated against the NSS, monofilaments, vibration thresholds, nerve conduction studies and the Diabetic Neuropathy Examination (DNE) score[20, 21], which is a sensitive, easy to perform physical examination score for polyneuropathy. Reasonably good test characteristics and high reproducibility were reported. However, since specificity is not optimal, which will result in a large number of false positive subjects, the DNS should be complemented with other tests or scores.[21]

Several other validated but less widely used questionnaires have been developed. Examples include the Type 2 Diabetes Symptom Checklist[22] and the Neuropathy Total Symptom Score-6[23], which were designed to detect or to follow complications of diabetes; the Subjective Peripheral Neuropathy Screen[24] and the Brief Peripheral Neuropathy Screen[25], which were developed to detect neuropathy in patients with HIV; the Total Symptom Score[26], which was developed to evaluate treatment effects in clinical trials. Several other researchers created a list of polyneuropathy related questions based on their personal experience and review of the literature.[3, 4, 27, 28] Table 2 provides more details about all questionnaires. There are also several scales available that assess toxicity of chemotherapeutic agents. Scales that cover multiple aspects of side effects, with a brief neurotoxicity subscale are not reviewed here, but can be found in another review.[29] Some scales were specifically designed for neuropathy, such as the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT)[30], the Chemotherapy-Induced

Table 2. Overview of different assessment scales that include symptoms of polyneuropathy

	NSS[7]	Freeman[27]	NSP[16]	Beghi[3]	Franklin[28]	TNS[42]	MNSI[35]	DSC-type 2[22]	Gentile[4]
Population	Diabetics	Neuropathy patients vs. controls	Diabetics	Hospital and GP population	Diabetic vs. non-diabetic patients	Patients on chemotherapy	Diabetics	Diabetics	Diabetics
Validation	NCS[a]	NCS	Not specified	Clinical	Neurologist	NSS and NIS[e]	Neurologist, NCS, Mayo criteria[f]	-	NCS
Sensitivity	73%[a]	65%	64%	92%[c]	87%[d]	-	40%[g]	-	87%
Specificity	30%[a]	73%	85%[b]	100%[c]	91%[d]	-	92%[g]	-	60%
Symptoms being asked for									
Abnormal feeling while walking	-	-	+	-	-	-	+	-	+
Autonomic symptoms	+	+	+	-	-	+	-	+	+
Burning sensation	+	+	+	+	+	-	+	+	+
Dry skin, cracks, sores	-	-	-	-	-	-	+	-	-
Distinguish hot from cold	-	-	+	+	-	-	+	-	-
Difficulty handling objects	+	+	+	-	-	-	-	-	-
Fatigue	-	-	+	-	+	-	+	+	-
Functional limitations	-	+	+	-	-	+	-	-	-
History of amputation	-	-	-	-	-	-	+	-	-
Muscle cramps	-	+	+	+	+	-	+	-	+
Muscle pain	-	+	+	+	-	+	-	+	-
Muscle weakness	+	-	+	-	-	+	+	-	+
Numbness	+	+	+	-	+	+	+	+	+
Previous diagnosis	-	-	-	+	-	-	+	-	-
Restless legs	-	-	-	-	-	-	-	-	-
Sensitive skin	+	-	-	-	-	-	+	+	-

Table 2. (*continued*)

	NSS[7]	Freeman[27]	NSP[16]	Beghi[3]	Franklin[28]	TNS[42]	MNSI[35]	DSC-type 2[22]	Gentile[4]
Sharp pain	+	-	+	-	+	-	+	+	+
Stiffness	-	-	-	-	-	-	-	-	-
Tight feeling	-	-	+	-	-	-	-	-	-
Tingling/prickling	+	+	+	+	+	+	+	+	+
Twitching of muscles	-	+	-	-	-	-	-	-	-
Unable to feel pain	-	-	+	+	-	-	-	-	-
Unsteady gait	+	-	+	-	-	-	-	-	+
Worse at night	-	-	-	-	+	-	+	-	-

+: present in scale; -: absent in scale

a Sensitivity and specificity of the NSS to detect polyneuropathy reported in a later validation study.[66] Associated with NCS and neuropathological abnormality of the sural nerve.[12]

b May contain more, not entire questionnaire available in publication.

c Sensitivity and specificity reported in a follow-up study in preparation of a larger field study was 78% and 82% respectively.[67]

d Includes a neurological examination.

e Includes a neurological examination and additional tests (several versions available; reduced, clinical, modified). Validated against NSS and NIS.[44]

f Mayo criteria are based on nerve conduction studies, the NDS, vibration thresholds, autonomic function testing and the NSP.[35]

g Sensitivity and specificity of the questionnaire part are not reported in original publication. These number are derived from a more recent study.[36]

h TCSS includes symptoms and a neurological examination. No sensitivity or specificity reported, but validated against sural nerve fiber density and NCS. Symptoms alone were poorly correlated.

i Validated against the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity questionnaire (FACT/GOG –Ntx).[33]

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Table 2. *(continued)*

	TSS[26]	NSC[14]	SPNS[24]	DNS[19]	TCSS[40]	NTSS-6[23]	Leonard[34]	CIPN20[31]	CIPNAT[30]
Population	Diabetics	Diabetics	HIV patients	Diabetics	Diabetics	Diabetics	Patients on chemotherapy	Patients on chemotherapy	Patients on chemotherapy
Validation	-	-	Neurologist	DNE	NCS and biopsy[h]	NSC and NIS	FACT/GOG[i]	-	FACT/GOG
Sensitivity	-	-	89%	79%	-	-	-	-	-
Specificity	-	-	36%	78%	-	-	-	-	-
Symptoms being asked for		[b]							
Abnormal feeling while walking	-	-	-	-	-	-	-	-	-
Autonomic symptoms	-	+	-	-	-	-	-	+	-
Burning sensation	+	-	+	+	+	+	+	-	-
Dry skin, cracks, sores	-	-	-	-	-	-	-	-	-
Distinguish hot from cold	-	+	-	-	-	-	+	+	-
Difficulty handling objects	-	-	-	-	-	-	+	+	-
Fatigue	-	-	-	-	-	-	-	-	-
Functional limitations	-	-	-	-	-	-	+	-	+
History of amputation	-	-	-	-	-	-	-	-	-
Muscle cramps	-	-	-	-	-	-	-	+	-
Muscle pain	-	-	-	-	-	-	-	-	+
Muscle weakness	-	+	-	-	+	-	-	+	+
Numbness	+	+	+	+	+	+	+	+	+
Previous diagnosis	-	-	-	-	-	-	-	-	-
Restless legs	-	-	-	-	-	-	-	-	-
Sensitive skin	-	+	-	-	-	+	+	-	-
Sharp pain	+	+	+	+	+	+	-	+	+
Stiffness	-	-	-	-	-	-	-	-	-

Table 2. (continued)

	TSS[26]	NSC[14]	SPNS[24]	DNS[19]	TCSS[40]	NTSS-6[23]	Leonard[34]	CIPN20[31]	CIPNAT[30]
Tight feeling	-	-	-	-	-	+	-	-	-
Tingling/prickling	+	+	+	+	+	+	+	+	+
Twitching of muscles	-	-	-	-	-	-	+	-	-
Unable to feel pain	-	+	-	-	-	+	-	-	-
Unsteady gait	-	-	-	+	+	-	-	+	+
Worse at night	-	-	-	-	-	-	-	-	-

+; present in scale; -; absent in scale

a Sensitivity and specificity of the NSS to detect polyneuropathy reported in a later validation study.[66] Associated with NCS and neuropathological abnormality of the sural nerve.[12]

b May contain more, not entire questionnaire available in publication.

c Sensitivity and specificity reported in a follow-up study in preparation of a larger field study was 78% and 82% respectively.[67]

d Includes a neurological examination.

e Includes a neurological examination and additional tests (several versions available; reduced, clinical, modified). Validated against NSS and NIS.[44]

f Mayo criteria are based on nerve conduction studies, the NDS, vibration thresholds, autonomic function testing and the NSP.[35]

g Sensitivity and specificity of the questionnaire part are not reported in original publication. These number are derived from a more recent study.[36]

h TCSS includes symptoms and a neurological examination. No sensitivity or specificity reported, but validated against sural nerve fiber density and NCS. Symptoms alone were poorly correlated.

i Validated against the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group-Neurotoxicity questionnaire (FACT/GOG –Ntx).[33]

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Peripheral Neuropathy-20 (CIPN20)[31, 32] and the Chemotherapy Induced Neurotoxicity Questionnaire (CINQ).[33, 34] These scales are included in Table 1 and 2.

Polyneuropathy scales using symptoms and signs

A frequently used tool that combines symptoms and signs is the Michigan Neuropathy Screening Instrument (MNSI). The MNSI was developed in order to simplify and adapt previously established diagnostic criteria for (diabetic) polyneuropathy, mainly for epidemiological screening purposes.[35] The aim was to design a simple instrument, which can be used to rapidly screen a large number of patients with widely available techniques. The MNSI contains a questionnaire, adapted from the NSP, and a clinical part, which consists of a short neurological examination involving foot inspection, testing of vibration sensation and grading of reflexes. The MNSI can serve as a first step in screening of a large number of patients in routine clinical settings. When this initial screening is positive, patients can be referred for further studies. For this purpose the Michigan Diabetic Neuropathy Score (MDNS) was introduced, which includes more physical examination tests and nerve conduction studies.[35] The clinical examination part of the MNSI had reasonably high sensitivity and specificity, 80% and 95% respectively, whereas the questionnaire alone was not able to distinguish diabetic patients with polyneuropathy from those without polyneuropathy (sensitivity 13% and specificity 99%) and did not correlate with examination scores, vibration thresholds, or nerve conduction studies. However, lowering the cut-off to define abnormality improved the questionnaire and resulted in a sensitivity of 40% and specificity of 92%. Optimal test characteristics for the questionnaire part and the exam part combined were a sensitivity of 48% and a specificity of 93%.[36] The clinical part of the MNSI has been used throughout other studies.[37-39] These studies concluded that this examination tool is a rapid, reproducible and reliable test to screen for peripheral diabetic neuropathy.

Another scale that combines symptoms and signs to screen for the presence and grade the severity of diabetic polyneuropathy is the Toronto Clinical Scoring System (TCSS, later named the Toronto Clinical Neuropathy Score, TCNS). The TCSS puts emphasis on sensory symptoms and deficits.[40] The TCSS was developed by neurologists and diabetologists and validated against electrophysiological criteria and morphology of sural nerve biopsies. Initially, the TCSS included reflex testing, but these were eliminated in a modified version (mTCNS), to improve sensitivity to early pathophysiological changes of polyneuropathy.[41] The mTCNS included sensory symptoms and pinprick, temperature, vibration, light touch and position sense.

A more extensive composite scale that combines symptoms and a neurological examination with additional test into a total score is the Total Neuropathy Score© (TNS©), developed to monitor changes in peripheral nerve function during and after treatment with chemotherapy.[42-47] Apart from symptoms and signs, the original TNS© includes a

combination of quantitative sensory testing and nerve conduction studies, but several adapted versions appeared, including the TNSc, a clinical version with only symptoms and signs and the TNSr, a reduced version of the TNS© without quantitative sensory testing.[46, 48-50] The use of the TNS© and modifications of it has been extended to hereditary, diabetic and HIV associated neuropathies. The TNS© has been validated against the NSS and the NIS in patients with diabetes and Charcot-Marie-Tooth disease. Inter- and intra-rater reliability was very high and the TNS© correlated very good with the NSS and NIS.[44] The TNS© may be useful to longitudinally assess progression of polyneuropathy or response to treatment. However, summing all components (symptoms, signs and nerve conduction or QST abnormalities) into a total score suggests equal weight of each component in the score, which might not reflect reality.

Polyneuropathy scales using only signs

The NSS was first developed in combination with the Neuropathy Disability Score (NDS), a score designed to measure deficits of the peripheral nervous system.[7] The NDS includes examination of cranial nerves, muscle strength of upper and lower extremities, tendon reflexes, and multiple modalities of sensation on the index finger and the big toe. The NDS is significantly associated with the NSS, neuropathological abnormalities in the sural nerve and several nerve conduction parameters.[12] The NDS was renamed into the Neurological Impairment Score (NIS) after eliminating tests not directly related to polyneuropathy, which in turn was modified into the NIS-LL to specifically address distal diabetic polyneuropathy in the lower limbs.[14] The latter was also expanded with a range of additional examinations (vibration thresholds, nerve conduction studies, NIS-LL+7 tests).[17] The NDS and NIS are weighted towards motor deficits. Application may therefore be less useful in patients with (early) symptoms of chronic axonal polyneuropathies or otherwise predominantly sensory neuropathies.[51]

The extensive NDS was reduced into the 8-item Diabetic Neuropathy Examination (DNE)[20], which only evaluates items that were considered as clinically relevant (unilateral muscle strength for extension of the knee and dorsiflexion of the foot, ankle reflex, pinprick on the index finger and big toe and vibration, touch and position sense on the big toe), in order to obtain a more accurate and easily manageable scoring system. The DNE is a relatively fast tool, taking only 5 minutes to apply. The DNE has been validated against monofilaments and quantitative sensory testing of vibration thresholds, has good reproducibility and is strongly related to autonomic function testing and nerve conduction studies.[20, 21]

Because several scales that (mainly) quantify motor deficits were already available, but no scales specifically addressing sensory deficits existed for patients with inflammatory neuropathies, the inflammatory neuropathy cause and treatment (INCAT) sensory sumscore (ISS) was created.[52] This scale includes pinprick and vibration sense on the

Table 3. Overview of different assessment scales that include a neurological examination for polyneuropathy

	NDS / NIS[7]	CNE[68]	MNSI[35]	MDNS[35]	TNS[42]	Gentile[4]	DNE[20]	ISS[52]	TCSS[40]	BPNS[25]	UENS[53]	ENS[54]
Population	Diabetics	Diabetics	Diabetics	Diabetics	Patients on chemo-therapy	Diabetics	Diabetics	Inflammatory neuropathies	Diabetics	HIV patients	Patients with IGT	Patients with IGT
Validation	NCS, biopsy	Vibration perception threshold	Mayo criteria[d]	Mayo criteria[d]	NSS and NIS	NCS	Monofilament	Nine-hole peg test, 10-meter walking test, disability sum score	NCS and biopsy	QST and biopsy	NCS, QST, biopsy	Published criteria[i]
Sensitivity	-	87%[c]	80%	80% / 97%[e]	-	94%	96%	-	-	-	92%	-
Specificity	-	62%[c]	95%	100% / 100%[f]	-	92%	51%	-	-	-	-	-
Contents of the scale												
Upper/lower extremities	Both	Lower	Lower	Lower	Both	Lower	Both	Both	Lower	Lower	Lower	Lower
Symptoms	-	-	+	-	+	+	-	-	+	+	-	-
Cranial nerves	+	-	-	-	-	-	-	-	-	-	-	-
Foot inspection	-	-	+	-	-	+	-	-	-	-	-	-
Pin prick	+	+	-	+	+	-	+	+	+	-	+	-
Light touch	+	+	-	+	-	-	+	(+)[h]	+	-	+	+
Vibration sense	+	+	+	+	+	-	+	+	+	+	+	+
Position sense	+	(+)[c]	-	-	-	-	+	(+)[h]	+	-	+	-
Temperature sense	-	-	-	-	-	-	-	-	+	-	-	+
Muscle strength	+	(+)[c]	-	+	+	+	+	-	-	-	+	-

Table 3. Overview of different assessment scales that include a neurological examination for polyneuropathy (*continued*)

	NDS / NIS[7]	CNE[68]	MNSI[35]	MDNS[35]	TNS[42]	Gentile[4]	DNE[20]	ISS[52]	TCSS[40]	BPNS[25]	UENS[53]	ENS[54]
Tendon reflexes	+	+	+	+	+	+	+	-	+	+	+	+
Nerve conduction studies	(+)[b]	-	-	+	(+)[g]	-	-	-	-	-	-	-
Quantitative sensory testing	(+)[b]	-	-	-	(+)[g]	-	-	-	-	-	-	-

+: present in scale; -: absent in scale

[a] The NDS was later renamed into the NIS. [14,17]

[b] The NIS was adapted into the NIS-LL (only lower limbs) and several expansions appeared: NIS-LL+ several tests (NCS, QST, autonomic testing). [17]

[c] Sensitivity and specificity are the average of two observers. [69] Position sense and muscle strength omitted in later version.

[d] Mayo criteria are based on nerve conduction studies, the NDS, vibration thresholds, autonomic function testing and the NSP.

[e] Sensitivity of the clinical part and the nerve conduction part of the MDNS respectively.

[f] Specificity of the clinical part and the nerve conduction part of the MDNS respectively.

[g] Original version has been adapted several times in a modified (no tuning fork, no NCS and no thermal QST), a reduced (no QST), and a clinical version (no NCS or QST). [50]

[h] These were included in the later version, the modified ISS (mISS).

[i] Criteria according to the Toronto Diabetic Neuropathy Expert Group guideline. [55]

arms and legs, evaluating presence of a proximal gradient and two-point discrimination on the index finger. The scale is validated with a disability sumscore, Nine-Hole Peg Test and a 10-Meter Walking test and is mainly used as outcome measure to grade the severity of sensory deficits in patients with inflammatory neuropathies.

To focus more on early signs of polyneuropathy, the Utah Early Neuropathy Scale (UENS) was developed.[53] In this scale the focus is more on pinprick sensibility than on muscle weakness (only extension of the big toe). Vibration and position sense are included as well as ankle reflexes. The UENS was developed to detect neuropathy in patients with diabetes and prediabetes. Although sensory signs are emphasized in this scale, there was still a good correlation with the more motor performance-based NIS-LL and MDNS. Moreover, there was a better correlation between UENS and nerve conduction studies, QST and intraepidermal nerve fiber density than there was between the NIS-LL and MDNS with these tests. The diagnostic sensitivity of the UENS was also higher than that of the MDNS and the NIS-LL. An advantage of the UENS is that loss of pinprick is mapped by anatomical distribution, making it possible to study change in severity over time.

Recently, the Early Neuropathy Scale (ENS) was developed with the same rationale as the UENS.[54] The ENS includes multiple sensory tests (monofilament testing, vibration testing with a Rydel-Seiffer tuning fork, pin perception on the hallux and cold perception on the dorsum of the foot) and ankle reflexes. The ENS was validated against nerve conduction studies and intraepidermal nerve fiber density. Sensitivity and specificity were investigated using the definition published by the Toronto Diabetic Neuropathy Expert Group as gold standard[55] and were 83% and 97% respectively.

Components and characteristics of all discussed scales for the quantification of the neurological examination are listed in Table 3.

DISCUSSION

We aimed to identify and summarize existing assessment scales that can be used for the diagnosis of chronic, length-dependent polyneuropathy in epidemiological studies. Other subtypes of polyneuropathy, such as acute inflammatory neuropathies, chronic demyelinating neuropathies with proximal weakness, small-fiber neuropathies or predominantly autonomic neuropathies probably require an alternative approach. Many different scales have been developed to screen for the presence or to grade the severity of a polyneuropathy. Most have been validated and showed reasonable correlations and discriminatory characteristics. However, several of the scoring systems are complex and time consuming. Some include a complete neurological examination or multiple advanced investigations or combine assessment at both levels of disability (impairments)

and functioning (participation). For population studies or other studies investigating a large number of people, it is important that the screening tool is fast, simple, highly reproducible and highly sensitive. If no further confirmatory investigations are performed after the initial screening, specificity also needs to be optimal.

We evaluated existing scales, and not single tests, for their possible usefulness to screen for the presence of a polyneuropathy. Therefore, we excluded studies that only used one test, such as monofilaments, vibration sense or nerve conduction studies. For screening studies, especially when aiming to describe the frequency of polyneuropathy in the unselected general population, a high sensitivity is important in order not to miss any cases. Studies have shown that this is often not optimal for single test, such as monofilament or tuning fork examination.[56-58] Moreover, distal sensory loss can also be found in healthy people without other signs of polyneuropathy, especially in elderly.[59] Therefore, using single tests as screening instrument may lead to a substantial proportion of false-negative and false-positive cases. Test characteristics like sensitivity and specificity of the different scales that combine several items are reported to be reasonable in most studies. However, when interpreting these characteristics, one must take into account in which population they have been tested, how participants were sampled and which reference test was used. Evaluating a test in a strictly selected population may lead to optimistic test characteristics, referred to as spectrum bias or spectrum variation.[60] Using only patients with severe disease as cases will yield an optimistic sensitivity and using only fully healthy controls will yield an optimistic specificity. Results of the test characteristics may be valid, but not generalizable to other populations, limiting the applicability of the test in clinical practice.[60, 61] The choice of the reference test can also bias the diagnostic accuracy of a test. This is referred to as inappropriate reference standard bias.[60] Diagnostic accuracy of the test under observation is calculated under the assumption that the reference test is 100% sensitive and specific. In polyneuropathy there is no such gold standard test: all reference tests that are used in the discussed studies are imperfect, possibly resulting in biased results. Moreover, different reference tests will yield different test characteristics for the same index tests.[60, 61] Additionally, filling in a simple score may not be a guarantee for accurate screening data, because reproducibility and intra- and inter-rater agreement of scoring symptoms and signs can vary considerably.[62] It is important to keep these issues in mind when interpreting the test characteristics of the discussed screening instruments.

Another issue with several of the discussed scales is that they are composed of different components that are assigned with a (random) score, which are subsequently summed into a total score. Not all components that form the total score in a scale may be clinically relevant and assigning equal weights to summed components assumes that the total score is linear, which is not likely.[63] Several of the discussed scales are also used as outcome measures in longitudinal studies. Recently, a more modern clinimetric

approach, using Rasch-analysis, has been applied to outcome measures, largely fixing these limitations.[63-65] The Rasch Overall Disability Scale (RODS) is an example of such an outcome measurement, which can be used to assess disability in patients with inflammatory neuropathy. In deciding which scale to use, that includes scales to diagnose polyneuropathy, these limitations should be taken into account.

Most of the scales are validated against other scales, nerve conduction studies or a clinical diagnosis, but a direct comparison between all these scales is not available. One study recently compared seven of the evaluated scoring scales (NDS, NIS-LL, MNDS, modified TCNS, clinical TNS©, UENS, ENS) in a population of patients with impaired glucose tolerance.[54] In this study the modified version of the TCNS (mTCNS) had the best discriminative ability, followed by the clinical version of the TNS© (TNSc), for detection of polyneuropathy in general, as well as for large and small fiber neuropathy subgroups separately. All seven scales in this study correlated with peroneal nerve motor conduction velocity and vibration detection thresholds, while none of the scales correlated with cold detection thresholds or intraepidermal nerve fiber density. The mTCNS was the only scale that did not correlate with sural nerve action potential amplitudes. The mTCNS and the TNSc were the only scales tested in this study that also include questions on symptoms of polyneuropathy.[54] These findings suggest that, while the presence of symptoms of polyneuropathy alone is considered to be not suitable for screening purposes, information about sensory complaints may have additional diagnostic relevance. Therefore, it seems advisable that future polyneuropathy screening studies incorporate both symptoms and signs into the screening protocol. Furthermore, the examination part must emphasize sensory deficits, especially when investigating persons that may only have minor symptoms of polyneuropathy. In many scales, several components are present that are usually mainly affected in advanced stages of polyneuropathy. Early signs are often underrepresented or overshadowed by impairment of muscle strength or reflexes, leading to a low sensitivity to detect polyneuropathy in an early stage of disease. Of course, this largely depends on the specific subtype of polyneuropathy being under investigation.

Assessment scales can help to detect the presence of chronic polyneuropathy. It is important to realize that most of the scales being discussed are developed for and investigated in specific, high-risk patient groups, such as patients with diabetes or patients who received chemotherapy. In epidemiological studies, valid, reliable and fast screening instruments are essential. Most existing scales have several limitations that are not easily overcome. Therefore, future studies are required to create clinimetrically correct screening instruments that can be used to determine the presence of polyneuropathy in large, low-risk population studies.

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Chapter 2.2

Diagnostic value of symptoms in chronic polyneuropathy: The Erasmus Polyneuropathy Symptom Score (E-PSS)

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ABSTRACT

Objective: To evaluate the diagnostic value of individual symptoms of chronic polyneuropathy and to construct and validate a simple screening questionnaire that can help to diagnose polyneuropathy in low-risk patient groups.

Methods: In a multi-step procedure, we initially compiled a twelve-item questionnaire concerning symptoms of polyneuropathy. The questionnaire was completed by 117 polyneuropathy patients and 188 controls (headache, transient ischemic attack, multiple sclerosis). We calculated the sensitivity, specificity and likelihood ratios of each individual symptom. Next, we used stepwise multivariable logistic regression to create a compact model that could discriminate cases from controls with only the most informative symptoms. Based on the regression coefficients of this compact model, we subsequently developed a simple scoring system (the Erasmus Polyneuropathy Symptom Score, E-PSS) and carried out external validation in a population of 140 cases with chronic idiopathic axonal polyneuropathy and 96 controls without polyneuropathy. We assessed performance of the E-PSS with discrimination (area under the curve, AUC) and calibration analyses.

Results: Numb and tingling feet were most frequently reported by polyneuropathy patients and had the highest sensitivity. Feeling as if walking on cotton wool and allodynia had the highest specificity. Multivariable logistic regression yielded a model that contained these four symptoms, complemented with balance problems and tingling hands. Based on regression analysis, the E-PSS was created with a score ranging from 0 to 14. This polyneuropathy symptom score had a good performance (AUC 0.92) in the derivation set and proved to be valid in the external population (AUC 0.95).

Conclusion: A simple, validated polyneuropathy symptom score (E-PSS) that takes into account the individual value and frequency of six different symptoms can be helpful as screening instrument in clinical practice and for future studies on polyneuropathy.

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INTRODUCTION

Patients with chronic axonal polyneuropathy can suffer from tingling sensations, numbness, weakness and invalidating pain, most frequently in the lower legs and feet.[1] These symptoms are well known and are used in clinical practice and in several screening protocols for polyneuropathy, such as the Michigan Neuropathy Screening Instrument and the Diabetic Neuropathy Symptom score.[2, 3] Some studies report that neuropathic symptoms correlate well with neurological signs or nerve conduction studies and can be adequately used for screening, while other publications state that symptoms alone are not useful for discrimination purposes, because they have poor diagnostic accuracy in detecting the presence of a (diabetic) polyneuropathy.[2-8] Sensitivity and specificity of questionnaires differ widely across studies, ranging from very low (<50%), to relatively high (around 90%).[2-4, 6, 7, 9, 10]

Most questionnaires were specifically developed to screen high-risk populations, for example patients with diabetes, or patients receiving chemotherapy. No symptom questionnaires for chronic polyneuropathy have been developed and properly validated for screening of a lower-risk population.[10] Such a questionnaire would be very useful in a primary care setting or outpatient clinic and for chronic polyneuropathy-related research. Most questionnaires include several nonspecific symptoms such as cramps or muscle pain, and apply equal weights to all symptoms. However, it is unlikely that all symptoms are equally informative. Furthermore, when a specific symptom is constantly present this may be more informative than when the same symptom only occurs intermittently. Taking these factors into account might improve the accuracy and clinical usefulness of screening questionnaires.

We extensively interviewed in a predefined standardized manner patients with polyneuropathy and controls without polyneuropathy about the presence of neuropathic symptoms, to investigate which symptoms are most common and which are most informative in the diagnostic process. We aimed to create and validate a short questionnaire that can be used in various settings to help discriminating persons with polyneuropathy from persons without polyneuropathy.

METHODS

Study participants

Persons who were diagnosed with polyneuropathy at the neurological outpatient clinic of the Erasmus University Medical Center Rotterdam between 2012 and 2014 were potentially eligible for the study. Polyneuropathy was diagnosed after thorough interview of the patients, combined with extensive neurological examination and confirmed with

nerve conduction studies according to the Dutch national Guideline on Polyneuropa-thy.[11] We contacted 213 patients with diabetic or idiopathic polyneuropathy by mail, inviting them to participate in the current study.

Controls were selected from the same neurological outpatient clinic. Patients who visited the outpatient clinic between 2012 and 2014 with headache, having no other neurological abnormalities and a normal neurological examination, served as control group. In a later stage, the control group was expanded with patients who had experi-enced a transient ischemic attack, as these persons were expected to be more similar to polyneuropathy cases with respect to age. We additionally included a group of patients with a recent diagnosis of multiple sclerosis with an expanded disability status scale < 4. This control group was added because these patients might have symptoms that could resemble symptoms of polyneuropathy. By extending the control groups we aimed to improve the clinical utility, specifically concerning the specificity of the questionnaire. All controls underwent a full neurological examination at the time of their visit. Controls with distal, sensory or motor deficits or bilaterally impaired tendon reflexes were not eli-gible. Additionally, persons with other neurological diseases or severe systemic diseases that are associated with polyneuropathy were not eligible.

We validated the final version of the questionnaire in an external population that consisted of 140 patients diagnosed with chronic idiopathic axonal polyneuropathy (CIAP) at the University Medical Center Utrecht, the Netherlands.[12] The partner of each of these patients, if present, was asked to act as control. Partners were suitable as control when they had no self-reported polyneuropathy. There were no other selection criteria. Therefore, this control group can be considered as a random sample of the same source population. In total, 102 partners returned a completed questionnaire, 6 of whom had a self-reported polyneuropathy and were excluded. The final control group in this valida-tion population consisted of 96 controls.

Development of the questionnaire

The development of the questionnaire was a multi-staged process (see Figure 1).

Initially, we compiled a list of questions based on previous known polyneuropathy questionnaires, advice of neuromuscular specialists in the field of polyneuropathy and personal experience.[4, 13]

First stage. The first version of the questionnaire included ten questions assessing the presence of numb feet, tingling feet, muscle cramps, weakness in the legs during standing or walking, feeling as if walking on foam or cotton wool, tightness of the legs, burning feet, muscle pain, restless legs, and difficulty opening jars. This first version of the questionnaire was sent to 213 cases and 245 headache controls.

Second stage. We modified the questionnaire based on preliminary analyses of the returned questionnaires, which showed that restless legs and difficulty opening jars had
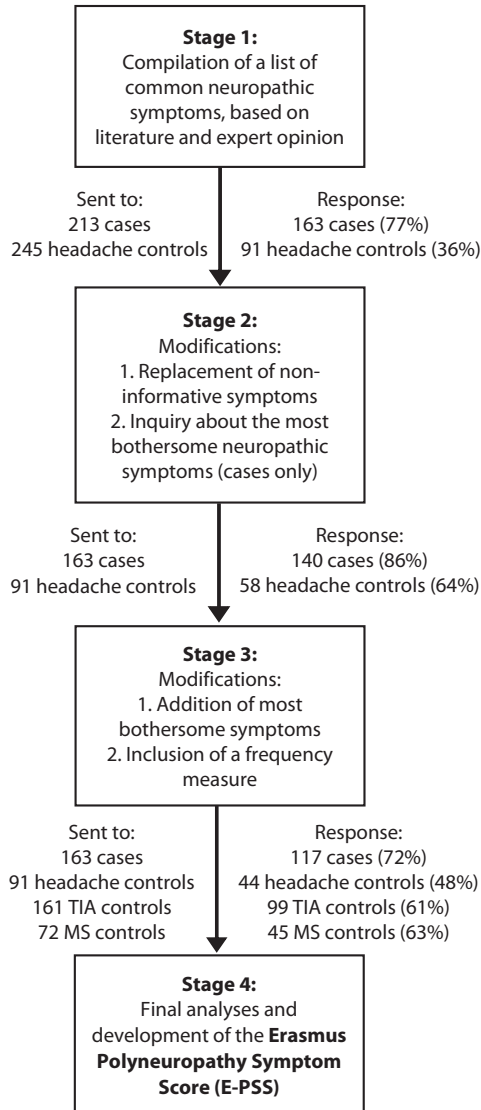
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┌─────────────────────────────┐
│          Stage 1:           │
│    Compilation of a list    │
│    of common neuropathic    │
│    symptoms, based on       │
│   literature and expert     │
│          opinion            │
└─────────────────────────────┘
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Sent to: Response:
213 cases   163 cases (77%)
245 headache controls   91 headache controls (36%)

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┌─────────────────────────────┐
│          Stage 2:           │
│        Modifications:       │
│   1. Replacement of non-    │
│    informative symptoms     │
│   2. Inquiry about the most │
│   bothersome neuropathic    │
│    symptoms (cases only)    │
└─────────────────────────────┘
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Sent to: Response:
163 cases   140 cases (86%)
91 headache controls   58 headache controls (64%)

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┌─────────────────────────────┐
│          Stage 3:           │
│        Modifications:       │
│    1. Addition of most      │
│    bothersome symptoms      │
│   2. Inclusion of a frequency│
│          measure            │
└─────────────────────────────┘
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Sent to: Response:
163 cases   117 cases (72%)
91 headache controls   44 headache controls (48%)
161 TIA controls   99 TIA controls (61%)
72 MS controls   45 MS controls (63%)

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┌─────────────────────────────┐
│          Stage 4:           │
│      Final analyses and     │
│    development of the       │
│    Erasmus                  │
│  Polyneuropathy Symptom     │
│       Score (E-PSS)         │
└─────────────────────────────┘
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Figure 1. Multi-staged development of the questionnaire. The development of the final score was a multi-staged process that involved several preliminary analyses and patient input. Modifications were made to the questionnaire accordingly.

both poor sensitivity and poor specificity. These questions were replaced by a question assessing the presence of allodynia (are your feet too sensitive to touch?) and a question assessing the presence of stabbing or shooting pain in the legs.[2, 9, 14, 15] In this stage, we additionally included an inquiry about the five most bothersome polyneuropathy-related symptoms cases experienced. This second version was sent to all respondents of the first version.

Third stage. We again modified the questionnaire by including two not previously listed symptoms that were often reported by the polyneuropathy patients: balance problems and tingling sensations in both hands. We also included a frequency measure in this version (never, sometimes, and (almost) continuously). The third version of the questionnaire consisted of twelve questions evaluating the presence of symptoms during the last three months. Eleven questions covered sensory and motor symptoms in the feet: numbness, tingling sensations, balance problems, cramps, weakness, walking on cotton wool, tightness, burning, muscle pain, allodynia, and stabbing pain, and one question concerned tingling sensations of both hands. This version was sent to all respondents of the first version. Moreover, in this stage the control group was expanded with patients who experienced a transient ischemic attack (n=161) or were diagnosed with multiple sclerosis (n=72).

Final stage. The results of the third version of the questionnaire and the development and validation of the final Erasmus Polyneuropathy Symptom Score (E-PSS) are described in the remainder of this article.

This study was approved by the medical ethics committee of the Erasmus MC University Rotterdam, the Netherlands. The validation study was approved by the medical ethics committee of the University Medical Center Utrecht.

Statistical analysis

Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of specific symptoms were calculated with standard two by two tables (symptoms present or absent), using the clinical diagnosis as gold standard. Sensitivity was calculated as the probability of having the specific symptom in the presence of polyneuropathy and specificity as the probability of not having the specific symptom in the absence of polyneuropathy. Positive likelihood ratio was calculated as the ratio between the probability of having the symptom given the presence of the polyneuropathy (sensitivity) and the probability of having the symptom given the absence of the polyneuropathy (1-specificity). Negative likelihood was calculated as the ratio between the probability of not having the symptom given the presence of the polyneuropathy (1-sensitivity) and the probability of not having the symptom given the absence of the polyneuropathy (specificity). A positive likelihood ratio above 1 and a negative likelihood ratio below 1 indicate an informative test and the further away from 1, the more informative the test. Specificity, and likelihood ratios were recalculated while restricting the control group to patients with multiple sclerosis to investigate whether symptoms can also differentiate polyneuropathy patients from controls in a more clinical setting of suspected patients. Presence of symptoms among cases and controls was compared using chi-square tests.

Multivariable logistic regression analysis was used to determine which symptoms were independently associated with the presence of polyneuropathy. We subsequently

used backward stepwise selection to achieve a compact model, leaving only the most important symptoms in the model, using a p-value cut-off of 0.1. Based on the regression coefficients of this multivariable model we created a scoring system to make the questionnaire clinically useful. The performance of this final scoring system was quantified with respect to discrimination (area under the receiver operating characteristics curve, AUC) for the control group in total and for each of the control groups separately. Internal validity was assessed by bootstrapping (using 1000 bootstrap samples), to estimate the over-optimism of the model.[16] The model was further validated in an external population with CIAP patients and controls. Calibration of predictions was assessed graphically by plotting observed frequencies against predicted probabilities. Statistical analyses were carried out using the SPSS statistical package, version 21 for Windows (IBM Corp., Armonk, NY) and R statistical software.

RESULTS

In total, 117 of the 163 (71.8%) polyneuropathy patients and 188 controls (58.0%) returned the third version of the questionnaire. The control group comprised 44 headache patients (response rate 48.4%), 45 multiple sclerosis patients (response rate 63.4%), and 99 transient ischemic attack patients (response rate 61.5%). Polyneuropathy patients were on average older than control patients (70.0 years, compared to 59.7 years), and 59.8% of cases were men, compared to 48.4% of controls (see Table 1).

All polyneuropathy patients were symptomatic, 92.3% reported at least five of the twelve symptoms and 93.2% experienced at least one symptom almost continuously. All patients had either tingling feet, numb feet, balance problems or a "walking on cotton wool" feeling of the feet. The most commonly reported symptoms were numbness of the feet (present in 87.2%; 62.4% experienced this symptom (almost) continuously), tingling feet (present in 84.6%; 46.2% continuously), and balance problems (present in 82.9%; 53.0% continuously). Figure 2 shows the frequency of all symptoms among cases and controls. All symptoms were significantly more present in cases than in controls. Cramps, balance problems, weakness and muscle pain were the most commonly reported

Table 1. Characteristics of the study populations

	Cases	Controls			
	Polyneuropathy (n=117)	Headache (n=44)	Transient ischemic attack (n=99)	Multiple sclerosis (n=45)	Total (n= 188)
Age	70.0 (10.6)	50.1 (12.6)	65.6 (11.2)	43.7 (11.3)	56.7 (15.0)
Male sex	70 (59.8)	14 (31.8)	64 (64.6)	13 (28.9)	91 (48.4)

Values represent age in years (standard deviation) and number (percentage) of male individuals
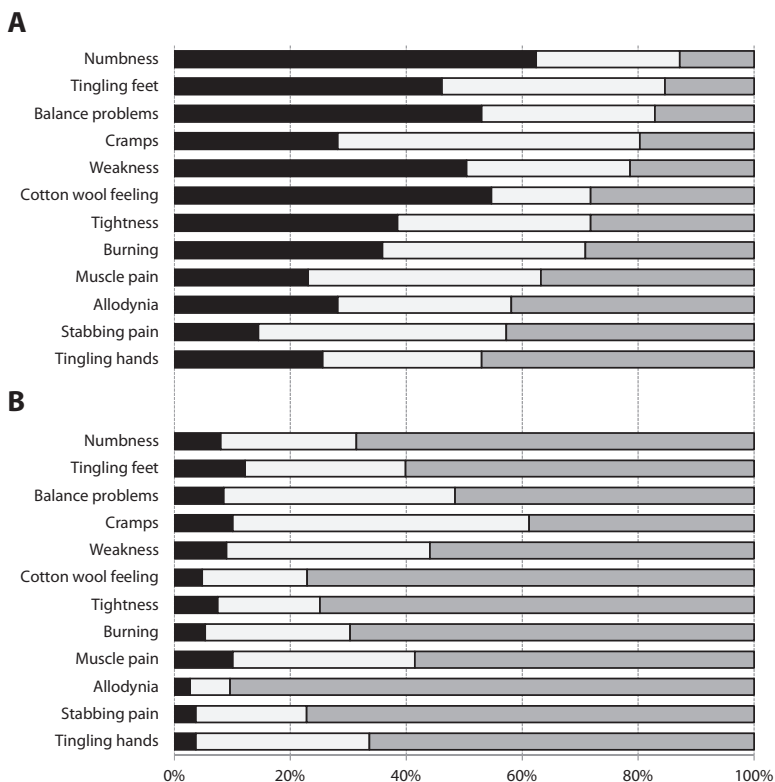
Figure 2. Frequency of symptoms in cases (A) and in controls (B). Black bars indicate the percentage of (almost) continuously occurring symptoms, light grey bars indicate the percentage of sometimes occurring symptoms and dark gray bars indicate the percentage of never occurring symptoms.

symptoms among controls. When comparing the presence of symptoms between cases and controls in each of the control groups separately, we found no significant difference in the occurrence of cramps, muscle pain and tingling hands between cases and headache controls and of balance problems between cases and controls with multiple sclerosis. All symptoms were significantly more present in polyneuropathy cases than in transient ischemic attack controls (Supplementary Figure 1).

The presence of numbness, tingling feet, and balance problems had the highest sensitivity (87%, 85% and 83% respectively) and allodynia and cotton wool feeling of the feet had the highest specificity (90% and 77% respectively). The most informative symptoms, if present, were allodynia (LR 6.07) and cotton wool feeling of the feet (LR 3.14), indicating that the presence of these symptoms greatly increases the probability of the presence of a polyneuropathy. The most informative symptoms, if absent, were numb feet (LR 0.19) and tingling feet (LR 0.26) indicating that the presence of polyneuropathy is much less likely if these symptoms are not present. Cramps and muscle pain were the least informative symptoms (Supplementary table 1).

Multivariable logistic regression showed that numb feet, cotton wool feeling of the feet and balance problems were most strongly associated with polyneuropathy, especially when these were continuously present. Backward stepwise selection resulted in a reduced model that included six symptoms: tingling feet, numb feet, cotton wool feeling of the feet, allodynia of the feet, balance problems and tingling hands (Table 2). Based on the regression coefficients of the six symptoms in the reduced model, we developed the Erasmus Polyneuropathy Symptom Score, E-PSS (Table 3). This score ranges from 0 to 14, with a maximum of 3 points for numb feet, 1 point for tingling feet, 2 points for allodynia, 4 points for cotton wool feeling, 3 points for balance problems, and 1 point for tingling hands, depending on the frequency of occurrence of these symptoms. The discriminative ability and calibration of the E-PSS using the total control group was very good (AUC 0.92, which did not change after bootstrapping). Applying the model to each of the control groups separately yielded an AUC of 0.92 for controls with headache, 0.95 for controls with a transient ischemic attack and 0.87 for controls with multiple sclerosis. The E-PSS was further tested in the independent validation set of 140 patients with chronic idiopathic axonal polyneuropathy (mean age 68.7 years) and 96 controls

Table 2. Final multivariable logistic regression of the symptom questionnaire

Symptom	Response	Odds ratio (95% confidence interval)
Numb feet	Never	1.00
	Sometimes	2.71 (1.00;7.35)
	(almost) continuously	5.92 (1.99;17.60)
Tingling feet	Never	1.00
	Sometimes	2.93 (1.12;7.70)
	(almost) continuously	1.58 (0.48;5.24)
Allodynia of the feet	Never	1.00
	Sometimes	4.04 (1.55;10.52)
	(almost) continuously	2.76 (0.75;10.08)
Cotton wool of the feet	Never	1.00
	Sometimes	0.85 (0.36;2.04)
	(almost) continuously	8.48 (2.75;26.21)
Balance problems	Never	1.00
	Sometimes	0.95 (0.39;2.35)
	(almost) continuously	5.38 (1.94;14.92)
Tingling hands	Never	1.00
	Sometimes	0.44 (0.19;1.01)
	(almost) continuously	2.32 (0.65;8.27)

Values represent odds ratios with 95% confidence intervals for the prediction of having polyneuropathy. Variables shown originate from logistic regression models applying backward selection of variables to reduce the original model containing all twelve symptoms of the questionnaire

Table 3. The Erasmus Polyneuropathy Symptom Score (E-PSS)

During the last 3 months, did you experience:	Responses	Score
Numbness of the feet	never	0
	sometimes	1
	(almost) continuously	3
Tingling or prickling sensations in your feet	never	0
	sometimes	1
	(almost) continuously	1
A painful feeling when your feet are touched	never	0
	sometimes	2
	(almost) continuously	1
A feeling as if you are walking on cotton wool	never	0
	sometimes	0
	(almost) continuously	4
Balance problems during standing or walking	never	0
	sometimes	0
	(almost) continuously	3
Tingling sensations in your hands	never	0
	sometimes	0
	(almost) continuously	1
Polyneuropathy Symptom Score		0-14

Points given to each symptom category, based on the multivariable logistic regression coefficients

without neuropathy (mean age 70.1 years), where it showed equally good performance (AUC 0.98) and reasonable calibration (Supplementary Figure 2).

Table 4 shows the sensitivity, specificity and percentage of correctly classified participants corresponding to different cut-offs of this score, calculated for both the derivation and the validation population.

DISCUSSION

In this case-control study, numbness and tingling of the feet were the most often encountered symptoms in patients with polyneuropathy. The absence of these symptoms greatly reduces the probability of the presence of polyneuropathy. Presence of a feeling like walking on cotton wool and allodynia of the feet greatly increase the probability of the presence of a polyneuropathy. Based on a multivariable logistic regression model, these four symptoms, together with balance problems and tingling sensations in the hands, were included in a newly developed, accurate and validated scoring system that can help discriminate persons with polyneuropathy from persons without polyneuropa-

Table 4. Sensitivity, specificity and percentage of correctly classified participants of the Erasmus Polyneuropathy Symptom Score (E-PSS)

Cut-off	Derivation set			Validation set		
	Sensitivity (%)	Specificity (%)	Correctly classified (%)	Sensitivity (%)	Specificity (%)	Correctly classified (%)
≥1	98.3	49.7	68.4	99.3	88.4	94.9
≥2	95.7	65.8	77.3	98.6	95.8	97.4
≥3	88.9	78.1	82.2	94.2	95.8	94.9
≥4	88.0	83.4	85.2	89.2	95.8	91.9
≥5	78.6	91.4	86.5	79.1	97.9	86.8
≥6	70.1	93.6	84.5	72.7	97.9	82.9
≥7	64.1	95.2	83.2	68.3	97.9	80.3
≥8	57.3	95.2	80.6	61.2	97.9	76.1
≥9	45.3	97.9	77.6	43.9	98.9	66.2
≥10	39.3	98.4	75.7	35.3	98.9	61.1
≥11	28.2	98.4	71.4	25.2	100	55.6
≥12	18.8	100	68.8	18.7	100	51.7
≥13	11.1	100	65.8	9.4	100	46.2
≥14	4.3	100	63.2	3.6	100	42.7

Sensitivity, specificity and percentage of correctly classified participants were calculated at different cut-offs of the Erasmus Polyneuropathy Symptom Score

thy. Due to the simplicity and very limited time-consuming nature of the E-PSS, it may also serve as a useful tool for screening purposes in both clinical and research settings.

We showed that numbness and tingling sensations in the feet were most frequently present in patients with polyneuropathy, yielding a high sensitivity of these symptoms. However, specificity of these symptoms was poor, especially when compared to controls with multiple sclerosis. In contrast, specificity of allodynia of the feet was very high, while this symptom was not very sensitive, a finding corroborated by others.[14] These findings show that although individual symptoms provide important information, they may not be suitable for screening purposes, since this would yield a large amount of false-positives or false-negatives.[7] Combining several symptoms in a screening protocol may therefore be more useful.

Several questionnaires combining multiple symptoms have been reported.[10] Most of these questionnaires were developed for high-risk patient groups, such as patients with diabetes or patients receiving chemotherapy. Additionally, most were based on literature, or on expert opinion, without consulting patients and without a developmental process that comprised several preliminary analyses and modifications to improve the questionnaire. Importantly, in most questionnaires an equal score is given to the presence of each symptom. However, we showed that not all symptoms are equally in-

formative, so assigning the same weight to for example the presence of muscle cramps as to presence of allodynia seems not appropriate. Given these limitations of previous questionnaires, we created the new E-PSS.

We showed that the E-PSS is highly accurate in discriminating patients from controls. Therefore, this score may be a useful tool to identify persons with a polyneuropathy in primary care, outpatient clinics, as well as research settings. Depending on the aim (determining the presence of polyneuropathy in a symptomatic patient, or screening of a population in a research setting) the performance of the model will differ and different cut-off scores may be required as positivity criterion. For application in neurology outpatient clinics, the setting in which we created the E-PSS, and perhaps also in primary care, the E-PSS can be used to estimate the likelihood of polyneuropathy in symptomatic patients. However, it must be realized that the E-PSS can only be used as a screening tool. Additional clinical investigation and preferably also nerve conduction studies are required to definitely assess whether a particular person has polyneuropathy. In research settings the E-PSS can be employed to screen persons for a polyneuropathy, for example in population-based settings. In this case, a low cut-off score is necessary to have a high sensitivity. However, further studies are required to assess the performance of the E-PSS in large population-based samples.

A limitation of our study is that we used relatively small control groups. Furthermore, cases and controls differed with regard to sex and age (with exception of the TIA controls). It is possible that certain symptoms are more prevalent in higher age, independent of the presence of polyneuropathy. We may therefore have overestimated the diagnostic value of these symptoms. However, given the good performance of the model in the external population, where the age of cases and controls is more comparable, this overestimation is probably minimal.

In summary, we created the new, externally validated, highly accurate symptom-weighed Erasmus Polyneuropathy Symptom Score (E-PSS), which may serve as a useful tool in clinical practice and for future studies.

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Supplementary table 1. Sensitivity, specificity and likelihood ratios for neuropathic symptoms

| Symptom	Controls	Sensitivity	Specificity	LR+	LR-
Numb feet	All	87%	69%	2.78	0.19
	MS only	-	49%	1.71	0.26
Tingling feet	All	85%	60%	2.12	0.26
	MS only	-	44%	1.52	0.35
Balance problems	All	83%	52%	1.71	0.33
	MS only	-	24%	1.10	0.70
Cramps	All	80%	39%	1.31	0.51
	MS only	-	56%	1.81	0.35
Weakness	All	79%	56%	1.78	0.38
	MS only	-	44%	1.42	0.48
Cotton wool feet	All	72%	77%	3.14	0.37
	MS only	-	69%	2.31	0.41
Tightness of feet	All	72%	75%	2.86	0.38
	MS only	-	64%	2.01	0.44
Burning feet	All	71%	70%	2.34	0.42
	MS only	-	64%	2.00	0.45
Muscle pain	All	63%	59%	1.52	0.63
	MS only	-	60%	1.58	0.61
Allodynia feet	All	58%	90%	6.07	0.46
	MS only	-	96%	13.07	0.44
Stabbing pain	All	57%	77%	2.50	0.55
	MS only	-	78%	2.58	0.55
Tingling hands	All	53%	66%	1.57	0.71
	MS only	-	67%	1.59	0.71

Sensitivity and specificity were calculated using the two by two tables. Positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were subsequently calculating using the sensitivity and specificity of each symptom
MS: multiple sclerosis; LR: likelihood ratio
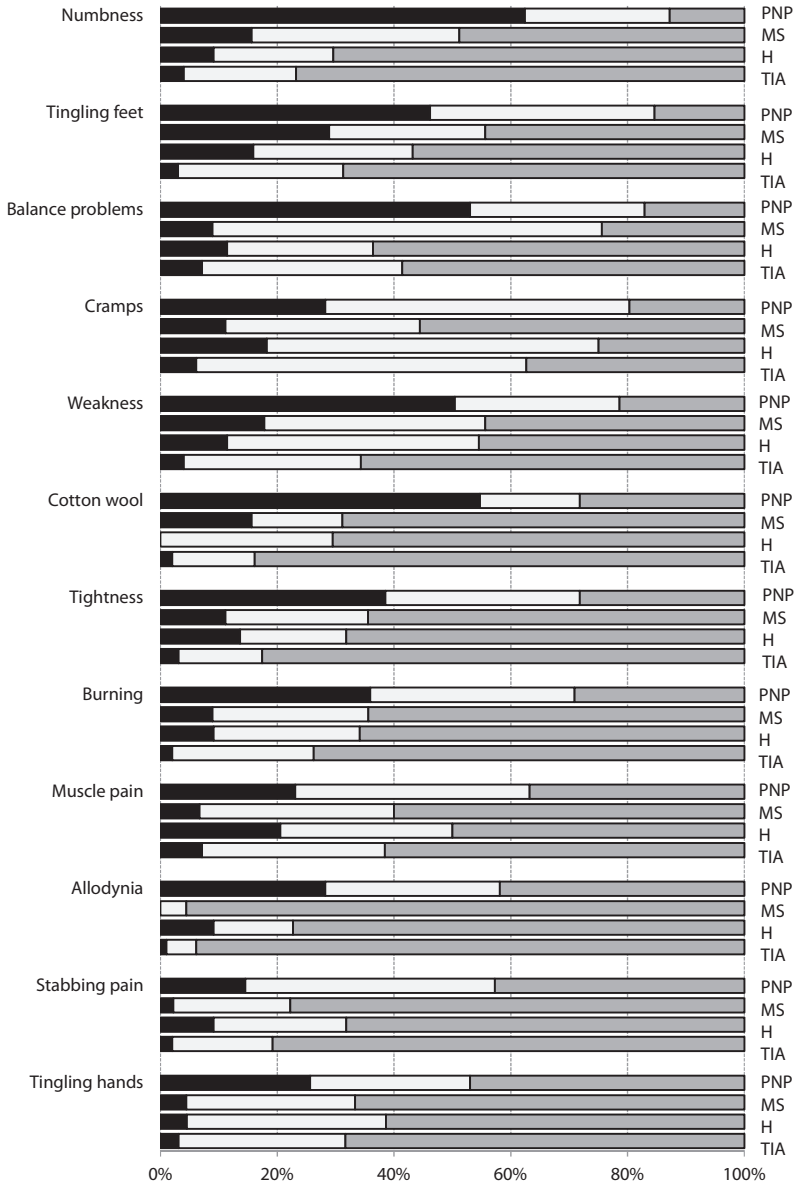
Supplementary figure 1. Frequency of symptoms in cases and in different control groups. Black bars indicate the percentage of (almost) continuously occurring symptoms, light grey bars indicate the percentage of sometimes occurring symptoms and dark gray bars indicate the percentage of never occurring symptoms.

PNP: polyneuropathy, MS: multiple sclerosis; H: headache; TIA: transient ischemic attack
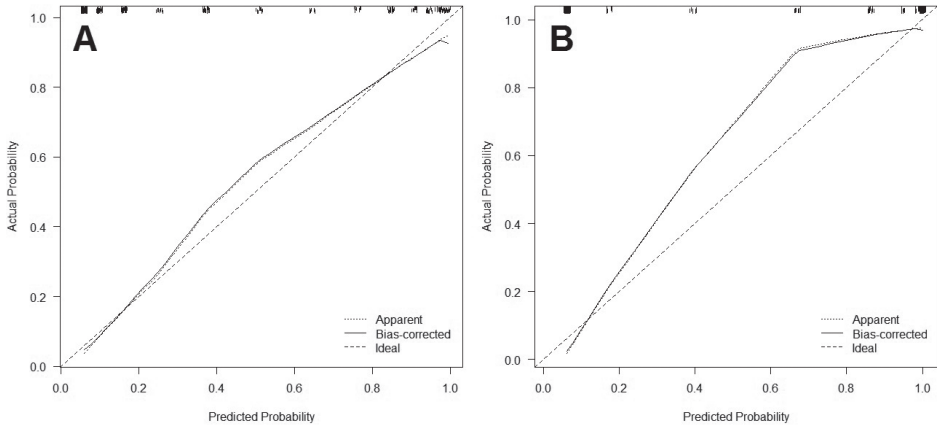
Supplementary figure 2. Calibration plots of the Polyneuropathy Symptom Score in the derivation set (A) and in the validation set (B). The dashed straight line from (0,0) to (1,1) indicate perfect calibration, the dotted line the calibration of the actual model, and the bias-corrected solid line the calibration after bootstrapping. The calibration of the model is very good in the derivation set, but underestimates the actual probability in the validation set.

Chapter 3

Prevalence of polyneuropathy in the general population

Chapter 3.1

The epidemiology and risk factors of chronic polyneuropathy: a review

Rens Hanewinckel, Marieke van Oijen, M. Arfan Ikram, Pieter A. van Doorn

ABSTRACT

Polyneuropathy is a disabling condition of the peripheral nerves, characterized by symmetrical distal numbness and paresthesia, often accompanied with pain and weakness. Although the disease is often encountered in neurological clinics and is well known by physicians, incidence and prevalence rates are not well known. We searched EMBASE, Medline, Web-of-science, Cochrane, PubMed Publisher, and Google Scholar, for population-based studies investigating the prevalence of polyneuropathy and its risk factors. Out of 5119 papers, we identified 29 eligible studies, consisting of 11 door-to-door survey studies, 7 case-control studies and 11 cohort/database studies. Prevalence of polyneuropathy across these studies varies substantially. This can partly be explained by differences in assessment protocols and study populations. The overall prevalence of polyneuropathy in the general population seems around 1% and rises to up to 7% in the elderly. Polyneuropathy seemed more common in Western countries than in developing countries and there are indications that females are more often affected than males. Risk factor profiles differ across countries. In developing countries communicable diseases, like leprosy, are more common causes of neuropathy, whereas in Western countries especially diabetes, alcohol overconsumption, cytostatic drugs and cardiovascular disease are more commonly associated with polyneuropathy. In all studies a substantial proportion of polyneuropathy cases (20-30%) remains idiopathic. Most of these studies have been performed over 15 years ago. More recent evidence suggests that the prevalence of polyneuropathy in the general population has increased over the years. Future research is necessary to confirm this increase in prevalence and to identify new and potentially modifiable risk factors.

INTRODUCTION

Polyneuropathy is a peripheral neuropathy characterized by symmetrical sensory symptoms, such as numbness, paresthesia and pain, and muscle weakness, which are predominantly located in the distal parts of arms and legs. Polyneuropathy is a disabling disease and has a negative impact on a person's quality of life.[1] Although it is assumed that polyneuropathy affects a considerable proportion of the population, the exact prevalence and incidence of the disease are not well known. Elderly probably are at higher risk to develop polyneuropathy[2], and are thus at higher risk for associated falls and related injuries. Since an increasing proportion of the population is over 50 years of age, especially in developed countries, it is important to recognize the disease and to screen for treatable causes. Information about the frequency of the disease and its risk factors is therefore crucial.

Over 100 different causes of polyneuropathy have been identified, with diabetes as most important risk factor.[2-6] Guidelines have been developed to distinguish between these different causes.[6-9] Differentiation into acquired versus inherited, chronic versus acute and axonal versus demyelinating variants helps the diagnostic process in clinical practice. Most polyneuropathies have a progressive phase over months or years and have predominantly axonal characteristics with reduced sensory and motor nerve action potential amplitudes on electrophysiological examination.[2] However, even when diagnostic guidelines in patients with a slowly progressive axonal neuropathy are strictly applied, no cause can be identified in about 20-30% of patients. These patients are often diagnosed with chronic idiopathic axonal neuropathy (CIAP).[10]

The aim of this review is to summarize the literature about the epidemiology of polyneuropathy and to obtain more information about differences across populations and between age groups. The review provides an overview of studies that investigated the prevalence and incidence of polyneuropathy and its associated risk factors.

METHODS

Literature search

On January 8, 2015 (date last searched), we comprehensively searched the literature, using electronic medical databases (EMBASE, Medline, Web-of-science, Cochrane, PubMed Publisher and Google Scholar), to identify published studies reporting the prevalence or incidence of polyneuropathy in the general population. Our search strategy included a combination of terms about the disease of interest (polyneuropathy, peripheral neuropathy) and about epidemiology (epidemiology, prevalence, incidence). The specific search terms for each database can be found in the supplement. The search was limited

to publications in the English language. We did not use a limitation for publication date. We initially selected publications that reported prevalence or incidence of peripheral neuropathy or polyneuropathy based on title and abstract. Studies that only investigated specific patients groups without a control group, for example only patients with diabetes, and studies that only investigated specific neuropathies, such as autonomic neuropathy, optic neuropathy, or mononeuropathy were not included. Studies about peripheral neuropathy were only included if the prevalence of polyneuropathy was also specified. When multiple articles from the same study were identified, the most recent or most comprehensive report was selected for this review. Our literature search was complemented by reviewing the reference lists of the identified articles, in order to gather other important publications that were missed with our search terms.

In addition to the prevalence of polyneuropathy in general, we further discuss some important risk factors for polyneuropathy and the prevalence of chronic idiopathic polyneuropathy. For this part of the review we also used hospital-based studies that specified risk factors like diabetes or intoxications. Therefore, we searched Medline for additional reports on frequency of different subtypes of polyneuropathy. We used the following search term: (neuropathy OR polyneuropathy OR neuropathies OR polyneuropathies) AND (workup OR diagnostic investigation OR cryptogenic OR idiopathic OR unspecified OR unclassified OR undetermined) and used the same limitations for this search as we did for the first one.

Data collection

The following information was extracted from the selected studies: study size; geographical location (country); age distribution of the study population; screening protocol used; crude and, if available, standardized prevalence rates; age- and sex specific prevalence rates; incidence rates; cause-specific prevalence and, if possible, relative risks or odds ratios for risk factors of polyneuropathy.

RESULTS

Our search yielded 5119 articles, of which 3065 were original articles. After excluding articles based on title or abstract, and after reading the full-text of the remaining articles, 28 studies remained. We included one additional reference that was identified after reviewing the reference lists of the selected articles. In total, 29 population-based studies that reported on the frequency of polyneuropathy were included in the review (Figure 1). Twenty-eight studies reported the prevalence, but only three reported the incidence of polyneuropathy. One study only investigated the incidence of polyneuropathy. The studies were divided into three categories, based on study design: eleven
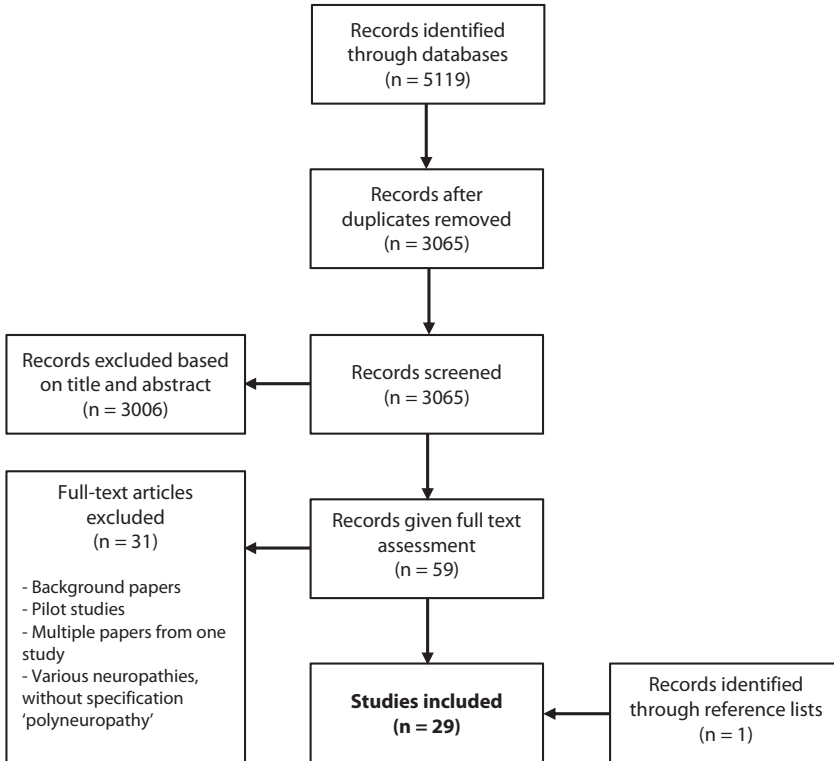
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┌─────────────────────┐
│ Records identified  │
│ through databases   │
│ (n = 5119)          │
└─────────────────────┘
          │
          ▼
┌─────────────────────┐
│ Records after       │
│ duplicates removed  │
│ (n = 3065)          │
└─────────────────────┘
          │
          ▼
┌─────────────────────┐      ┌─────────────────────┐
│ Records excluded    │◄─────│ Records screened    │
│ based on title and  │      │ (n = 3065)          │
│ abstract (n = 3006) │      └─────────────────────┘
└─────────────────────┘                │
                                        ▼
┌─────────────────────┐      ┌─────────────────────┐
│ Full-text articles  │◄─────│ Records given full  │
│ excluded (n = 31)   │      │ text assessment     │
│                     │      │ (n = 59)            │
│ - Background papers │      └─────────────────────┘
│ - Pilot studies     │                │
│ - Multiple papers   │                ▼
│   from one study    │      ┌─────────────────────┐    ┌─────────────────────┐
│ - Various           │◄─────│ Studies included    │◄───│ Records identified   │
│   neuropathies,     │      │ (n = 29)            │    │ through reference    │
│   without           │      └─────────────────────┘    │ lists (n = 1)        │
│   specification     │                                 └─────────────────────┘
│   'polyneuropathy'  │
└─────────────────────┘
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Figure 1. Selection of 29 studies that reported on the epidemiology of polyneuropathy.

door-to-door survey studies[11-21], seven case-control studies[22-28] and eleven cohort studies (seven cohort studies and four database studies).[29-39]

Door-to-door survey studies (Table 1)

The World Health Organization (WHO) developed a protocol to study the epidemiology of major neurological disorders, which was specifically designed for developing countries where financial and medical resources are limited.[40] This protocol consists of two stages. In the first stage, a questionnaire to determine the presence of neurological symptoms and a brief examination to detect major neurological dysfunction are administered to the entire study population. This stage is often carried out by non-medical personnel (teachers, students, social workers) under supervision of a nurse or a neurologist. In screen-positive participants a neurologist performs a neurological examination to document the presence and type of the neurological disorder. The protocol includes screening for headache, epilepsy, stroke and peripheral neuropathy, among others. Peripheral neuropathy in this protocol includes mononeuropathies, radiculopathy and polyneuropathy. Only studies that specified the frequency of polyneuropathy cases were included in this review.

Table 1. Door-to-door survey studies reporting prevalence of polyneuropathy

Study and study period	Study size	Age of the study population	Assessment protocol	Prevalence of polyneuropathy	Prevalence of polyneuropathy related causes (per 1000)
Cruz[11] Ecuador 1982	1113	All ages included; >50 years: 18%	WHO protocol[a]	Crude: 9.0 per 1000	
Osuntokun[12] Nigeria 1982-1983	18954	All ages included; >50 years: 11%	WHO protocol	Crude: 2.5 per 1000	1.9 tropical 0.4 idiopathic 0.1 diabetic 0.1 hereditary 0.1 nutritional
Gutierrez-del-Olmo[13] Spain 1984	961	All ages included; >50 years: 30%	WHO protocol[b]	Crude: 7.3 per 1000	3.1 idiopathic 2.1 diabetic 2.1 alcoholic
Longe[14] Nigeria 1986	2925	All ages included; >50 years: 10%	WHO protocol	Crude: 1.4 per 1000	
Bharucha[15] India 1985	14010	All ages included; >50 years: 44%	Adapted WHO protocol	Crude: 7.1 per 1000	3.7 diabetic 2.1 idiopathic 0.4 toxic 0.3 inflammatory 0.1 hereditary
Al Rajeh[16] Saudi Arabia 1989	22630	All ages included; >50 years: 4%	Adapted WHO protocol	Crude: 0.8 per 1000	
Savettieri[17] Italy 1993	14540	All ages included; >40 years: 40%	Adapted WHO protocol	Crude: 7% screen positive[c]	2.1 diabetic
Lor[18] Malaysia	100	Only subjects >65 years included	Bilateral distal symptoms and/or bilateral loss of pinprick or joint position sensation	Crude: 200 per 1000	
Kandil[19] Egypt 1997	42223	All ages included; >50 years: 10%	Adapted WHO protocol	Crude: 8.3 per 1000	6.5 diabetic 0.9 idiopathic 0.5 metabolic[d] 0.2 inflammatory 0.1 hereditary
Kruja[20] Albania 2006-2008	9869	All ages included; >50 years: 31%	≥2 symptoms + bilateral impairment of strength and/or sensation and/or reflexes with symmetrical distribution[e]	Crude: 32.5 per 1000 Adjusted[f]: 23.6 per 1000	
Dewhurst[21] Tanzania 2009-2010	2232	Only subjects >70 years included	Self-developed two-phased screening tool. First phase based on questionnaire. Diagnosis according to WHO definition	Crude: 18.8 per 1000 Adjusted[f]: 18.6 per 1000	

Survey studies reporting prevalence of polyneuropathy. If reported, prevalence of polyneuropathy sub-types is also shown.

[a] WHO protocol: door-to-door survey screening with a questionnaire and short examination, followed by a more comprehensive neurological examination performed by a neurologist to detect neurological disorders when initial screening is positive.

[b] Protocol not specified, most likely WHO protocol

[c] Screening for all neuropathies, but only prevalence of diabetic neuropathy reported

[d] Including hypothyroidism, uremic and hepatic neuropathy

[e] Same protocol as Beghi et al.[29] (possible polyneuropathy criterion). Screening based on questionnaire, neurologist diagnosed polyneuropathy according to given definition

[f] Age-standardized to the WHO world standard population

Crude point prevalence of polyneuropathy in studies using this, or a similar protocol, ranged from 0.8 to 32.5 per 1000 (0.1-3.3%) persons across all ages.[11-17, 19, 20] When only elderly are studied, prevalence ranges from 18.8 to 200 per 1000 persons (1.9-20%).[18, 21] There is a large variation in reported rates, but also in age distribution across different study populations, study area and study protocol (Table 1). Studies that report a low prevalence of polyneuropathy (0.8-2.5 per 1000) originate from African and Middle Eastern countries, such as Nigeria[12, 14], and Saudi Arabia.[16] In these studies only 4-11% of the population is over the age of 50 years. In contrast, in European countries such as Spain[13], where polyneuropathy affects 7.3 per 1000 people, and in Albania[20], where polyneuropathy is reported in 32.5 per 1000 people, around 30% is over 50 years of age. However, the latter study used a different assessment protocol and was performed 20 years after most of the other studies (Table 1).

Only two studies standardized the reported prevalence rates to a reference population.[20, 21] Adjusting the prevalence to the WHO world standard population resulted in an adjusted prevalence of 23.6 per 1000 (crude 32.5 per 1000) in Albania[20] and of 18.6 per 1000 (crude 18.8 per 1000) in Tanzania.[21]

Case-control studies (Table 2)

Seven reports compared the prevalence of polyneuropathy in patients with diabetes or prediabetes to a non-diabetic population-based sample of controls (Table 2).[22-28] In four of these studies, persons known with diabetes or impaired glycemia were identified from medical databases and invited to participate in the study.[22, 23, 25, 28] A random sample of controls was selected from the same community[22, 25, 28] or practice[23] and matched to the diabetes patients on age[22, 23, 25, 28], sex[22, 23, 28] and ethnicity.[22] The three remaining case-control studies included participants from population-based surveys, where diabetes was assessed by self-report[24, 27] or by an oral glucose tolerance test.[26] Controls were randomly sampled from those without diabetes. Controls were categorized into (new) diabetes, impaired glucose tolerance, impaired fasting glucose or normal glycemia according to the results of an oral glucose tolerance test in four studies.[22, 26-28]

These studies reported a crude prevalence of polyneuropathy in 7-42% of patients with (newly diagnosed or known) diabetes, in 6-13% of patients with prediabetes and in 2-13% of controls. The main aim of these studies is to show whether prevalence of polyneuropathy varies across different stages of glycemic impairment and to determine which determinants are associated with polyneuropathy. Assessment methods, exclusion criteria and polyneuropathy definitions across these studies differ substantially (Table 2).

Cohort studies (Table 3)

Three cohort studies also compared the prevalence of polyneuropathy in individuals with diabetes to individuals without diabetes.[36-38] However, in these studies all members from a specific community were invited before stratification on diabetes status, giving the opportunity to also assess prevalence of polyneuropathy in the whole population. In a study conducted in Canada, an adult population with a very high prevalence of diabetes (29%) was investigated and an overall crude neuropathy prevalence of 7% was reported.[36] Neuropathy was defined as loss of monofilament sensation at one or more sites on the feet in order to obtain a highly sensitive, but not very specific, screening tool. The two other studies were performed in China.[37, 38] Polyneuropathy was present in 13% of adults of the She ethnic minority group of China[37] and in 4% of the Han Chinese population over 25 years of age, free of renal failure or type 1 diabetes.[38] These studies used scoring systems (Toronto Clinical Neuropathy Scoring System and Neuropathy Symptom Score with Neuropathy Deficit Score respectively) to evaluate the presence of polyneuropathy (Table 3).

In an effort to give a more precise population prevalence estimate of polyneuropathy, a large study in two Italian regions was conducted from 1990 to 1993. In this study 4191 subjects of 55 years and older, seen in General Practitioners' office consultations for any reason, were investigated as a reflection of the general population.[29] Participants were screened with a 7-point yes/no screening questionnaire (muscle cramps, restless legs, burning feet, muscle pain, problems with object handling, impairment in standing and gait, and paresthesia). The questionnaire was pretested and validated in a hospital setting before initiation of the study. In this validation study sensitivity and specificity were 78% and 82% respectively, using a cut-off of two positive answers. After two or more positive answers on the questionnaire, participants were examined by a neurologist for signs of polyneuropathy. Possible polyneuropathy (defined as neuropathic symptoms with bilateral impairment in at least one of the following modalities: strength, sensation or deep tendon reflexes) was present in 7.3% of participants and probable polyneuropathy (symptoms and at least two abnormal modalities) in 3.6% of participants. The age- and sex-adjusted prevalence rates for the two regions (adjusted to the 1990 Italian population) were 3.6% for Varese and 3.3% for San Giovanni Rotondo.

Table 2. Case-control (survey) studies reporting prevalence of polyneuropathy

Study and study period	Selection of cases	Selection of controls	Number of participants	Assessment protocol	Definition of polyneuropathy	Prevalence of polyneuropathy
Franklin[22] USA 1984-1986	Medical records from hospitals and physicians, and self-reports of persons aged 20-74 years	Random sample of households, matched on age, sex and ethnicity. Assessment with OGTT	DM: 277 IGT: 89 NGT: 486	Discomfort in the legs Reflexes Temperature sensation	≥2 abnormal items	DM: 25.8% IGT: 11.2% NGT: 3.5%
Walters[23] UK	Medical records from 10 practices. All >30 years of age	Non-diabetics without glycosuria matched on practice, sex and birthdate.	DM: 1077 No DM: 480	Symptoms (numbness, burning, prickling, aching, tingling), light touch, pinprick, reflexes, vibration perception threshold (biothesiometer)	≥2 abnormal items	DM: 16.3% No DM: 2.9%
Harris[24] Finland 1979-1981	National Health Interview Survey of people over 18 years. Self-reported diabetes	Random sample from those without diabetes	DM: 2829 No DM: 20037	Numbness, pain or tingling, decreased ability to feel hot or cold	≥1 symptom	DM: 37.9% No DM: males 9.8, females 11.8%[a]
Partanen[25] Finland 1979-1981	Newly diagnosed diabetes patients from district health centers, aged 45-64 years, Exclusion criteria: alcoholism, thyroid dysfunction, renal failure	Randomly selected controls without diabetes from the same age group, selected from population registry. Same exclusion criteria as cases	New DM: 132 No DM: 142	Symptoms: bilateral neuropathic pain, paresthesia Signs: atrophy, reflexes, touch, pinprick, vibration Nerve conduction velocity and amplitude in peroneal and sural nerves (4 values) and sural nerves (2 values)	Definite: ≥4 abnormal NCS values, including peroneal and sural nerve, and symptoms Probable: Same as definite but without symptoms, or one of the nerves involved with symptoms	Baseline:[b] New DM: 8.3% No DM: 2.1% After 10 years: New DM: 41.9% No DM: 5.8%

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Table 2. (continued)

Study and study period	Selection of cases	Selection of controls	Number of participants	Assessment protocol	Definition of polyneuropathy	Prevalence of polyneuropathy
Tapp[26] Australia 1999-2000	AusDiab survey study of people >25 years of age. Assessment with OGTT to diagnose diabetes (and evaluation of current treatment)	Random sample of those with normoglycemia after OGTT	DM: 398 New DM: 423 IGT: 1009 IFG: 142 NGT: 464	Modified Neuropathy Symptoms Score (NSS) Modified Neuropathy Disability Score (NDS) Pressure perception test (PPT) with monofilament Postural blood pressure drop	≥2 of the scales abnormal (NSS>4, NDS>5, PPT<6, fall in systolic blood pressure of ≥20 mmHg)	DM: 13.1% New DM: 7.1% IGT: 5.7% IFG: 5.6% NGT: 2.8%
Ziegler[27] Germany 1997-1998	Participants with self-reported diabetes from two surveys of the MONICA/KORA study, aged 24-74 years	Matched (age and sex) nondiabetic subjects were assessed with OGTT to determine glycemic status	DM: 195 IGT: 46 IFG: 71 NGT: 81	Michigan Neuropathy Screening Instrument (MNSI)	MNSI > 2	DM: 28.0% IGT: 13.0% IFG: 11.3% NGT: 7.4%
Dyck[28] USA 2004	Patients known as having impaired glycemia were selected through databases and assessed with OGTT	Patients known as having a normal glucose, matched on age and sex, were assessed with OGTT	New DM: 218 IG: 174 NGT: 150	Neuropathy Symptoms and Change (NSC) Neuropathy Impairment Score (NIS) Composite scores of nerve conduction	Clinical judgment after abnormality in nerve conduction, NSC or NIS	New DM: 17.4% IG: 12.6% NGT: 12.7%

Case-control studies reporting prevalence of polyneuropathy in patients with diabetes, prediabetes and a population-based control group

[a] Males 9.8%, females 11.8%. No numbers of total males and females are reported, average could not be calculated.

[b] Probable and definite polyneuropathy are both considered polyneuropathy.

OGTT: oral glucose tolerance test; DM: diabetes mellitus; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; NGT: normal glucose tolerance; IG: impaired glycemia: IFG, IGT or impaired HbA1c

In the Italian Longitudinal Study on Aging (ILSA), a population-based cohort study, the prevalence of polyneuropathy was also investigated (Table 3).[35] Participants were randomly included from eight municipalities, based on population registries (704 participants per municipality, 88 males and 88 females per 5-year age group; range 65 to 84 years). The polyneuropathy screening procedure consisted of an interview about symptoms ("have you ever had the feeling of burning pain and/or numbness, or paresthesia in the feet or legs"), a previous neuropathy diagnosis ("has a doctor ever told you that you suffer from neuropathy of the legs") and drug treatments and of a brief neurological examination (heel gait, ankle tendon reflexes and touch and pain sensation), administered by a clinical investigator. Individuals with a self-reported diagnosis, at least one symptom, or at least one abnormal test on the examination underwent a clinical work up, which consisted of an evaluation of the medical history, an extensive neurological examination and a review of medical records. Nerve conduction studies and laboratory investigations were not part of the study protocol, but information about these measurements was extracted from medical records if available. The screening procedure had a sensitivity of 94.7% and a specificity of 70% in a pilot study of 20 cases and 20 controls. The ILSA study reported an adjusted prevalence of 7.0% among 4500 participants aged 65-84.[35] Three years after the baseline investigation, 2845 participants were screened for a second time with the same case-finding procedure. This yielded an incidence rate of 7.9 per 1000 person-years.

Other studies that are listed in Table 3 include four database studies.[30-32, 39] Two database studies used hospital registries to identify patients with polyneuropathy from a specific community.[32, 39] The other two additionally used medical records and notes from general practices.[30, 31] The diagnosis of polyneuropathy was based on the clinical picture, complemented with EMG according to local guidelines. In one study, no polyneuropathy definition was reported.[30] With this database approach, only registered cases are used to calculate prevalence or incidence rates, taking the whole population of the community as the denominator. The last two studies described in Table 3 include one general practitioner study assessing elderly with a less strict definition of polyneuropathy (at least one bilateral peripheral neurological deficit)[33], and one study investigating only idiopathic polyneuropathy in Gulf war veterans.[34]

Age and sex-specific prevalence across all studies

Studies that reported age-specific prevalence rates consistently showed a higher polyneuropathy prevalence in higher age categories of the studied population.[12, 15, 17, 19, 20, 27, 29, 35, 38, 39] Crude sex-specific prevalence rates are less consistent; most authors reported a higher prevalence in females, with a ratio of 1.5-2:1.[15, 17, 19, 20, 35, 36] Two of these studies reported age-standardized, sex-specific prevalence rates and showed

Table 3. Cohort studies reporting prevalence of polyneuropathy

Study and study period	Population	Age of the study population	Assessment protocol	Definition of polyneuropathy	Prevalence of polyneuropathy
Beghi[29] Italy 1990-1993	4191 patients seen in GP's office consultations for any reason	All >55 years	Questionnaire followed by examination (strength, sensation, reflexes) when ≥2 symptoms	Possible: ≥1 abnormal item of exam Probable: ≥ 2 abnormal items	Crude: 3.6%[a] Adjusted: 3.5%[b] - Diabetes: 44% - Neoplasm: 10% - Alcohol: 6%
Nakashima[30] Japan 1991	Database of 7685 residents of Daisen Town	All ages included, about 45% >50 years	Medical records of hospitals, GPs and other sources	Not specified	Crude: 3.3 per 1000 Adjusted: 2.2 per 1000[c]
MacDonald[31] Norway 1999	Database of 27657 subjects from 3 GP practices in London	All ages included, about 28% >50 years	Medical records and notes from GPs and referral hospital	Clinical objective signs in the presence of an established cause, such as diabetes. Alternatively, an EMG diagnosis was required	Diabetes: Adjusted: 2 per 1000[d] Other (excluding alcoholic): Adjusted: 1 per 1000[d] Incidence[e]: Diabetes: adjusted: 0.5 per 1000/yr[d] Other: adjusted: 0.2 per 1000/yr[d]
Mygland[32] Norway 1999	Database of 155464 inhabitants of Vest-Agder	All ages	Database of all patients with polyneuropathy referred to the only neurology center in the county	Clinically and electrophysiologically classified	Crude: 1.2 per 1000 - Idiopathic: 26% - Diabetes: 19% - Hereditary: 12% - Alcohol: 10% - CIDP: 8%
Mold[33] USA 1999-2000	795 non-institutionalized subjects recruited from 9 GP practices	All >65 years	Symptom questionnaire, fine touch, position and vibration sensation and ankle reflexes	1 or more complete bilateral peripheral neurologic deficits	Crude: 30.9%
Eisen[34] USA 1999-2001	1061 deployed and 1128 non-deployed Gulf war veterans	Mean age 31-33 years	Neurologic examination and nerve conduction studies	Idiopathic distal sensory, motor or sensorimotor polyneuropathy based on exam and/or NCS[f]	Crude: Deployed: 4.8% Non deployed: 5.9%
Baldereschi[35] Italy 1992-1993	4500 participants of the Italian Longitudinal Study on Aging (ILSA); population-based cohort study	65-84 years	Screening: self-reported diagnosis, symptoms, ankle reflexes, heel gait, touch and pain sensation. Diagnosis: clinical judgment	Full neurological exam, history and record review when positive on any of the screening items Diagnosis: clinical judgment	Crude: 7.4% Adjusted: 7.0%[g] - Diabetes: 39.2% - Idiopathic: 51.5%

Table 3. (*continued*)

Study and study period	Population	Age of the study population	Assessment protocol	Definition of polyneuropathy	Prevalence of polyneuropathy
					- Other: 9.3% Incidence: 7.9 per 1000/yr
Bruce[36] Canada 2003	467 nonpregnant community members of the Sandy Bay First Nation	All >18 years >50y: 18%	10-g Monofilament on 10 sites of the foot	Unable to sense monofilament on one or more sites	Crude: 7.3%
Lin[37] China 2009	5385 subjects from the She population of China	All > 20 years, mean age 47 years	Toronto Clinical Neuropathy Scoring System (TCSS)	TCSS ≥ 6	Crude: 12.6%
Lu[38] China 2011-2012	2035 nonpregnant Han community members without type 1 diabetes or renal failure	All >25 years	Modified Neuropathy Deficit Score (NDS) and Neuropathy Symptom Score (NSS)	NDS ≥ 6, or NDS ≥ 3 and NSS ≥ 5	Crude: 4.0%
Visser[39] Netherlands 2010	Adult population of the province of Utrecht: 953110	All ≥18 years	New cases that are registered in databases of all hospitals in the proximity of the province of Utrecht during a period of 1 year	Local guidelines: combination of symptoms and deficits compatible with polyneuropathy and diagnostic work-up for etiological diagnosis	Only incidence: Crude: 0.7/1000/yr Adjusted: 0.5/1000/yr[h] - Diabetes: 32% - Idiopathic: 26% - Toxic: 14% - Immune-mediated: 9%

Cohort studies reporting prevalence of polyneuropathy in a general population

[a] Average probable polyneuropathy prevalence from two regions

[b] Age- and sex-standardized to the 1990 Italian population

[c] Age- and sex-standardized to the 1990 Japanese population

[d] Age- and sex-standardized to the 1991 United Kingdom population

[e] Incidence was calculated with data from 13 general practices, covering a population of 100230 patients

[f] Only idiopathic or unexplained neuropathy. Alcohol abuse, HIV, hypothyroidism diabetes and medication excluded

[g] Age- and sex-standardized to the 1992 Italian population

[h] Age- and sex-standardized to the WHO world standard population

that this female predominance is not confounded by age.[20, 35] Other studies found no difference[27, 38], or a slight opposite result with a female:male ratio of about 1:1.4.[22, 39]

Risk factors for chronic polyneuropathy

Several diseases and factors have been associated with polyneuropathy. Since polyneuropathy probably is a multifactorial disease, it is not entirely appropriate to attribute the development of polyneuropathy to only one factor. These factors should be considered as component causes, and not as one sufficient cause. For instance, not all patients with diabetes or alcoholism will develop polyneuropathy, so multiple (known and unknown) component causes probably contribute to the development of the disease.[41] In clinical practice often one factor or disease, such as diabetes or alcohol abuse, is considered as a main (sufficient) cause of polyneuropathy in an individual. Some of the aforementioned survey studies sub-classified polyneuropathy according to these different causes. Tropical neuropathies like leprosy are common causes of polyneuropathy in developing countries such as Nigeria, whereas diabetes is more common in countries or study populations with a higher socio-economic status like Italy, the Netherlands and Spain (Table 1 and 3). However, there is not much population-based data available.

Several investigators studied causes of polyneuropathy in hospital settings (Table 4).[32, 39, 42-48] In all of these studies, diabetes is the most common cause of polyneuropathy, accounting for 18-49% of all cases. Other known important causes of polyneuropathy include alcohol abuse, toxic agents, such as chemotherapeutic drugs, nutritional deficiencies, immune-mediated causes and hereditary factors. Despite laboratory investigations, the cause in patients with a chronic axonal polyneuropathy cannot be identified in 12-49%. Although there are probably some differences in the etiology of these polyneuropathy subtypes, it is likely that they share multiple common etiological factors. Investigation of risk factors in specific subtypes is therefore also important for polyneuropathy in general. Some of the most common conditions related to polyneuropathy and chronic idiopathic axonal polyneuropathy will be discussed briefly.

Diabetic polyneuropathy

Prevalence of diabetes is 6.4% worldwide and this number is expected to rise the next decades.[49] Diabetes can lead to several types of peripheral neuropathy, such as distal symmetric polyneuropathy, autonomic neuropathy, mononeuropathy and non-compressive radiculopathy. Polyneuropathy is the most common presentation.[50] The Italian General Practitioner Study Group reported a relative risk of polyneuropathy associated with diabetes of 8.8 (95% confidence interval 6.1-12.8).[51] Polyneuropathy occurs in up to 50% of patients with diabetes and diabetes accounts for 18-49% of all polyneuropathy cases (Table 3). Sensory symptoms are usually more prominent than motor involvement and neuropathic pain is a common disabling symptom, occurring in 40-60% of patients

Table 4. Hospital-based studies investigated causes of polyneuropathy

Study	George[42]	Lin[43]	Johannsen[44]	Mygland[32]	Verghese[45]		Rosenberg[46]	Vrancken[47]	Rudolph[48]	Visser[39]
Country	UK	Taiwan	Denmark	Norway	USA		Netherlands	Netherlands	Norway	Netherlands
Study period	1980-1984	1988-1989	1993-1999	1999	1990-1999		1993-1997	1999-2002	2000-2005	2010
Population	Patients referred for NCS	Patients of neurological centers	Patients referred for NCS	Patients referred to neurologist	Patients referred for NCS		Patients at outpatient department	Multicenter study of patients with a diagnostic work-up for PNP	Patients referred to neurologist	New hospital-registered cases
Number of patients	74	520	147	192	231	171	172	137	226	743
Age	≥65	-	18-70	-	65-75	≥75	26-93	≥18	9-92	≥18
Associated risk factor (%)										
- Cryptogenic/CIAP	28	12	25	26	13	27	20	49[e]	28	26
- Diabetes	27	49	32	19	46	31	38	26	18	32
- Malignancy	13	2	1	4	3	4	1	3	3	-
- Inflammatory	11	8	2	8	7	4	1	4	16	9[f]
- Toxic medication	4	3	5	6	7	6	5	3	-	14[g]
- Connective tissue disorder/vasculitis	4	-	3	5	1	2	1	4	4	5
- Nutritional deficiency[a]	4	1	2	4	1	1	1	9	4	3
- Alcohol	3	9	19	10	6	1	9	6	10	14[g]
- Renal failure	3	4	1	-	2	2	4	4	-	4[h]
- Hereditary	1	4	1	12	7	8	3	7	14	5
- Sarcoidosis	1	-	-	2	-	-	1	-	-	-
- Hypothyroidism	-	2	-	-	1	1	1	3	4	4[h]

Table 4. (continued)

Study	George[42]	Lin[43]	Johannsen[44]	Mygland[32]	Verghese[45]	Rosenberg[46]	Vrancken[47]	Rudolph[48]	Visser[39]
- Ischemic	-	2	1	-	0	-	-	-	-
- Paraproteinemia	-	2	5	4	1	1	9	-	-
- Liver disease	-	1	-	-	-	-	-	1	-
- Infection[b]	-	-	1	1	0	1	-	2	-
- Critical illness	-	-	1	-	3	1	-	-	-
- HIV	-	-	1	-	-	12[d]	-	-	-
- Other causes	-	2	3[c]	-	2	-	-	-	-

[a] Including vitamin B1 and vitamin B12 deficiency
[b] Infection includes borrelia infection, leprosy and other unspecified infections
[c] 2% unspecified metabolic disorder. Thyroid dysfunction not reported
[d] HIV referral center
[e] Largest center is a CIAP referral center
[f] Inflammatory neuropathies in this study not only include GBS and CIDP, but also polyneuropathies associated with paraproteinemia, paraneoplastic antibodies/malignancy and HIV-associated neuropathy
[g] Toxic medication and alcohol abuse are combined in this study and accounts for 14%
[h] Thyroid dysfunction and renal function are combined in this study and accounts for 4%

with diabetic neuropathy.[50] Diabetic polyneuropathy has an axonal subtype in most cases. Treatment is mainly symptomatic. Potential modifiable risk factors associated with neuropathy in patients with diabetes include dyslipidemia, hypertension and obesity.[50, 52-56] Whether these factors also contribute to the development of polyneuropathy in non-diabetic subjects remains to be verified.

Alcoholic polyneuropathy

Polyneuropathy is reported to be present in 13-66% of chronic alcoholics, depending on diagnostic criteria used to diagnose neuropathy.[57, 58] The relative risk of polyneuropathy in chronic alcoholics is estimated at 3.9 (95% confidence interval 1.5-9.0).[51] There has been debate whether neuropathy in alcoholics occurs due to direct toxic effects of ethanol, due to a secondary thiamine deficiency or due to a failure of tissues to utilize thiamine in the presence of alcohol.[57, 58] Both alcoholic neuropathy and thiamine-deficiency neuropathy are mainly of the axonal type and are usually characterized by (painful) sensory disturbance and weakness in the distal parts of the lower extremities. Autonomic dysfunction often occurs. There is accumulating evidence that there are differences in the clinical phenotype between alcoholic neuropathy and thiamine-deficiency neuropathy. Pure alcoholic neuropathy without accompanying thiamine deficiency mainly affects small fibers, leading to slowly progressive sensory-dominant symptoms, neuropathic pain and impaired superficial sensation, whereas thiamine-deficiency neuropathy predominantly affects large fibers, leading to a more progressive, or even acute, polyneuropathy with predominantly motor symptoms.[57, 58] Since alcohol abuse often coexists with nutritional deficiencies, combined small and large fiber polyneuropathies are frequently found. Treatment, other than alcohol cessation and improvement of nutritional intake, is symptomatic.

Hereditary polyneuropathy

Hereditary motor and sensory neuropathy, also called Charcot-Marie-Tooth disease (CMT) is the most common form of inherited peripheral neuropathy. CMT has an estimated prevalence of 40-82 per 100 000 people.[59, 60] Mutations in genes encoding major structural proteins of myelin, axonal transport and mitochondrial metabolism have been described.[60] These gene mutations ultimately lead to slowly progressive weakness, wasting and sensory symptoms in distal body parts, starting at the feet. These patients usually have high arches, hammer toes and weakness and wasting of intrinsic muscles of the feet that will progress in the lower legs in later stages of the disease. There are demyelinating (CMT1, CMT3 and CMT4), axonal (CMT2) and mixed or intermediate (CMTX and dominant intermediate CMT) types of CMT. Age of onset, severity and type of symptoms, family history, presence of other neurological signs (such as involvement of the central nervous system), and especially nerve conduction studies can give clues

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to determine the specific subtype and possibly involved genes. No specific treatment is currently available.[59]

Inflammatory neuropathies

Inflammatory neuropathies are reported in 2-16% of all polyneuropathy cases depending on the clinical setting of the study (Table 4). Inflammatory neuropathies can present as a rapidly progressive sensorimotor polyneuropathy with a nadir within 4 weeks, known as the Guillain-Barre syndrome[61] and as a more chronic, relapsing-remitting or gradually progressive polyneuropathy that develops over a period of more than 8 weeks, as in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).[62]

CIDP is the most common chronic acquired demyelinating polyneuropathy. Prevalence rates vary between 1 and 7 per 100 000 people, but this may be an underestimation since the clinical presentation can be rather diverse, leading to under diagnosis.[62] CIDP likely has an autoimmune origin and is a treatable disorder. Patients can be treated with intravenous immunoglobulins, steroids or plasma exchange.[62, 63]

Other causes

There are many more factors, such as vitamin B1 or B12 deficiency, paraproteins, connective tissue disorders (systemic lupus erythematosus, Sjögren's syndrome) and toxic agents (like chemotherapy) that are associated with polyneuropathy. When patients over the age of 50 have a slowly progressive symmetrical axonal polyneuropathy and no cause can be established, these individuals are usually diagnosed as chronic idiopathic axonal polyneuropathy (CIAP).[64-68]

Chronic idiopathic axonal polyneuropathy

CIAP occurs in 12-49% of polyneuropathy cases (Table 4), depending on the clinical setting (secondary versus tertiary center, or referral center for specific diseases). Precise population-based prevalence estimates are lacking. A recent population-based database study from the Netherlands reported that 26% of incident polyneuropathy cases were idiopathic. An incidence rate of 30.3/100 000 person-years for persons 40 years or older was found.[39]

CIAP is characterized by an insidious onset of symptoms usually starting in the sixth decade or later, and seems to affect males more than females.[10, 39, 64, 69] Symptoms are predominantly sensory, characterized by distal loss of sensation (pain, numbness and tingling), with or without weakness. The legs are more affected than the arms and distribution is usually symmetrical. The disease is slowly progressive and most patients remain ambulatory with mild to moderate disability, but all patients experience a reduced quality of life. Neurological examination shows decreased or loss of vibration sense, diminished perception of pain and light touch in a stocking like distribution and

ankle reflexes are often absent.[64, 70] Electrophysiological examination shows features of an axonal polyneuropathy, usually with reduced or absent sensory nerve action potentials of the sural nerves and decreased amplitudes of the peroneal compound motor action potential.[64, 70] Quantitative sensory testing may show abnormal temperature and vibration thresholds.[70] Diagnostic criteria have been developed to improve recognition and diagnosis of CIAP.[70]

CIAP probably constitutes of a heterogeneous group of conditions. Current research suggests a role for the metabolic syndrome, which includes impaired glucose tolerance, dyslipidemia, hypertension and obesity.[65] Studies showed that the metabolic syndrome is an independent risk factors for macro- and microvascular complications such as retinopathy, nephropathy and neuropathy in patients with diabetes.[54, 71, 72] Studies also showed that the metabolic syndrome is more prevalent in patients with CIAP.[65, 73] Impaired glucose metabolism probably is the most important factor attributing to the development of polyneuropathy, although results are not entirely consistent. Independent associations with dyslipidemia and obesity have also been reported.[22, 27, 28, 65, 68, 73-80] It is likely however that yet undiscovered factors also contribute to the development of CIAP.

DISCUSSION

We identified 29 population-based studies that investigated the epidemiology of polyneuropathy. There is a large variation in reported prevalence rates across these studies (0.1-12.6% across all ages, 1.9-30.9% in elderly), which is probably due to the diversity in assessment protocols, definition of polyneuropathy, study populations and study designs. Many studies rely on a two-step screening protocol. Participants are screened with a questionnaire, sometimes in combination with a short neurological examination, and only screen-positive participants are examined by a trained physician, usually a neurologist. In order to get a valid estimate of the prevalence of a disease, this first stage should identify all cases as screen-positive (sensitivity should be 100%). A low number of screen positive participants without disease (high specificity) is also preferred, especially when resources and time are limited. Studies that do not use a two-step approach, but only use symptoms or signs, or a combination of both into a component score as diagnostic protocol need to be both sensitive and specific in order to obtain a valid estimate of the prevalence.

Most information is derived from door-to-door survey studies. An advantage of these studies is that similar research protocols have been used in large study populations and that the diagnostics can be done with relatively few resources. These studies give insight in the epidemiology of several neurological disorders, but may underestimate the prevalence of polyneuropathy, since subclinical polyneuropathy can be missed and

refusal to participate in the study may give rise to selection bias. As these studies were not primarily focused on polyneuropathy and did not include an extensive neuropathy work-up, including nerve conduction studies, the results highly depend on the sensitivity of the screening procedure in the first stage, which is often not optimal. Despite this, most studies report a high sensitivity for the entire screening protocol. Overall, prevalence of polyneuropathy in door-to-door survey studies from developed countries seems higher than in studies performed in developing countries. This may partly be explained by a larger proportion of elderly people included in studies from developed countries. Standardizing prevalence to the same reference population is helpful to investigate this confounding effect of age, but unfortunately not many studies have standardized their prevalence rates. Other reasons for this variation can be differences in genetic, socioeconomic and environmental factors and differences in prevalence of associated risk factors for neuropathy. For example, alcohol consumption is considered to be less common in most developing countries[81], and prevalence of diabetes is lower, especially in Africa.[49]

The case-control studies that were identified were primarily focused on determining an association between diabetes, prediabetes and neuropathy. Although these case-control studies give an estimate of the occurrence of non-diabetic polyneuropathy in controls, they are not suitable to give a population prevalence of polyneuropathy, because the distribution of cases and controls likely differs from the general population. Although three other studies included all inhabitants from a specific community before stratifying for diabetes, the assessment methods (with low sensitivity or low specificity), exclusion criteria or low participation rate, indicate that the population prevalence estimates are most likely overestimated or biased.[36-38]

The four database studies that investigated the frequency of polyneuropathy probably all underestimate the true incidence or prevalence, since only previously diagnosed patients were identified in these studies. Symptomatic individuals who do not visit a doctor, asymptomatic individuals, and individuals not being referred to a hospital (in case of hospital-based database studies) because there is a clear cause for the complaints (e.g. diabetes) are missed with this approach. The cohort study performed by the Italian General Practitioner Study Group was one of the first extensive community studies specifically designed to investigate polyneuropathy in an unselected elderly population. A 'probable' neuropathy was present in 4% and a 'possible' polyneuropathy was diagnosed in 7% of the participants who visited their general practitioner.[29] The results found in this study might lack validity due to selection bias. On the one hand, patients who visit a general practitioner may be less healthy and at a higher risk for polyneuropathy, due to chronic diseases or medication use, leading to an overestimated prevalence rate. On the other hand, some persons who have an increased risk to develop neuropathy, such as alcoholics or severely impaired patients, might be less likely to visit

a general practitioner, leading to an underestimation of the prevalence. An unselected sample of 93 patients from the same general practitioners was visited and assessed at home. In this small sample, probable polyneuropathy was present in 4.3%. This suggest a modest underestimation in the screened population (3.6%). However, prevalence might also be underestimated, because only symptomatic patients were included in the study and sensitivity of the screening instrument was only 78%. Moreover, nerve conduction studies were not performed.

The ILSA study reported a prevalence of polyneuropathy in persons over 65 years of age of 7%.[35] Participants were randomly selected from database registries, probably leading to an unbiased and random sample of the general population. The case-finding procedure had a desirably high sensitivity and did not only rely on symptoms. This probably resulted in the most unbiased and reliable estimate of the prevalence of chronic polyneuropathy in the general elderly population. However, nerve conduction studies were not part of the study protocol and no polyneuropathy work-up, including laboratory investigations, was performed. Therefore, detailed information about causes and subtypes of polyneuropathy was not available.

Both these cohort studies reported a polyneuropathy prevalence of around 7%[29, 35],which is much higher than the rates found in the door-to-door surveys, which are close to 1%.[13] In the two Italian cohorts only elderly were included and the screening protocols were primarily focused on the detection of polyneuropathy, whereas most survey studies screened for a variety of neurological disorders across all ages. This might explain the higher prevalence found in these cohort studies.

Almost all before mentioned studies, including the ILSA study, were performed fifteen to twenty years ago. Since that time, life-expectancy, the proportion of elderly in the population and prevalence of obesity and diabetes increased.[49, 82] Perhaps this resulted in an increase in the incidence of polyneuropathy as well, which is also suggested by the results of the survey study performed in Albania from 2006 to 2008.[20] This study reported a polyneuropathy prevalence of 3% in the total general population (including all age categories), using a similar screening method as the Italian General Practitioner Study Group. Whether polyneuropathy is truly more prevalent than it was 20 years ago has to be confirmed in properly designed, large population-based studies.

CONCLUSIONS AND FUTURE DIRECTIONS

Prevalence of polyneuropathy in the general population ranges from 1% to 3% and increases to 7% in the elderly. Prevalence seems to depend on socioeconomic status and the age distribution of the study population. In developing countries the prevalence is lower, which can possibly be explained by a smaller proportion of elderly in the popula-

tion and by differences in the prevalence of polyneuropathy risk factors. Life-expectancy and prevalence of associated risk factors have increased in the last decades. Whether this resulted in more patients with polyneuropathy is yet unknown. There is a need for more, properly designed, large studies that investigate the prevalence and risk factors of polyneuropathy in the general population. A cohort study of a general, unselected population would be the most ideal study design to give an unbiased estimate of the prevalence and incidence of polyneuropathy. Population surveys may also be used, but in general, available data and case definitions in these studies are less detailed than in cohort studies. To assess risk factors for polyneuropathy, case-control studies may be more efficient than cohort studies, but may also be more prone to biases. Heterogeneity in polyneuropathy definitions in past studies makes comparison between studies difficult. To overcome this, future studies should use a similar definition and screening protocol for polyneuropathy. Unfortunately, a gold standard test for polyneuropathy does not exist. A combination of neuropathic symptoms, neuropathic signs and abnormal nerve conduction studies provides the most accurate diagnosis of polyneuropathy. Therefore investigating prevalence of polyneuropathy in a large population is challenging. Ideally, new studies should uniformly include all these three aspects.[7] Standardizing results to a reference population is encouraged in order to ease comparison between studies.

Hopefully, future large prospective cohort studies that assess the presence of chronic diseases together with cardiovascular, metabolic, hereditary and lifestyle factors will also focus on disorders of the peripheral nervous system. These studies should also incorporate the assessment of polyneuropathy both cross-sectionally and longitudinally during follow-up over the years. This will hopefully give insight into new risk factors for this disabling condition.

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Chapter 3.2

Prevalence of polyneuropathy in the general middle-aged and elderly population: the Rotterdam Study

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ABSTRACT

Objectives: To determine the prevalence of chronic polyneuropathy in an unselected community-dwelling population of middle-aged and elderly people.

Methods: The current study was embedded in the prospective, population-based Rotterdam Study. Between June 2013 and October 2015, 1310 participants (mean age 70 years, 55% female) were screened for the presence of polyneuropathy. This screening consisted of a questionnaire, neurological examination and nerve conduction studies. Polyneuropathy was diagnosed by a consensus panel that categorized participants into no, possible, probable or definite polyneuropathy, depending on the level of abnormality of the screening. Medical records were scrutinized to evaluate whether the disorder was diagnosed before and laboratory investigations were performed to determine the presence of associated risk factors.

Results: Prevalence of definite polyneuropathy was 5.5% (95% confidence interval 4.4-6.9), age-standardized to the population of the Netherlands 4.0% (3.1-5.3). Prevalence was higher in males (6.7% compared to 4.5%) and increased with age. When combining probable and definite polyneuropathy, age-standardized prevalence was 9.4% (7.9-11.1). Almost half of the polyneuropathies (49%) was newly diagnosed. The majority of polyneuropathies was idiopathic (46%). Diabetes, present in 31% of participants with polyneuropathy, was the most commonly found risk factor.

Conclusions: Prevalence of polyneuropathy in the general middle-aged and elderly population is at least 4%, and increases with age. Almost half of the cases was newly diagnosed, indicating that the presence of polyneuropathy is underreported or underdiagnosed. Currently, almost half of the polyneuropathies is idiopathic. Future prospective cohort studies should focus on identifying new determinants of polyneuropathy.

INTRODUCTION

Chronic polyneuropathy, or distal symmetric neuropathy, is a commonly seen disabling neurological disorder.[1-6] Patients suffer from cumbersome sensory and motor symptoms that can lead to falls, amputations, impairment in daily activities and other comorbidity. Despite this, polyneuropathy remains an under acknowledged disorder in daily practice, both by patients and medical practitioners.[1, 2, 7]

There is little reliable population-based information about the frequency of chronic polyneuropathy available. The majority of previous studies used less than optimal screening methods and were performed almost two decades ago.[5] More recent studies used medical databases of registered polyneuropathy cases[1, 8, 9], which probably led to an underestimation of the prevalence, since polyneuropathy is often underreported.[3] Since life-expectancy and incidence of cardiovascular and metabolic diseases have increased the last decades, it is likely that prevalence of polyneuropathy has increased likewise, especially in a rapidly aging population.[5, 10] However, extensive population-based studies that study trends in the frequency of polyneuropathy, utilizing a full work-up, including nerve conduction studies (NCS) and laboratory investigations to screen for putative causes do not exist.[5]

Therefore, we prospectively screened participants of the population-based Rotterdam Study to investigate the prevalence and risk factors of polyneuropathy in a middle-aged and elderly population.

METHODS

Study population

This study was embedded in the prospective population-based Rotterdam Study, a cohort study in the Netherlands, that focuses on the epidemiology of chronic diseases in elderly.[11] In 1990 and 2000, inhabitants aged 55 years and older living in a well-defined district of Rotterdam, a homogenous middle-class population, predominantly of Caucasian origin, were invited to participate. In 2006, the study was extended with inhabitants aged 45 years and older. In total, 14926 participants (response rate 72%) participated in the Rotterdam Study. Every three to four years, all participants undergo a comprehensive set of interviews and examinations.

From June 2013 onwards, polyneuropathy screening was included in the core protocol of the Rotterdam Study. The current study includes all participants that underwent the polyneuropathy screening between June 2013 and September 2015. During this period, 1544 participants were randomly invited. Ninety-three participants did not undergo the screening procedure, mainly due to logistic reasons in the initiation phase
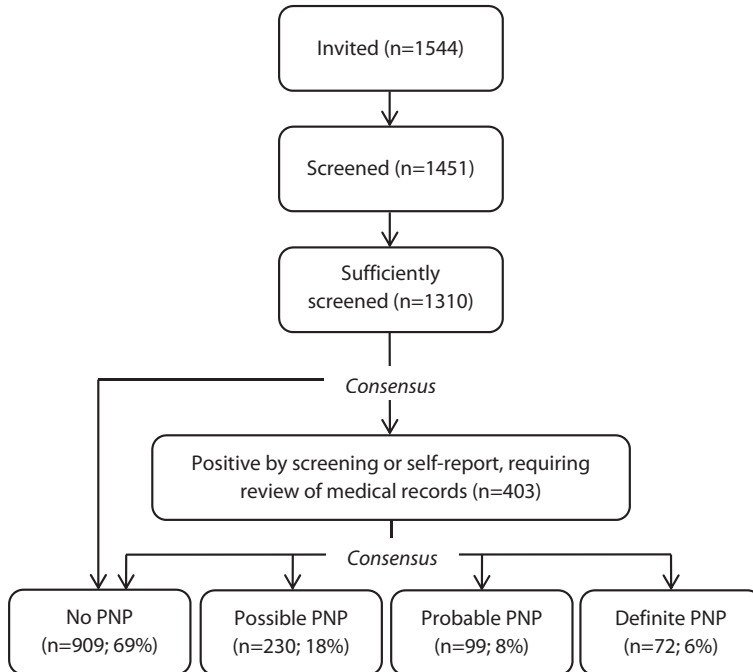
Figure 1. Flowchart of the study population and case-finding procedure. In total, 1544 participants were invited. After exclusion of participants that did not (completely) undergo the screening 1310 participants were included in the study. A consensus panel categorized participants based on the results of the screening (questionnaire, neurological examination, nerve conduction studies and self-report) and review of medical records. In two persons medical records were reviewed because of a self-reported diagnosis of polyneuropathy, while the rest of the screening was completely normal. Since no diagnosis of polyneuropathy was found in their medical records, these persons were categorized as no polyneuropathy.

of the study. Additionally, 141 participants were excluded because there was insufficient data collected to complete the diagnostic process. In total, 1310 people were included (Figure 1).

Standard protocol approvals, registrations and patient consents

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Polyneuropathy screening

We implemented a protocol to screen participants for polyneuropathy, comprising an in-person screening, self-report and review of medical records. In-person screening

comprised three components: a symptom questionnaire, a standardized neurological examination, and short non-invasive NCS. Items of the examination and NCS were chosen after consulting with experts worldwide in the field of polyneuropathy. The examinations were performed by carefully trained examiners and a high quality was ascertained by routine checks and repeated training.

Neuropathic symptoms were evaluated with a questionnaire that was based on previous studies.[4, 12, 13] Participants were asked whether they bilaterally experienced tingling or prickling sensations, burning, cotton-wool feeling while walking, muscle cramps, muscle pain, stabbing pain, weakness, numbness, tightness, and allodynia in the legs or feet during the last three months. Answers included 'never', 'sometimes' and '(almost) continuously'.

The presence of neuropathic signs was assessed with a neurological examination of the legs. Examination involved bilateral assessment of tendon reflexes, several sensory modalities and muscle strength of the feet. Ankle and knee tendon reflexes were assessed in seated position and scored as normal, reduced, or absent. Vibration sense was evaluated using a Rydel-Seiffer tuning fork, a graduated tuning fork that carries calibrated weights imprinted with a scale from 0 (minimum score) to 8 (maximum score), which can be used to determine vibration thresholds.[14] Vibration thresholds were determined at the hallux of both feet. Superficial pain sensation was evaluated using a disposable wooden pin. Stimulation was applied on the lower legs, starting on the knee and descending the anterior lower leg towards the big toe. When participants reported a numb feeling right from the start at the level of the knee, the examination was extended to a more proximal part of the leg. Sensation was scored as normal, abnormal distal of the toes, ankles, lower part of the lower leg, knee, or abnormal from above the knee. Muscle strength of the anterior tibial muscles was scored with the modified, Rasch-built Medical Research Council (MRC) grading scale.[15] In this scale, the six options of the original MRC score have been reduced to 4 options: paralysis, severe weakness (>50% loss of strength), slight weakness (<50% loss of strength) and normal strength. Dorsiflexion of the feet was also tested by asking the participants to stand on their heels, using balance support if necessary.

NCS were performed using a Nicolet™ Viking Quest (Natus Medical Incorporated, San Carlos, California, USA). The sural sensory nerve was measured bilaterally and the peroneal motor nerve unilaterally. Together these nerves are considered the most sensitive nerves to detect polyneuropathy.[16] The distal peroneal nerve compound muscle action potential (CMAP) amplitude and distal motor latency (DML) were recorded at the extensor digitorum brevis muscle. Stimulation was applied to the anterior side of the ankle, 8 cm proximal to the recording electrode. CMAP baseline-peak amplitudes below 1.1 mV and DML values above 6.5 ms were considered abnormal.[17] Sural sensory nerve action potential (SNAP) amplitudes were measured bilaterally with a standard recording

electrode placed behind the lateral malleolus. Stimulation was applied on the posterior side of the calf, 14 cm proximal to the recording electrode. SNAP baseline-peak amplitudes below 4.0 μV were considered abnormal.[18] Electrophysiology was performed using standard techniques of percutaneous supramaximal stimulation. The setting of our study did not allow extensive NCS in upper and lower extremities or invasive needle examination. NCS were performed at room temperature. Limb temperature was measured and documented, but maintaining the limb temperature above a certain degree was not possible in the current setting.

Case ascertainment and diagnostic work-up

Since there is no gold standard test for polyneuropathy, we discussed each individual participant case by case in an expert panel, using all collected information on symptoms, signs and NCS, to diagnose polyneuropathy. This panel was led by a neuromuscular specialist (PvD) and also included a neurophysiology specialist (JD) and a physician trained in epidemiology with a special interest in neuromuscular diseases (RH). In panel discussions, participants were categorized into "no", "possible", "probable" or "definite polyneuropathy", depending on the perceived likelihood of the diagnosis.[16] Participants were discussed until unanimity was reached.

Each screening component (questionnaire, examination and NCS) was evaluated separately, before establishing the overall conclusion. Like in clinical practice, the panel judged whether symptoms, as assessed with the questionnaire, matched symptoms of polyneuropathy (e.g. sometimes occurring tingling, cramps or muscle pain was judged to be within the spectrum of normal). The examination was deemed compatible with polyneuropathy when multiple items of the examination were abnormal; to be compatible with usual neurological decision making, decreased tendon reflexes or vibration sensation alone was considered to be insufficient to be rated as abnormal. Furthermore, since polyneuropathy generally is a symmetrical disorder, the items of the examination were only considered compatible with polyneuropathy if both sides were abnormal, to avoid symptoms not caused by a polyneuropathy. As a result, asymmetric neuropathies, like mononeuritis multiplex, multifocal motor neuropathy and multifocal acquired demyelinating sensory and motor neuropathy may be missed. These disorders however are extremely rare in the general population.[19] NCS were interpreted using published normal values[17, 18], while taking limb temperature into consideration. Sural SNAP amplitudes were considered to be the most sensitive parameters. Bilateral abnormal sural SNAP amplitudes were considered reflective of polyneuropathy. When only a single sural nerve measurement was available (e.g. due to signal disturbance), the peroneal CMAP amplitude was used to assess abnormality. If both the sural SNAP amplitude and the peroneal CMAP amplitude were abnormal, results could also be considered compatible with polyneuropathy.

Medical records of participants with one or more abnormal components of the screening were scrutinized to investigate whether participants were previously diagnosed with polyneuropathy. Records were also reviewed when participants self-reported a diagnosis of polyneuropathy. Participants who were previously diagnosed by a neurologist were categorized as definite polyneuropathy, irrespective of the results of the panel, since we consider a complete polyneuropathy work-up according to hospital guidelines executed by a neurologist superior to our screening. Definite polyneuropathy was also diagnosed when symptoms, signs and NCS were all abnormal. Occasionally, when NCS were unavailable but symptoms and signs were abundantly clear, participants could still be considered as having definite polyneuropathy when the panel was unanimously convinced of the certainty of this diagnosis. This occurred in 7 instances. When none of the components was abnormal, participants were categorized as no polyneuropathy. Participants who met neither the definite, nor the no polyneuropathy criterion, were categorized as possible or probable polyneuropathy, depending of the level of abnormality. Typically, participants were categorized as possible polyneuropathy when one component was abnormal and as probable polyneuropathy when two components were abnormal. Participants with missing data in more than one component were excluded (n=141).

Participants with newly diagnosed definite polyneuropathy underwent extra blood sampling to screen for associated risk factors, such as vitamin deficiencies (B1, B12), presence of monoclonal gammopathies and thyroid dysfunction. Routine blood sampling of the Rotterdam Study included measurement of fasting glucose. Information about alcohol use (self-reported), and medication use was also collected. Diabetes was defined as a fasting glucose level >7.0 mmol/L, a non-fasting glucose level >11.1 mmol/L (when fasting data was not available) or use of anti-diabetic therapy. Medical records were reviewed for known causes of polyneuropathy in all definite polyneuropathy cases.

Data analysis

Prevalence of polyneuropathy was calculated by dividing the number of cases by the total number of participants in the respective groups. We reported crude prevalence with confidence intervals (Wilson interval[20]), as well as age-standardized prevalence, standardized to the 2013 population of the Netherlands[21], European Union[22], WHO population[23] and the 2010 Census population of the United States of America[24], restricted to persons over 50 years of age. Age-standardization adjusts rates to take the age structure of the study population into account. Standardized prevalence was calculated using the direct method of standardization; 95% confidence intervals were calculated with the method described by Fay and Feuer[25], using R version 3.2.1. Difference in prevalence between sexes (age-adjusted) and age decades (sex-adjusted) was tested with logistic regression using SPSS, version 21.

RESULTS

In total, 1310 participants were sufficiently screened for polyneuropathy (Table 1). This sample consisted of 55% females and 45% males. Mean age was 70 years (range 52-95 years).

In total, 72 participants were diagnosed with definite polyneuropathy (Table 1 and Figure 1). The crude prevalence of polyneuropathy was 5.5% (95% Confidence Interval 4.4-6.9). Age-standardized prevalence to the population of the Netherlands was 4.0% (3.1-5.3) and to the USA population 3.9% (2.9-5.2). Prevalence was slightly higher in males than in females (6.7% compared to 4.5%, p-value 0.09), and was higher in older people (p-trend <0.01). When applying a wider definition of polyneuropathy, which combined probable and definite polyneuropathy (see Table 1 and Figure 2), crude prevalence was 13.1% (11.3-15.0).

In 49% of cases with definite polyneuropathy, this had not been previously recognized. This proportion was higher among females and subjects without diabetes (Table 2). Of those that were already diagnosed with a polyneuropathy, more than half (51%) responded negatively on the question "have you ever been diagnosed with polyneuropathy".

Table 1. Sex- and age specific prevalence of polyneuropathy

	Population, n	Prevalence of definite polyneuropathy, % (95% CI)	Prevalence of probable and definite polyneuropathy, % (95% C.I.)
Total sample	1310	5.5 (4.4-6.9)	13.1 (11.3-15.0)
Age-standardized			
Dutch population 2013		4.0 (3.1-5.3)	9.4 (7.9-11.1)
European Union population		4.3 (3.3-5.6)	10.0 (8.5-11.8)
USA 2010 census population		3.9 (2.9-5.2)	9.0 (7.6-10.8)
WHO standard population		3.4 (2.5-4.7)	7.9 (6.5-9.6)
Stratified by sex			
Males	595	6.7 (5.0-9.0)	14.6 (12.0-17.7)
Females	715	4.5 (3.2-6.3)	11.7 (9.6-14.3)
Stratified by age			
50-60	250	1.2 (0.4-3.5)	2.4 (1.1-5.1)
60-70	439	3.9 (2.4-6.1)	8.0 (5.8-10.9)
70-80	341	4.4 (2.7-7.1)	12.6 (9.5-16.6)
>80	280	13.2 (9.7-17.7)	31.1 (25.9-36.7)

Sex- and age specific prevalence, with 95% confidence intervals, of definite and combined probable and definite polyneuropathy in participants of the Rotterdam Study. Crude as well as age-standardized prevalence is reported.
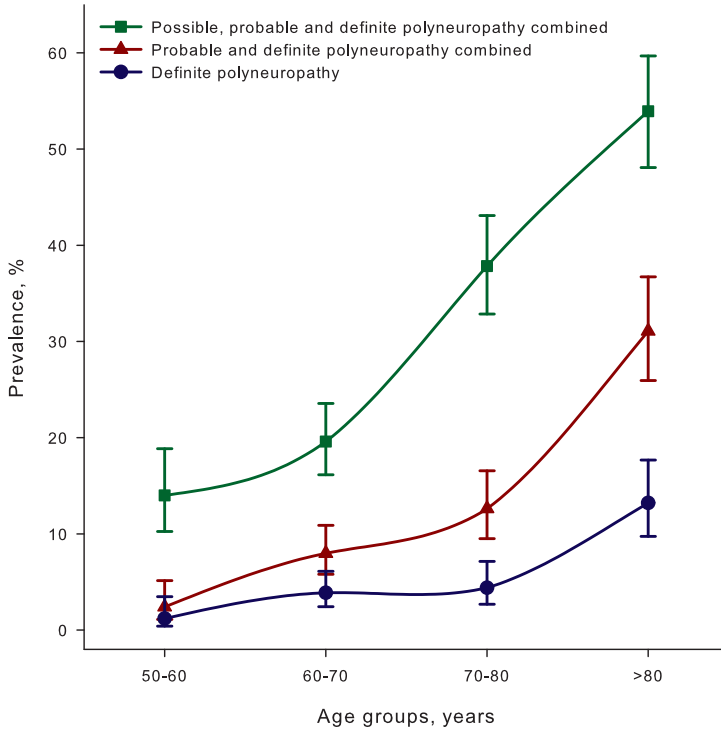
Figure 2. Prevalence of polyneuropathy per age decade. The figure shows the age-specific prevalence of polyneuropathy, using different polyneuropathy definitions (green squares: possible, probable and definite polyneuropathy combined; red triangles: probable and definite polyneuropathy combined; blue dots: definite polyneuropathy).

Table 2. Proportion of previously and newly diagnosed polyneuropathy cases

	Previously diagnosed polyneuropathy, n (%)	Newly diagnosed polyneuropathy, n (%)	Total cases n/N
Total sample	37 (51%)	35 (49%)	72/1310
Males	24 (60%)	16 (40%)	40/595
Females	13 (41%)	19 (59%)	32/715
<60 years	1 (33%)	2 (67%)	3/250
60-70 years	9 (53%)	8 (47%)	17/439
70-80 years	7 (47%)	8 (53%)	15/341
>80 years	20 (54%)	17 (46%)	37/280
Participants with type 2 diabetes	17 (77%)	5 (23%)	22/181
Participants without diabetes	20 (40%)	30 (60%)	50/1109*

Number and proportion of newly diagnosed and previously diagnosed cases of definite polyneuropathy per sex, age decade and diabetes status.

* Diabetes status was unknown in 20 participants without polyneuropathy

Previously diagnosed polyneuropathies were mainly associated with diabetes, or were considered as chronic idiopathic axonal polyneuropathy (Table 3). Review of medical records and additional laboratory investigations in participants with newly diagnosed polyneuropathy revealed that in the majority no associated risk factor was present. Overall, 31% of participants with polyneuropathy had diabetes and in 46% of all polyneuropathy cases, no known risk factor was found. These cases can be considered as having idiopathic polyneuropathy (Table 3).

Table 3. Potential causes in cases with definite polyneuropathy

Associated risk factor	Cases with a previous diagnosis (n=37), n (%)	Cases with a new diagnosis (n=35), n (%)	All cases (n=72), n (%)
Diabetes	17 (46%)	5 (14%)	22 (31%)
Vitamin deficiency[a]	4 (11%)	6 (17%)	10 (14%)
Possible alcohol abuse[b]	2 (5%)	1 (3%)	3 (4%)
Toxic	3 (8%)	1 (3%)	4 (6%)
Hereditary	1 (3%)	-	1 (1%)
Immune-mediated[c]	4 (11%)	3 (9%)	7 (10%)
Thyroid dysfunction	2 (5%)	3 (9%)	5 (7%)
Renal failure	4 (11%)	1 (3%)	5 (7%)
Systemic disease[d]	2 (5%)	-	2 (3%)
No risk factor present/CIAP	13 (35%)	20 (57%)	33 (46%)
Total	52 (141%)	40 (114%)	92 (128%)

Presence of risk factors in participants with definite polyneuropathy, based on review of medical records in all definite cases, and additional laboratory investigations in newly diagnosed cases. Multiple risk factors may be present in one participant, the total may thus exceed 100%. Participants are diagnosed with chronic idiopathic axonal polyneuropathy (CIAP) when no risk factors were identified. Participants did not undergo genetic testing, therefore hereditary neuropathies were not evaluated.
[a] Vitamin B12 deficiency, none of the cases had a B1 deficiency
[b] Alcohol use as possible risk factor was defined as >21 glasses per week (based on self-report)
[c] Immune mediated includes monoclonal gammopathies and inflammatory neuropathies
[d] Systemic disease includes vasculitis and connective tissue diseases

DISCUSSION

The prevalence of polyneuropathy in our population-based study was 5.5%, which increased with age to 13% of persons over 80 years. In a substantial proportion of cases polyneuropathy was not previously diagnosed and of the participants with a previous diagnosis, a high proportion was unaware of having it. Approximately a third of participants with polyneuropathy concomitantly had diabetes, while the vast majority of polyneuropathies could be considered as idiopathic.

We screened participants with a protocol that included assessment of symptoms, a neurological examination and NCS. Previous studies included only symptomatic individuals or used less extensive screening methods, often consisting of only a single test, such as a monofilament.[5] Unfortunately, there is no simple diagnostic test that has a high sensitivity and specificity for the diagnosis of polyneuropathy. Screening tools have been developed that can help detect polyneuropathy, like the Michigan Diabetic Neuropathy Screen[26], Total Neuropathy Score[27] and Toronto Clinical Neuropathy Score.[28] However, these tools were designed to screen high-risk patients, such as diabetics or patients receiving chemotherapy. We did not use these tools, since their sensitivity and specificity have not been evaluated in an unselected, low-risk population, like ours.[29] Moreover, as opposed to assigning scores to symptoms and signs, we discussed all collected data from each participant in an expert panel to form an overall conclusion about polyneuropathy. With this approach we avoid making (arbitrary) cut-off points for the diagnosis. Additionally, in population-based research a consensus panel approach is as close to clinical practice as possible.

In our sample of middle-aged and elderly participants, we found a polyneuropathy prevalence of 5.5%. Age-standardized prevalence to the Dutch population and to the USA population was 4.0% and 3.9% respectively. In the USA, this relates to approximately 3.8 million persons over 50 years with polyneuropathy, with an additional 5 million persons when probable cases are also included. Aging of the population and the rising prevalence of diabetes, the most important risk factor for polyneuropathy, will probably lead to even higher numbers in the future.[30] Additionally, prevalence of prediabetes, obesity and metabolic syndrome, factors that have all been associated with polyneuropathy, is also reaching epidemic proportions.[10] This will probably contribute to a further rise in polyneuropathy cases.

Our age-standardized prevalence of 4.0% is lower than 7.0% found in the Italian Longitudinal Study on Aging (ILSA), the most comprehensive study on polyneuropathy prevalence that had been performed to date.[3] However, in this study polyneuropathy was clinically diagnosed without NCS. In our study the combination of probable and definite polyneuropathy would result in a standardized prevalence of 9.4%, which is perhaps better comparable. Importantly, similar to our study, a large proportion of cases in the ILSA was undiagnosed.[3] Aside from bothersome symptoms, polyneuropathy is also related to sleep disturbance, depression, impairment in daily activities, fall-related injuries and even mortality.[1, 7] This makes it an important health problem, posing a high burden on both individuals and society. Despite these disabling consequences, a substantial proportion of patients with polyneuropathy remains undiagnosed, and therefore probably not receiving appropriate treatment and education. Recognition, early detection and patient education of this common disorder is very important in order to prevent or treat comorbidity.

In addition to the prevalence of polyneuropathy, we also investigated how often associated risk factors were present in patients with polyneuropathy. Currently, most information about the distribution of risk factors for polyneuropathy originates from hospital-based studies, where referral bias is a serious issue. In these studies, roughly a third of polyneuropathy cases is considered as idiopathic.[5] In our study, this proportion was 46%. Aside from referral bias, this difference may be explained by the identification of milder forms of polyneuropathy, which are probably missed in hospital-based studies. However, detection of mild or early forms is crucial, since these are the patients that might benefit most from future interventions.

One of the strengths of our study is the population-based design of our study. Another important strength is the use of a polyneuropathy work-up that included NCS and review of medical records. To our knowledge, there are no other prospective population studies that included NCS. An advantage of population-based studies over clinical studies is the high external validity. However, we must note that our results may not directly translate to non-Caucasian populations. There are also other limitations to our study. First, there might have been some selection bias in our study population. We included relatively healthy individuals, since polyneuropathy was assessed in persons that visited the research center, which might have prevented persons with severe physical disability to participate. Second, we used a questionnaire instead of a live interview, which might have resulted in some misclassification due to bilateral radiculopathy or focal neuropathies. Additionally, misclassification may occur in elderly due to occurrence of non-specific symptoms attributable to osteoarthritis or other locomotor problems, and due to a lack of normative data for vibration sensation, ankle reflexes, and NCS for the oldest old. Differentiating normal aging from pathology can therefore be difficult. As a result, the prevalence in elderly might be overestimated. However, it is reasonable to assume that this misclassification is limited, because we combined symptoms, neurological examination and NCS to come to the overall conclusion. Another limitation is that we did not preheat the legs of participants before performing NCS. Some participants with cold feet might have had artificially high amplitudes. Therefore, although we did take the temperature into account, some NCS might have been misclassified as normal while in normal temperature the amplitudes would have been below the threshold for abnormality. In this case, our prevalence might be slightly underestimated.

Our study showed that polyneuropathy is a common disorder, especially in elderly. Polyneuropathy is an important health problem since it is associated with several comorbidities. Polyneuropathy is underdiagnosed and deserves more public attention. Future studies are required to estimate risks attributable to associated diseases, but also to find new, potentially modifiable determinants involved in the development and progression of polyneuropathy.

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Chapter 4

Determinants of polyneuropathy and peripheral nerve function

Chapter 4.1

Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: a prospective population-based cohort study

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ABSTRACT

Objective: Diabetes mellitus is a known risk factor for polyneuropathy, but the role of prediabetes and metabolic syndrome remains unclear. We aimed to investigate the role of these factors in a community-dwelling middle-aged and elderly population.

Methods: 1256 participants of the population-based Rotterdam Study (mean age 70.0, 54.5% females) were screened for polyneuropathy with a questionnaire, neurological examination and nerve conduction studies. Data on type 2 diabetes and components of metabolic syndrome were also collected. Logistic regression was used to investigate associations of diabetes, prediabetes, and metabolic syndrome and its separate components with polyneuropathy. Linear regression was used to investigate associations with nerve conduction parameters in participants without polyneuropathy.

Findings: Diabetes was associated with polyneuropathy (OR 3.01, 95% CI 1.60;5.65), while impaired fasting glucose was not (OR 1.55, 95% CI 0.70;3.44). Metabolic syndrome was associated with polyneuropathy (OR 1.92, 95% CI 1.09;3.38), with a stronger association when more components of the syndrome were present. Analyzing separate components of metabolic syndrome revealed associations for elevated waist circumference (OR 2.84, 95% CI 1.35;5.99) and elevated triglycerides (OR 2.01, 95% CI 1.11;3.62). Similar associations were found after excluding participants with diabetes. In participants without polyneuropathy, metabolic syndrome associated with lower sural sensory nerve action potential amplitudes.

Conclusions: Metabolic syndrome, abdominal obesity and dyslipidemia, are strongly associated with polyneuropathy, irrespective of the presence of diabetes. Metabolic syndrome also associates with impaired nerve function in people without polyneuropathy. Our study therefore suggests that cardiometabolic disturbances have an impact on peripheral nerve function that extends beyond clinically manifest disease.

INTRODUCTION

Diabetes mellitus is a major risk factor for polyneuropathy, a disabling condition that is associated with falls, fractures, ulcers and mortality.[1] Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), together commonly called prediabetes, might also increase the risk of polyneuropathy.[2] With the globally increasing prevalence of both diabetes and prediabetes, incidence of polyneuropathy and its consequences is also expected to increase.[3] However, evidence supporting the association between prediabetes and neuropathy has so far been inconclusive. Several studies showed a higher prevalence of prediabetes in patients with idiopathic neuropathy compared to previously published prevalence numbers in the general population. However, since these studies did not include a control group, a true association cannot be inferred.[4-8] Results from studies that did investigate the association between prediabetes and neuropathy using a control group have been inconsistent.[9-15] The uncontrolled nature, often retrospective study design, lack of appropriate adjustments and potential referral bias of most of these studies have previously been indicated.[16]

More recently, attention has shifted from hyperglycemia as a single cause of polyneuropathy to a more multifactorial hypothesis suggesting an interaction of glucose metabolism with other metabolic factors.[17, 18] Obesity, another global epidemic, is one of these factors. Hyperglycemia and obesity are central components of the metabolic syndrome (MetS).[19] This syndrome comprises a combination of interrelated risk factors for cardiovascular diseases and diabetes and also includes high blood pressure, elevated triglycerides and reduced high-density lipoprotein cholesterol.[19] Prevalence of MetS has also been rising and nowadays almost 50% of the US population meets the criteria. MetS is related to cardiovascular disease, neurodegenerative disease and cancer[18] and several components of this syndrome have also been implicated in the development of neuropathy in patients with diabetes.[20-23] A few case-control studies even suggested an association between MetS and idiopathic polyneuropathy[12, 24, 25], but more well-developed, extensive epidemiological studies are necessary to confirm this association.[17, 18, 26]

Therefore, we investigated the association of prediabetes and MetS with chronic polyneuropathy in an unselected sample of community-dwelling middle-aged and elderly people.

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MATERIALS AND METHODS

Setting

The current study was part of the Rotterdam Study, a large prospective, population-based cohort study in the Ommoord district of Rotterdam, the Netherlands.[27] The study was initiated in 1990 when all inhabitants aged 55 years or older were invited to participate. There were no other eligibility criteria besides minimum age and postal code. The study was expanded in 2000 and 2006, this last time inviting all persons aged 45 years or older, living in the Ommoord district. Currently, 14926 participants have been enrolled in the Rotterdam Study. At baseline, and at follow-up every four years, participants undergo extensive interviews and examinations at home and at the research center. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Centre and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Since June 2013, a polyneuropathy screening has been implemented in the core protocol of the Rotterdam Study. The current study includes all participants that have been invited for this assessment between June 2013 and October 2015. During this period, 1544 participants were invited for the polyneuropathy screening. Of these participants, 262 were excluded: 93 did not undergo the screening and 141 participants were not sufficiently screened, mainly due to logistic reasons (shortage of time to complete all examinations or due to a lack of personnel or on some occasions). Of the 1310 participants who were sufficiently screened, information on diabetes and MetS was present in 1256 participants. These 1256 participants were included in the analyses.

Assessment of type 2 diabetes, prediabetes, and metabolic syndrome

Diabetes mellitus type 2 was diagnosed using serum glucose measurements performed at the research centre, data on medication use (through linkage with pharmacy dispensing data), and general practitioners' records. Participants with a fasting glucose ≥7.0 mmol/L, a non-fasting glucose level ≥11.1 mmol/L (if fasting samples were not available), and participants that used anti-diabetic treatment were considered as having diabetes. Additionally, when participants were diagnosed with incident diabetes in between previous follow-up measurements of the Rotterdam Study, as identified through the link with the general practitioner records, participants were also considered as having diabetes.[28] We defined impaired fasting glucose using the World Health Organization (WHO) 2006 criteria (fasting glucose level ≥6.1 mmol/L and <7.0 mmol/L, in the absence of diabetes).[2] Glucose tolerance test were not performed, precluding the possibility to investigate the effect of impaired glucose tolerance.

MetS was defined according to the harmonized criteria published in 2009.[19] The presence of at least three of the following five components defined MetS: elevated waist circumference (≥94 cm for males, ≥80 cm for females), elevated triglycerides (≥1.7 mmol/L, or drug treatment for elevated triglycerides), reduced high-density lipoprotein cholesterol (HDL-C; <1.0 mmol/L in males, <1.3 mmol/L in females, or specific treatment for reduced HDL-C), elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg, and/or use of antihypertensive treatment) and elevated fasting glucose (≥5.6 mmol/L, or use of glucose lowering medication). Medication use was assessed by self-report and by going through the medication cabinets at the house of the participants during the home interview. Participants using lipid-lowering medication (the drugs that are mainly prescribed for lipid abnormalities in the Netherlands are statins) were considered to fulfil the triglyceride criterion, but not the HDL-C criterion, since statins only have a marginal effect on HDL-C. Specific drugs that are meant to raise HDL-C levels are very rarely prescribed in our population sample. Waist circumference, height, weight, and blood pressure (mean of two consecutive measurements) were measured at the research center. Information on glucose, cholesterol, and triglyceride levels was derived from blood samples taken as close to the polyneuropathy screening as possible. For 730 participants data on these cardiometabolic factors was collected on average two months before the polyneuropathy screening. In the remaining 526 participants evaluation of these factors took place at a previous visit (mean 4.9 years before polyneuropathy screening).

Polyneuropathy screening

Participants were screened for the presence of polyneuropathy with an in-person screening consisting of a symptom questionnaire, neurological examination and nerve conduction studies. The questionnaire consisted of sensory and motor symptoms of the legs or feet, like weakness, tingling, numbness, burning, allodynia, cramps, and pain. The neurological examination comprised assessment of vibration (Rydel-Seiffer tuning fork) on the hallux of both feet, pain sensation (wooden pin) on the lower legs, muscle strength for dorsiflexion of the feet (Rasch-MRC), and knee and ankle tendon reflexes. Nerve conduction studies were performed on the sural nerve bilaterally and on the peroneal nerve unilaterally. The distal peroneal compound muscle action potential (CMAP) amplitude (mV, baseline-peak) and distal motor latency (ms) were recorded while stimulating 8 cm proximal to the recording electrode, which was placed on the extensor digitorum brevis muscle. The sural sensory nerve action potential (SNAP) amplitude (μV, baseline-peak) and sensory nerve conduction velocity (m/s) were measured by applying stimuli 14 cm proximal to the recording electrode, which was placed behind the lateral malleolus. Standard methods of supramaximal stimulation were applied. Examination took place at room temperature. Skin temperature was documented, but maintaining the temperature above a certain degree was not possible in the current setting.

Medical records were scrutinized when participants scored abnormal on any of the three elements in the screening procedure (symptoms, signs, or abnormal nerve conduction parameters) to investigate whether participants received a previous specialist's diagnosis of polyneuropathy. Participants could also self-report a previous diagnosis of polyneuropathy, which was subsequently checked in records. All collected data, both from the screening and medical records, from each individual participant was evaluated by an expert panel with extensive experience in diagnosing neuromuscular diseases. The panel consisted of an experienced neuromuscular specialist, a neurophysiology specialist and a medical doctor trained in epidemiology with a special interest in neuromuscular diseases. The panel categorized participants into no, possible, probable, and definite polyneuropathy, depending on the certainty of the diagnosis. Participants were discussed until unanimity was reached. When all three elements of the screening were abnormal participants were categorized as definite polyneuropathy, and when no elements were abnormal participants were categorized as no polyneuropathy. The remaining participants were categorized as possible and probable polyneuropathy, depending on the level of abnormality. Typically, one abnormal element or two slightly abnormal elements yielded a possible polyneuropathy categorization, and two abnormal elements a probable categorization. All participants with a previous diagnosis of polyneuropathy made by a neurologist were categorized as definite polyneuropathy, since we consider a complete clinical work-up performed by a neurologist as superior to our screening. More details on the screening and diagnostic work-up can be found elsewhere.[29]

Data analysis

Logistic regression analyses were performed to investigate the association of diabetes, prediabetes, continuous glucose levels and MetS with (categories of) polyneuropathy. Analyses involving continuous glucose levels were performed using restricted cubic splines regression to assess potential non-linear associations. Analyses involving MetS were repeated after excluding participants with diabetes.

Additionally, linear regression analyses were used to investigate the association of diabetes, prediabetes, and MetS and its individual components with nerve conduction parameters. These analyses were performed in participants without polyneuropathy in order to investigate whether associations could already be found in the absence of polyneuropathy. For the sural nerve, the side with the highest SNAP amplitude and conduction velocity was used in the analyses.

All analyses were adjusted for age, sex, height and time between assessment of cardiometabolic factors and polyneuropathy screening. Logistic regression analyses involving diabetes and prediabetes were additionally adjusted for weight, diastolic blood pressure, systolic blood pressure, blood pressure lowering medication, smoking, serum

triglyceride level, serum HDL-cholesterol level and lipid lowering medication in a second model. Analyses involving components of MetS were additionally adjusted for the other components of the syndrome. Interaction terms for sex were explored in all models to investigate effect modification. Interaction between components of MetS in analyses involving these components was also investigated.

To further exclude the possibility that the time between polyneuropathy screening and assessment of cardiometabolic factors influenced the results, we performed a sensitivity analyses in which we repeated the logistic regression analyses into diabetes, impaired fasting glucose, and (components of) MetS, restricted to the 730 participants with assessment of cardiometabolic factors on average 2 months before the polyneu-ropathy screening.

Splines regression for continuous glucose levels was performed in R version 3.2.0, all other analyses were performed in SPSS statistical package, version 21 for Windows (IBM Corp., Armonk, NY),

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RESULTS

In total, 1256 participants were included in the analyses. The sample consisted of 685 females (54.5%) and 571 males (45.5%), and the mean age was 70.0 years (see Table 1). Type 2 diabetes was present in 175 participants (13.9%) and IFG in 153 participants (12.2%). MetS was present in 659 participants (52.5%). Elevated waist circumference and elevated blood pressure were the most common components, present in 67.5% and 78.0% of participants respectively. Sixty-four participants (5.1%) were diagnosed with a definite polyneuropathy, 92 (7.3%) with a probable polyneuropathy, and 218 (17.4%) with a possible polyneuropathy.

Diabetes was associated with definite polyneuropathy (odds ratio (OR) 3.01, 95% confidence interval (CI) 1.60;5.65, see Table 2). This association was mostly confined to males and slightly attenuated after adjusting for cardiovascular risk factors. We did not observe an association between IFG and polyneuropathy (OR 1.55, 95% CI 0.70;3.44). When investigating fasting glucose levels continuously, there was no association after exclusion of participants using anti-diabetic treatment. No associations were found with possible or probable polyneuropathy (Table 2).

MetS, defined as the presence of at least three out of five criteria, also associated with definite polyneuropathy (OR 1.92, 95% CI 1.09;3.38, Figure 1). This association was stronger when more components of the syndrome were present (at least four compo-nents: OR 2.64, 95% 1.40;4.98 and all five components OR 3.23, 95% CI 1.22;8.55). Of the individual components, elevated waist circumference (OR 2.84, 95% CI 1.35;5.99) and elevated triglycerides (OR 2.01, 95% CI 1.11;3.62) were both related to definite polyneu-

Table 1. Population characteristics

Characteristic	Total population (n=1256)
Age, years	70.0 (10.0)
Females, n	685 (54.5)
Diabetes mellitus, n	175 (13.9)
Impaired fasting glucose[a], n	153 (12.2)
Waist circumference, cm	92.4 (12.5)
Height, cm	169.8 (9.4)
Weight, kg	78.1 (13.7)
Serum triglycerides, mmol/L	1.4 (0.7)
Serum HDL cholesterol, mmol/L	1.5 (0.4)
Systolic blood pressure, mmHg	140.6 (21.3)
Diastolic blood pressure, mmHg	82.6 (10.7)
Serum glucose, mmol/L	5.8 (1.2)
Current smokers, n	189 (15.2)
Former smokers, n	656 (52.6)
Never smokers, n	401 (32.2)
MetS[b], n	659 (52.5)
Elevated waist circumference, n	848 (67.5)
Elevated triglycerides, n	566 (45.1)
Reduced HDL cholesterol, n	237 (18.9)
Elevated blood pressure, n	980 (78.0)
Elevated fasting glucose, n	617 (49.1)

Values represent number (%) or mean (SD).
[a] Fasting glucose ≥6.1 mmol/L and <7.0 mmol/L (WHO 2006 definition)
[b]MetS was defined according to the IDF 2009 criteria
MetS: metabolic syndrome; HDL: high-density lipoprotein
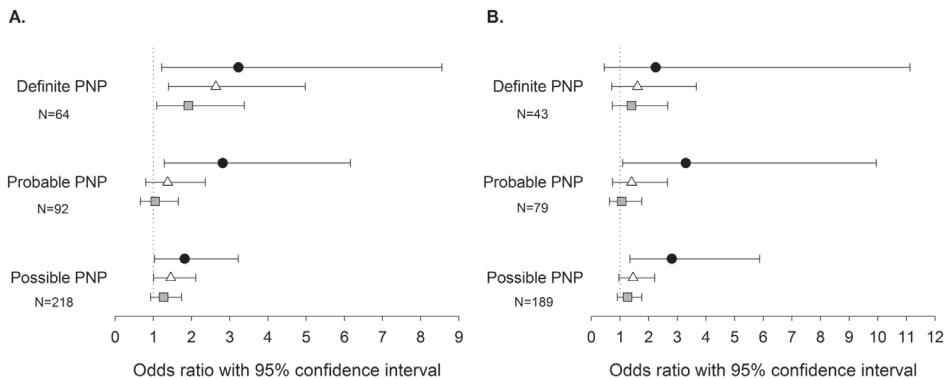
Figure 1. Association of number of MetS components with polyneuropathy. Panel A shows the association of MetS with polyneuropathy in the total study population. In panel B participants with diabetes have been excluded to investigate whether the association is also present in the non-diabetic population. Grey squares represent the presence of MetS (at least 3 components present). The white triangles and black dots represent the presence of at least 4 and 5 components respectively. All groups are compared to no MetS (<3 components). MetS: metabolic syndrome; PNP: polyneuropathy.

Table 2. Association of diabetes mellitus and impaired fasting glucose with polyneuropathy

		Possible polyneuropathy OR (95% CI)	Probable polyneuropathy OR (95% CI)	Definite polyneuropathy OR (95% CI)
Total sample				
Diabetes	Model 1	0.92 (0.58;1.46)	1.10 (0.57;2.14)	3.01 (1.60;5.65)[a]
	Model 2	0.73 (0.44;1.21)	0.87 (0.43;1.77)	2.18 (1.09;4.34)[a]
Impaired fasting glucose	Model 1	1.03 (0.64;1.67)	0.81 (0.38;1.73)	1.55 (0.70;3.44)
	Model 2	0.92 (0.56;1.51)	0.71 (0.33;1.56)	1.26 (0.54;2.91)
Males				
Diabetes	Model 1	0.74 (0.36;1.53)	1.54 (0.64;3.70)	6.04 (2.48;14.71)
	Model 2	0.65 (0.30;1.39)	1.37 (0.54;3.51)	4.88 (1.82;13.10)
Impaired fasting glucose	Model 1	0.79 (0.39;1.62)	0.62 (0.21;1.89)	2.04 (0.70;5.94)
	Model 2	0.77 (0.36;1.64)	0.61 (0.19;1.92)	1.62 (0.50;5.29)
Females				
Diabetes	Model 1	1.08 (0.59;1.99)	0.66 (0.23;1.90)	1.22 (0.41;3.68)
	Model 2	0.75 (0.38;1.50)	0.51 (0.16;1.57)	0.91 (0.28;2.95)
Impaired fasting glucose	Model 1	1.32 (0.68;2.54)	1.18 (0.41;3.40)	1.32 (0.37;4.78)
	Model 2	1.09 (0.55;2.16)	1.03 (0.35;3.03)	1.16 (0.31;4.30)

Values represent odds ratios (95% confidence interval) of diabetes and impaired fasting glucose compared to normoglycemia

Model 1: adjusted for age, sex (only for the non-stratified analyses), height and time between assessment of cardiometabolic factors and polyneuropathy screening

Model 2: additionally adjusted for diastolic blood pressure, systolic blood pressure, antihypertensive treatment, triglyceride level, HDL-cholesterol level, lipid lowering medication and smoking

[a] Significant sex interaction. HDL: high-density lipoprotein

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ropathy (Table 3). Reduced HDL-C levels were associated with possible polyneuropathy (OR 1.50, 95% CI 1.01;2.24). A similar, although not significant effect estimate was found for probable, but not for definite polyneuropathy. After excluding participants with diabetes a similar pattern of associations, especially between elevated waist circumference and definite polyneuropathy (OR 2.36, 95% CI 1.04;5.32), was found. There was no significant difference between genders in these analyses, nor was there significant interaction between different components of the syndrome.

Restricting the analyses to the 730 participants with assessment of cardiometabolic factors on average two months before the polyneuropathy screening yielded even stronger associations, be it with wider confidence intervals (Supplementary Table 1). Diabetes (OR 5.98, 95% C.I. 2.11;16.93) strongly associated with definite polyneuropathy, as did the number of MetS components, elevated waist circumference and elevated triglycerides.

Table 3. Association of MetS components with polyneuropathy

	Possible polyneuropathy OR (95% CI)	Probable polyneuropathy OR (95% CI)	Definite polyneuropathy OR (95% CI)
Elevated waist circumference	1.03 (0.72;1.47)	0.87 (0.52;1.46)	2.84 (1.35;5.99)
Elevated triglycerides	1.18 (0.85;1.65)	1.49 (0.91;2.46)	2.01 (1.11;3.62)
Reduced HDL cholesterol	1.50 (1.01;2.24)	1.58 (0.86;2.90)	1.21 (0.61;2.42)
Elevated blood pressure	0.93 (0.61;1.42)	0.71 (0.36;1.40)	1.43 (0.56;3.65)
Elevated fasting glucose	1.00 (0.72;1.38)	1.10 (0.68;1.79)	0.72 (0.41;1.29)

Adjusted for age, sex, height, time between assessment of cardiometabolic factors and polyneuropathy screening and all other components of MetS
No significant interactions with sex or between different components were found.
MetS: metabolic syndrome; HDL: high-density lipoprotein

In individuals without clinical or neurophysiological suspicion on polyneuropathy, MetS was associated with lower sural SNAP amplitudes in both the total and the non-diabetic population. Additionally, MetS related to lower peroneal CMAP amplitudes, but this association was present in males only (Table 4). When focusing on the separate components of MetS, we found that elevated fasting glucose and reduced HDL-C related to a lower sural SNAP amplitude, especially in males, and that elevated waist circumference related to a lower peroneal CMAP amplitude in males only. There were no associations between any of the metabolic factors and peroneal distal latency or sural sensory nerve conduction velocity.

DISCUSSION

In this population-based study, both diabetes and MetS were strongly associated with the presence of polyneuropathy. Elevated waist circumference and elevated triglycerides were the metabolic factors contributing the most to this association. We also showed that the effect of these factors is independent of the presence of diabetes. Although no association was found between IFG and polyneuropathy, an elevated fasting glucose was related to lower sural SNAP amplitudes in participants without polyneuropathy. Additionally, we showed that MetS in participants without polyneuropathy related to lower sural SNAP amplitudes in males and females and to lower peroneal CMAP amplitudes in males.

The strong association between MetS and polyneuropathy has also been found in some other studies. These studies suggested an association of dyslipidemia or abdominal obesity with polyneuropathy in cohorts of patients with diabetes[20-23] and in case-control studies of patients with idiopathic neuropathy.[12, 24, 25, 30] A recent population-based study,

Table 4. Association of MetS with nerve conduction parameters in males and females categorized as no polyneuropathy

	Peroneal CMAP amplitude, mV		Sural SNAP amplitude, µV	
	Males	Females	Males	Females
Glycemic state				
Diabetes	-0.27 (-1.18;0.64)	0.01 (-0.80;0.82)	-0.58 (-1.67;0.52)	-1.18 (-2.89;0.53)
Impaired fasting glucose	-0.33 (-1.16;0.49)	-0.11 (-1.02;0.79)	-0.98 (-2.06;0.09)	-1.40 (-3.14;0.33)
MetS				
Total sample				
≥3 criteria of MetS	**-0.84 (-1.44;-0.23)**[b]	0.44 (-0.06;0.94)[b]	**-0.99 (-1.75;-0.22)**	**-1.24 (-2.28;-0.21)**
≥4 criteria of MetS	**-0.92 (-1.68;-0.16)**[b]	0.44 (-0.24;1.11)[b]	**-1.38 (-2.36;-0.40)**	**-1.80 (-3.16;-0.44)**
5 criteria of MetS	0.25 (-1.20;1.71)	0.56 (-0.53;1.66)	-1.72 (-3.61; 0.17)	-0.51 (-2.92;1.90)
Elevated waist circumference[a]	**-0.78 (-1.44;-0.13)**[b]	0.03 (-0.55;0.61)[b]	-0.42 (-1.24;0.40)	-0.64 (-1.83;0.54)
Elevated triglycerides[a]	0.27 (-0.37;0.91)	0.46 (-0.08;0.99)	-0.06 (-0.88;0.76)	-0.18 (-1.28;0.92)
Reduced HDL cholesterol[a]	0.27 (-0.63;1.17)	0.11 (-0.55;0.77)	-0.74 (-1.90;0.43)	-0.40 (-1.78;0.98)
Elevated blood pressure[a]	0.04 (-0.79;0.88)	0.03 (-0.57;0.62)	-0.15 (-1.21;0.91)	0.49 (-0.72;1.71)
Elevated fasting glucose[a]	-0.48 (-1.12;0.16)[b]	0.17 (-0.35;0.68)[b]	**-0.90 (-1.71;-0.10)**	-0.71 (-1.77;0.36)
Participants without diabetes				
≥3 criteria of MetS	**-0.94 (-1.60;-0.28)**[b]	0.39 (-0.15;0.94)[b]	**-1.13 (-1.97;-0.30)**	**-1.30 (-2.38;-0.23)**
≥4 criteria of MetS	**-1.03 (-1.90;-0.17)**[b]	0.48 (-0.31;1.27)[b]	**-1.84 (-2.92;-0.77)**	**-2.11 (-3.58;-0.64)**
5 criteria of MetS	0.21 (-1.60;2.01)	0.37 (-1.38;2.11)	**-3.08 (-5.43;-0.74)**[b]	0.94 (-2.56;4.43)[b]
Elevated waist circumference[a]	**-0.74 (-1.46;-0.03)**[b]	0.03 (-0.58;0.64)[b]	-0.46 (-1.34;0.42)	-0.57 (-1.78;0.64)
Elevated triglycerides[a]	0.36 (-0.34;1.06)	**0.59 (0.02;1.16)**	-0.28 (-1.16;0.61)	-0.26 (-1.39;0.88)
Reduced HDL cholesterol[a]	-0.11 (-1.15;0.93)	0.02 (-0.72;0.76)	**-1.41 (-2.72;-0.10)**	-0.43 (-1.93;1.07)
Elevated blood pressure[a]	0.09 (-0.81;0.99)	-0.11 (-0.75;0.52)	0.16 (-0.95;1.27)	0.20 (-1.06;1.46)
Elevated fasting glucose[a]	-0.50 (-1.20;0.19)[b]	0.26 (-0.31;0.82)[b]	**-0.93 (-1.78;-0.07)**	-0.60 (-1.73;0.53)

Values represent the difference in the specific nerve conduction parameters between participants with diabetes or impaired fasting glucose compared to participants with normoglycemia, or between presence of MetS or its components compared to absence of the syndrome or the specific component

Adjusted for age, height and time between assessment of cardiometabolic factors and polyneuropathy screening

Bold values are significant (p<0.05)

[a] Additionally adjusted for the other components of MetS

[b] Significant interaction by sex.

MetS: metabolic syndrome; HDL: high-density lipoprotein

similar to ours, also showed an association of MetS with polyneuropathy, with a stronger association in the presence of more components. In contrast to our study, independent associations of specific MetS components were only found with secondary neuropathy outcomes, but not with the primary outcome, which was presence of polyneuropathy.[31] Our findings further contribute to the hypothesis that neuropathy in patients with diabetes is not only related to consequences of long-standing hyperglycemia, but is also influenced by the presence of other metabolic factors, especially abdominal obesity and dyslipidemia. We also showed that these factors likely are evenly important in persons without diabetes. Potential pathways through which these metabolic factors may lead to neuropathy include oxidative stress, possibly in combination with neuronal and axonal mitochondrial dysfunction, which can lead to nerve injury via chronic metabolic inflammation, insulin resistance and nerve ischemia.[18]

Our study is cross-sectional, which makes it difficult to draw firm conclusions about causality. It is possible that persons with polyneuropathy become less active, and consequently gain weight and develop dyslipidemia. However, we showed that the association with polyneuropathy got stronger when more components of MetS were present, suggesting a dose-response relation. Additionally, we found that MetS, elevated fasting glucose and dyslipidemia related to lower sural SNAP amplitudes in males and females without any suspicion on polyneuropathy and to lower peroneal CMAP amplitudes in males without polyneuropathy. Impaired function of these nerves, especially the SNAP amplitude of the sural nerves, is a fairly sensitive marker for axonal polyneuropathy.[32] Together these findings suggest that these metabolic factors increase the risk to develop polyneuropathy and not the other way around. Still, longitudinal studies are required to further strengthen this hypothesis. The observed differences between males and females in the association of diabetes, prediabetes and (components) of MetS with polyneuropathy and peripheral nerve function warrant further investigation.

Our study further showed that diabetes was associated with polyneuropathy. This is a well-established association which has been documented before.[33] After adjusting for other cardiovascular risk factors, the association with polyneuropathy remained significant. This suggests that although other metabolic factors contribute to the pathophysiology of polyneuropathy in patients with diabetes, consequences of prolonged hyperglycemia are probably most important. In contrast with some other studies, we did not find an association of polyneuropathy with IFG. Most studies that suggested an association between prediabetes and polyneuropathy lacked a control group[4-8], or did not control for age, which is strongly related to both polyneuropathy and (pre)diabetes.[10, 34, 35] One controlled study did show an association of impaired glucose tolerance and neuropathy[9], while the majority of controlled studies, especially the studies that took the confounding effect of age into account, found no association.[11-13, 15, 25, 30, 31, 36] Despite these findings, prediabetes is still often considered a risk factor for polyneuropathy.

Our study does not support this assumption, but it is possible that we lacked sufficient power to show an effect. Moreover, we did not include impaired glucose tolerance into the definition of prediabetes, since oral glucose tolerance tests were not performed. Impaired glucose tolerance might be a better measure of prediabetes. Additionally, since we included an elderly population, with a mean age of 70 years, we cannot comment on the potential role of prediabetes earlier in life.

Our study is one of the very few studies that approaches the question if prediabetes and MetS are associated with polyneuropathy using a study design that includes an unselected sample of the middle-aged and elderly general population, without specific sampling techniques for cases or controls. Moreover, we used a rigorous definition of polyneuropathy, which is diagnosed with a protocol that largely resembles clinical practice and also includes nerve conduction studies. However, since we performed our study in a homogeneous, middle-aged to elderly population, we must note that our results may not directly translate to more heterogeneous, or younger populations. Our study also has other limitations. First, for some of the subgroup analyses samples were limited, yielding insufficient power to show small associations. Second, due to logistics of the study, in 526 participants the presence of diabetes and MetS was assessed approximately four years before the polyneuropathy screening. It is possible that participants developed incident (pre)diabetes during this period and lipid levels may have changed since the blood samples were collected. Therefore, we adjusted all analyses for the time between the assessment of cardiometabolic factors and the polyneuropathy screening to take this into account. Additionally, we performed a sensitivity analyses while excluding these 526 participants, which suggested that the results in the main analyses might even be an underestimation of the true effect. Third, we did not perform an oral glucose tolerance test. Possibly, post load hyperglycemia in the postprandial phase plays a key role in the pathogenesis of complications such as polyneuropathy.[26] Finally, although our screening approach is as close to clinical practice as possible, it has not been validated and it is possible that some participants were misclassified as having polyneuropathy, while instead abnormality was due to focal neuropathies, radiculopathy, or non-specific symptoms attributable to osteoarthritis or other locomotor problems. This especially concerns the possible and probable polyneuropathy categories, which might explain the inconsistent findings in these groups. It is reasonable to assume that misclassification in the definite polyneuropathy category is very minimal, because we combined symptoms, neurological examination and NCS to make this categorization. The association with definite polyneuropathy thus provides an accurate estimate of the effect.

In conclusion, this population-based study showed that cardiometabolic disturbances, like abdominal obesity and dyslipidemia, are strongly related to the presence of polyneuropathy and impaired peripheral nerve function in participants without poly-

neuropathy, irrespective of the presence of diabetes. Therefore, screening and optimal control of these risk factors may be warranted. Whether this also reduces neuropathic symptoms, or may even prevent the development or progression of polyneuropathy needs to be further evaluated in longitudinal studies.

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Supplementary table 1. Sensitivity analyses in 730 participants with collection of cardiometabolic factors on average 2 months before polyneuropathy screening

	Definite polyneuropathy OR (95% C.I.
Glycemic state	
Diabetes	5.98 (2.11;16.93)
Impaired fasting glucose	2.09 (0.62;7.10)
MetS	
≥3 criteria of MetS	2.24 (0.84;6.01)
≥4 criteria of MetS	2.99 (1.00;8.95)
5 criteria of MetS	5.16 (1.12;23.78)
Components of MetS	
Elevated waist circumference	8.55 (1.09;67.05)
Elevated triglycerides	2.49 (0.94;6.58)
Reduced HDL cholesterol	0.96 (0.33;2.79)
Elevated blood pressure	1.12 (0.38;3.31)
Elevated fasting glucose	0.65 (0.25;1.69)

Adjusted for age, sex and height

Analyses involving components of MetS are additionally adjusted for all other components of MetS

No significant effect modification by sex

MetS: metabolic syndrome; HDL: high-density lipoprotein

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Chapter 4.2

High body mass and kidney dysfunction relate to worse nerve function, even in adults without polyneuropathy

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ABSTRACT

Polyneuropathy is a prevalent and disabling disorder. Despite extensive evaluation, the cause often remains unknown. Factors that predispose for the development of polyneuropathy need to be identified. We investigated the effect of anthropometric and metabolic factors on peripheral nerve function in 908 participants of the population-based Rotterdam Study without any symptoms or signs of polyneuropathy. Participants underwent nerve conduction studies of the sural and peroneal nerve. Data on age, height, weight, waist circumference, diabetes, lipid levels, hypertension and kidney function were collected. Regression analyses were used to investigate determinants of nerve action potential amplitudes. The frequency of abnormal sural sensory nerve action potential (SNAP) amplitudes increased with age from 1% under 60 years to 23% over 80 years. Similarly, the frequency of abnormal peroneal nerve compound motor action potential (CMAP) amplitudes increased from 4% to 13%. High weight and BMI were independently associated with reduced sural SNAP amplitudes and peroneal CMAP amplitudes. Participants with hypertension and kidney dysfunction were more likely to have abnormal sural SNAP amplitudes. Older age, high weight, hypertension and moderate kidney dysfunction might thus lead to peripheral nerve dysfunction in persons yet without symptoms or signs of polyneuropathy.

INTRODUCTION

Polyneuropathy is a common disorder, especially in elderly.[1, 2] Due to aging of the population, polyneuropathy prevalence will increase and so will the burden on individuals and society. Identification of (modifiable) risk factors for polyneuropathy is therefore highly important.

The development of polyneuropathy is thought to be gradual, with incremental deterioration of peripheral nerve function due to accumulating damage.[3, 4] Once a certain threshold is passed, nerve function may be considered to be abnormal. When clinical symptoms and signs develop, a diagnosis of polyneuropathy can be made.[5] A milder, yet similar deteriorating process also occurs with advancing age, with a decrease in nerve fibers density.[6] Consequently, sensory and motor nerve action potential amplitudes, as measured with nerve conduction studies (NCS) also decrease with age.[7-17] These age-related morphological and electrophysiological changes to peripheral nerves might be considered as a very subtle start of the gradual process towards polyneuropathy, eventually leading to clinical symptoms if everyone would live long enough. Some persons however deviate from this subtle process and develop manifest polyneuropathy earlier in life. This can often be attributed to co-occurrence of diabetes, end-stage kidney disease, alcohol overuse, and other risk factors.[1, 18-21] In a large proportion however, polyneuropathy remains idiopathic.[1]

So far, knowledge on risk factors comes from clinical studies, usually involving patients with a diagnosis of polyneuropathy. Far less research focused on factors that contribute to nerve damage before overt polyneuropathy develops. Information about preclinical changes can be insightful to better understand pathophysiology and perhaps to identify persons at risk for polyneuropathy, who might benefit from preventive strategies. We aimed to investigate the effect of several anthropometric and metabolic determinants on peripheral nerve function in a population-based study of older adults without clinical symptoms or signs of polyneuropathy.

METHODS AND MATERIALS

Setting

This study was part of the Rotterdam Study, a prospective, population-based cohort study, conducted in a suburb of Rotterdam, the Netherlands.[22] In 1990 and in 2000, all inhabitants over 55 years of age living in this area were invited to participate. In 2005, the study was expanded with persons over 45 years of age, living in the area. Overall, 14926 individuals agreed to participate (response rate 72%). Every three to four years participants undergo extensive evaluations to investigate determinants of chronic diseases.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sports of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". A written informed consent to participate in the study and to obtain information from their treating physicians was obtained from all participants.

Assessment of anthropometric and metabolic determinants

Demographic, anthropometric and metabolic determinants that were evaluated included age, sex, height, weight, body mass index (BMI), waist circumference, waist-to-hip ratio, hypertension, diabetes mellitus, high-density cholesterol and triglyceride levels, kidney and liver function, smoking habits and alcohol use. These variables measure several factors that have previously been related to polyneuropathy.[1, 18-21] Height, weight and waist and hip circumference were measured at the research center. BMI was calculated by dividing weight in kilogram by height in squared meters. A BMI above 25 was considered as overweight and above 30 as obese. Waist circumference was dichotomized into normal and elevated, at 94 centimeters for males and 80 centimeters for females.[23] Waist-to-hip ratio was calculated by dividing waist circumference by hip circumference. Blood pressure was assessed by the mean of two consecutive measurements. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or use of antihypertensive medication. Blood sampling included assessment of fasting glucose, high-density lipoprotein cholesterol levels, triglyceride levels, creatinine, liver transaminases, bilirubin, alkaline phosphatase, and gamma-glutamyl transferase. Blood samples were collected as close to the polyneuropathy screening as possible, mostly within one year. However, due to logistics of the study blood samples taken at a previous visit had to be used in a third of participants (approximately 5 years before neuropathy screening). We defined diabetes mellitus as a fasting glucose ≥7.0 mmol/L, a non-fasting glucose ≥11.1 mmol/l, use of antidiabetic medication, or a previous diagnosis of diabetes (as identified through links with general practitioners' records).[24] The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate the estimated glomerular filtration rate (eGFR).[25] Participants also collected timed overnight urine in which albumin and creatinine were determined. Albuminuria was assessed with the albumin-to-creatinine ratio (AC-ratio, mg/g), estimated by dividing albumin by creatinine. Kidney function was categorized into three groups: normal eGFR (>60 mL/min/1.73 m^2) and no albuminuria (AC-ratio <30 mg/g); reduced eGFR (<60 mL/min/1.73 m^2) or albuminuria (AC-ratio ≥30 mg/g); and reduced eGFR and albuminuria.[26, 27] Smoking habits and alcohol use were assessed by questionnaire.

Polyneuropathy screening and nerve conduction studies

Details about the polyneuropathy screening have previously been published.[28] In brief, the screening comprised assessment of symptoms with a questionnaire, neurological examination of the lower legs and NCS. The examination involved assessment of tendon reflexes, vibration sensation, pin sensibility and muscle strength of the feet. NCS involved bilateral assessment of the sural nerve and unilateral assessment of the peroneal nerve. Participants were also asked about a previous polyneuropathy diagnosis, which was subsequently checked in medical records. Medical records of all participants with any abnormality in the screening were also investigated for a previous diagnosis. An expert panel categorized all participants into definite, probable, possible or no polyneuropathy, depending on the estimated likelihood of the diagnosis.

NCS were performed using a Nicolet™ Viking Quest (Natus Medical Incorporated, San Carlos, California, USA). Standard techniques of supramaximal stimulation were used and examination was performed at room temperature. The nature of our study precluded the possibility to preheat the legs. Sural sensory nerve action potential (SNAP) amplitudes were measured using antidromic standardized techniques, with a recording electrode placed behind the lateral malleolus. Stimulation was applied on the calves 14 cm proximal to the recording electrode. In accordance with published normative values, baseline-peak amplitudes below 4 μV were considered abnormal for this middle-aged and elderly population.[11] The peroneal nerve was stimulated lateral to the tibialis anterior tendon, 8 centimeters proximal to the recording electrode, which was placed on the midpoint of the extensor digitorum brevis muscle on the dorsum of the right foot. Compound muscle action potential (CMAP) baseline-peak amplitudes below 1.1 mV were considered abnormal.[29]

Population for analyses

Between June 2013 and January 2016, 1464 participants successfully underwent the polyneuropathy screening. As we were interested in participants yet without polyneuropathy, those categorized as probable or definite polyneuropathy were excluded (n=196), since per definition these patients had either neuropathic symptoms, signs or both. From the remaining participants, we excluded another 198 participants who were classified as possible polyneuropathy based on the presence of symptoms or signs. Participants with abnormal NCS in the absence of symptoms or signs were not excluded, since these are part of the group of interest for this study. Participants with impaired vibration sensation on the big toe or reduced or absent ankle tendon reflexes, without symptoms or other signs of polyneuropathy were not excluded, since these signs may also reflect "normal aging". Of the remaining 1070 participants, 162 were excluded because they did not sufficiently undergo nerve conduction studies, or had non-interpretable results (due to edema, signal disturbance, or other technical problems). In

total, 908 participants without symptoms or signs of polyneuropathy were included in the analyses.

Statistical analyses

Continuous determinants were visually checked for normality and, if necessary, log-transformed (all were right-skewed distributions). Continuous determinants were subsequently standardized to describe associations uniformly per standard deviation. Sural SNAP and peroneal CMAP amplitudes were dichotomized into normal and abnormal, using a sural SNAP amplitude of 4 µV and a peroneal CMAP amplitude of 1.1 mV according to the discussed normative values. For the sural nerve the side with the highest amplitude was used in the analyses. We calculated the frequency of abnormal and absent NCS amplitudes with regard to the total sample and by 10-year age categories.

We then performed two sequential analyses. First, logistic regression analyses were used to investigate whether anthropometric and metabolic determinants were associated with abnormal sural SNAP amplitudes and abnormal peroneal CMAP amplitudes. Second, we excluded participants with abnormal amplitudes and used linear regression analyses to investigate which determinants associated continuously with sural and peroneal amplitudes within the normal range. We performed continuous analyses only among those that were normal to rule out the possibility that subclinical disease or changes could influence the results. Analyses were adjusted for age, sex, height and time between blood sampling and neuropathy screening (if applicable) in model 1 (only in data supplement), since these variables are known to influence NCS parameters. In model 2 we additionally adjusted for the other determinants of interest in this study (weight, diabetes mellitus, hypertension, high-density lipoprotein cholesterol, triglycerides, eGFR and AC-ratio, liver enzymes, smoking and alcohol), to investigate whether the reported associations were independent. Analyses involving other anthropometric measures than weight (BMI, waist circumference and waist-to-hip ratio) were not adjusted for weight to avoid over-adjustment. Similarly, analyses involving categorical measures of kidney function were not adjusted for the continuous measurements of kidney function. In all analyses, effect modification by age and sex was investigated by including an interaction term.

As sensitivity analyses we repeated the two sets of analyses while excluding participants with limbs <29 degrees Celsius, to avoid cold temperatures influencing NCS results. With these analyses, we expect to get an impression of what the result would have been were we able to preheat the legs of participants. All analyses were performed in SPSS version 21 for Windows (IBM Corp., Armonk, NY).

RESULTS

The sample consisted of 908 participants, of which 493 (54%) were females. Mean age was 69 years. Prevalence of overweight, obesity and elevated waist circumference was 49%, 17% and 69% respectively. The mean BMI was 26.7 and the mean waist-to-hip ratio was 0.9. Diabetes was present in 12% of participants and hypertension in 62% (Table 1). Sural SNAP amplitudes were reliably measured in 876 participants. Amplitudes

Table 1. Characteristics of the study sample

Characteristic		Total population (n=908)
Age, years		69.0 (9.4)
Female sex, n		493 (54.3)
Height, cm		169.5 (9.1)
Weight, kilograms		76.9 (13.0)
Body mass index, kg/m^2		26.7 (3.8)
Overweight*, n		447 (49.2)
Obese*, n		154 (17.0)
Waist circumference, cm		92.5 (11.7)
Elevated waist circumference†, n		624 (68.8)
Waist-to-hip ratio		0.9 (0.1)
Diabetes mellitus, n		108 (12.1)
Hypertension, n		563 (62.0)
High-density lipoprotein cholesterol, mmol/L		1.5 (0.4)
Triglycerides, mmol/L		1.2 (1.0-1.7)
eGFR, ml/min/1.73 m^2		76.3 (19.9)
Albumin-to-creatinine ratio, mg/g		3.4 (2.0-6.4)
Abnormal AC-ratio or eGFR, n		234 (27.0)
Abnormal AC-ratio and eGFR, n		24 (2.8)
Alanine transaminase, U/L		20.0 (15.0-25.0)
Aspartate transaminase, U/L		24.0 (21.0-28.0)
Bilirubin, μmol/L		8.0 (6.0-11.0)
Alkaline phosphatase, U/L		71.0 (21.4)
Gamma-glutamyl transferase, U/L		23.0 (16.0-33.0)
Smoking	Never, n	301 (33.3)
	Past, n	474 (52.5)
	Current, n	128 (14.2)
Alcohol, drinks per month		21.2 (22.7)

Values represent mean (standard deviation), median (25th - 75th percentile) or number (%)
* Body mass index above 25 was considered as overweight, above 30 as obese
† Waist circumference above 94 centimeters for males, and 80 centimeters for females
n: number; eGFR: estimated glomerular filtration rate; AC-ratio: albumin-to-creatinine ratio; U/L: units per liter
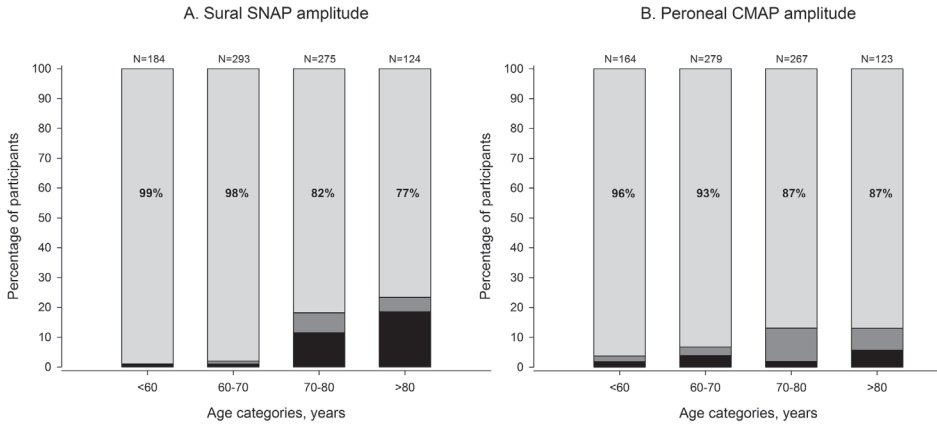
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Figure 1. Percentage of abnormal nerve amplitudes by age in participants *without clinical suspicion on polyneuropathy*. The figure shows the percentage of participants with normal (light grey bars) abnormal (dark grey bars) and absent (black bars) sural sensory nerve action potential (SNAP) amplitudes (Panel A) and peroneal nerve compound muscle action potential (CMAP) amplitudes (Panel B). An abnormal sural SNAP amplitude is defined as an amplitude < 4 μV and an abnormal peroneal CMAP amplitude is defined as an amplitude < 1.1 mV.

were abnormal in 87 participants (10%), 60 (7%) of which were absent. Peroneal CMAP amplitudes were reliably measured in 833 participants. These were abnormal in 76 participants (9%), 26 (3%) of which were absent. Of the overlapping 808 participants with both nerves reliably measured, 18 (2%) had abnormal amplitudes for both nerves, 65 (8%) only for the sural, and 57 (7%) only for the peroneal nerve.

Age was strongly related to abnormal values for both the sural SNAP and the peroneal CMAP amplitude (Fig. 1). Tall, heavy, (abdominally) obese and hypertensive
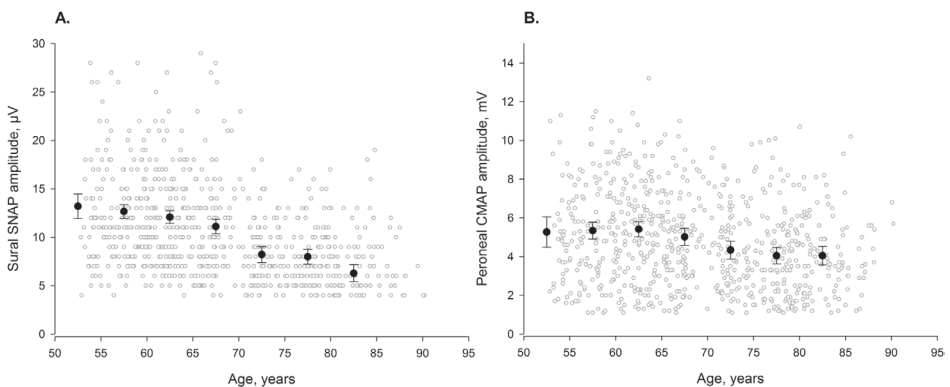
Figure 2. Effect of age on nerve amplitudes in individuals *without clinical or electrophysiological suspicion* on polyneuropathy. Grey circles represent all individual persons with their corresponding age and amplitude. Black circles with error bars represent the adjusted mean value, with confidence interval, of the specific nerve conduction parameter per five-year age group. Values are adjusted for sex and height.

participants were more likely to have abnormal sural SNAP amplitudes. Participants with chronic kidney dysfunction (reduced eGFR and albuminuria) were also more likely to have abnormal sural SNAP amplitudes, independent of other covariates (OR 4.8, 95% C.I. 1.4;16.4). Aside from age, a high weight and BMI were associated with abnormal peroneal CMAP amplitudes, but waist circumference and waist-to-hip ratio were not. Sex, diabetes, lipid levels, liver enzymes, alcohol use and smoking were not related to impairment in either sural SNAP or peroneal CMAP amplitude (Table 2). There was no effect modification by age or sex in these analyses.

After excluding participants with abnormal amplitudes (87 and 76 participants for the sural and peroneal nerve respectively), we still observed a lower sural SNAP and peroneal CMAP amplitude with higher age, especially after the age of 70 (Fig. 2). The effect of age on the sural SNAP amplitude was stronger in females (-2.64 µV per standard deviation increase in age, 95% C.I. -3.14;-2.15) than in males (-1.81 µV, 95% C.I. -2.21;-1.42). A similar pattern of associations as in the dichotomous analyses was found for the sural nerve: being tall, heavy, and (abdominally) obese related to lower sural SNAP amplitudes within the normal range (Table 3). These effects were similar in males and females. There were no associations with the peroneal CMAP amplitude.

When restricting the analyses to NCS performed in participants with a limb temperature >29 degrees Celsius, we found a slightly higher percentage of abnormal sural SNAPs and peroneal CMAPs of 12.5% (76 out of 606) and 9.6% (61 out of 638) respectively. Effect estimates of the logistic and linear regression models were similar to those of the main analyses (supplementary tables 1 and 2).

DISCUSSION

In our study of community-dwelling older adults without symptoms or signs of polyneuropathy, abnormal sural SNAP and peroneal CMAP amplitudes were found in almost 10% of participants. Both the sural SNAP and the peroneal CMAP amplitude declined with increasing age, especially after the age of 70. Weight, BMI and the presence of obesity, hypertension and kidney dysfunction were also independently related to abnormal amplitudes. Most factors were also associated with lower amplitudes within the normal range. These results suggest that metabolic factors are related to a decline in peripheral nerve function, even before symptoms or signs of polyneuropathy become apparent.

Our study is one of the very few studies that investigates the significance and determinants of abnormal NCS in an unselected older population, utilizing a population-based study as source population. This minimizes the chances of selection bias and improves the generalizability of the results. Previous clinic-based studies that investigated aging effects on NCS also found a decreasing amplitude with increasing age. However, results

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Table 2. Determinants of abnormal nerve conduction parameters in individuals *without clinical suspicion* of polyneuropathy

	Abnormal sural SNAP amplitude OR (95% C.I.)	Abnormal peroneal CMAP amplitude OR (95% C.I.)
Age, per SD	1.64 (0.92;2.93)	**2.03 (1.20;3.42)**
Female sex	2.49 (0.77;8.06)	1.46 (0.45;4.75)
Height, per SD	**1.70 (1.08;2.68)**	1.25 (0.81;1.91)
Weight, per SD	**1.69 (1.16;2.46)**	**1.59 (1.12;2.25)**
Body mass index, SD	**1.53 (1.13;2.09)**	**1.49 (1.11;1.99)**
Overweight[a]	**2.46 (1.26;4.78)**	1.77 (0.96;3.29)
Obese[a]	**3.01 (1.23;7.40)**	2.09 (0.89;4.92)
Waist circumference, per SD	**1.64 (1.21;2.23)**	1.29 (0.96;1.75)
Elevated waist circumference	**2.34 (1.16;4.74)**	1.18 (0.64;2.18)
Waist-to-hip ratio, per SD	**1.36 (1.01;1.85)**	1.15 (0.83;1.58)
Diabetes	0.77 (0.34;1.76)	0.39 (0.13;1.14)
Hypertension	**2.14 (1.07;4.27)**	0.82 (0.45;1.46)
High-density lipoprotein cholesterol, per SD	0.99 (0.67;1.46)	1.09 (0.75;1.58)
Triglycerides, per SD*	1.04 (0.75;1.44)	1.05 (0.76;1.43)
eGFR, per SD	0.92 (0.55;1.54)	0.93 (0.57;1.54)
Albumin-to-creatinine ratio, per SD*	1.19 (0.93;1.51)	0.99 (0.77;1.26)
Abnormal AC-ratio or eGFR[b]	1.20 (0.58;2.49)	1.00 (0.49;2.05)
Abnormal AC-ratio and eGFR[b]	**4.80 (1.40;16.41)**	2.77 (0.76;10.15)
Alanine transaminase, per SD*	0.76 (0.54;1.08)	0.88 (0.63;1.25)
Aspartate transaminase, per SD*	1.29 (0.89;1.86)	1.20 (0.86;1.67)
Bilirubin, per SD*	0.97 (0.73;1.28)	0.94 (0.72;1.24)
Alkaline phosphatase, per SD	0.98 (0.79;1.22)	1.00 (0.79;1.28)
Gamma-glutamyl transferase, per SD*	0.92 (0.66;1.28)	0.97 (0.71;1.33)
Past smoking[c]	1.33 (0.73;2.42)	1.19 (0.66;2.15)
Current smoking[c]	0.97 (0.32;2.91)	2.03 (0.90;4.56)
Alcohol, per SD	0.74 (0.51;1.07)	0.75 (0.53;1.07)

Values represent odds ratios comparing odds on impairment in nerve conduction parameter per SD (continuous determinants) or per category (categorical determinants).

Adjusted for age, sex, height, weight (if applicable), diabetes mellitus, high-density lipoprotein cholesterol, triglycerides, hypertension, eGFR and AC-ratio (if applicable), liver enzymes, smoking, alcohol and time between laboratory assessment and NCS (if applicable)

[a] Compared to body mass index < 25

[b] Compared to normal eGFR and normal AC-ratio

[c] Compared to never smokers

* Log-transformed values

SD: standard deviation; eGFR: estimated glomerular filtration rate; AC-ratio: albumin-to-creatinine ratio

Table 3. Determinants of nerve conduction parameters in individuals *without clinical or electrophysiological suspicion* of polyneuropathy

	Change in suralSNAP amplitude, μV β (95% C.I.)	Change in peroneal CMAP amplitude, mV β (95% C.I.)
Age, per SD	**-1.81 (-2.45;-1.18)**	-0.26 (-0.64;0.12)
Female sex	-0.31 (-1.82;1.20)	-0.38 (-1.29;0.53)
Height, per SD	**-1.42 (-1.93;-0.90)**	-0.13 (-0.44;0.18)
Weight, per SD	**-0.49 (-0.91;-0.07)**	-0.19 (-0.44;0.06)
Body mass index, per SD	**-0.42 (-0.77;-0.07)**	-0.16 (-0.36;0.05)
Overweight[a]	-0.00 (-0.73;0.73)	-0.35 (-0.78;0.07)
Obese[a]	**-1.44 (-2.45;-0.42)**	-0.47 (-1.07;0.13)
Waist circumference, per SD	**-0.48 (-0.85;-0.10)**	-0.01 (-0.23;0.21)
Elevated waist circumference	**-0.81 (-1.54;-0.07)**	-0.27 (-0.71;0.17)
Waist-to-hip ratio, per SD	**-0.49 (-0.90;-0.09)**	0.18 (-0.07;0.42)
Diabetes	-0.43 (-1.40;0.55)	-0.13 (-0.72;0.46)
Hypertension	-0.09 (-0.78;0.59)	0.13 (-0.28;0.54)
High-density lipoprotein cholesterol, per SD	0.32 (-0.11;0.75)	-0.10 (-0.35;0.16)
Triglycerides, per SD*	0.31 (-0.07;0.69)	0.05 (-0.17;0.28)
eGFR, per SD	-0.16 (-0.82;0.50)	0.16 (-0.23;0.55)
Albumin-to-creatinine ratio, per SD*	-0.08 (-0.40;0.23)	0.02 (-0.16;0.21)
Abnormal AC-ratio or eGFR[b]	0.38 (-0.49;1.25)	-0.21 (-0.74;0.32)
Abnormal AC-ratio and eGFR[b]	-0.01 (-2.23;2.20)	-0.32 (-1.73;1.09)
Alanine transaminase, per SD*	0.19 (-0.25;0.63)	-0.00 (-0.26;0.26)
Aspartate transaminase, per SD*	-0.27 (-0.68;0.13)	-0.13 (-0.37;0.11)
Bilirubin, per SD*	-0.15 (-0.48;0.17)	-0.03 (-0.22;0.17)
Alkaline phosphatase, per SD	-0.24 (-0.55;0.08)	-0.01 (-0.20;0.17)
Gamma-glutamyl transferase, per SD*	0.15 (-0.24;0.53)	0.06 (-0.17;0.29)
Past smoking[c]	0.06 (-0.64;0.76)	0.26 (-0.15;0.67)
Current smoking[c]	-0.47 (-1.47;0.52)	-0.04 (-0.65;0.56)
Alcohol, per SD	0.20 (-0.14;0.55)	-0.01 (-0.23;0.20)

Values represent the change in nerve conduction parameter per SD (continuous determinants) or per category (categorical determinants) difference of the characteristics shown.

Adjusted for age, sex, height, weight (if applicable), diabetes mellitus, high-density lipoprotein cholesterol, triglycerides, hypertension, eGFR and AC-ratio (if applicable), liver enzymes, smoking, alcohol and time between laboratory assessment and NCS (if applicable)

[a] Compared to body mass index < 25

[b] Compared to normal eGFR and normal AC-ratio

[c] Compared to never smokers

* Log-transformed values

SD: standard deviation; eGFR: estimated glomerular filtration rate; AC-ratio: albumin-to-creatinine ratio

concerning the frequency and significance of abnormal NCS amplitudes in otherwise healthy elderly have been inconsistent.[10-13, 16, 17] One large retrospective study found a high percentage of absent NCS responses in old age groups[10], while other smaller, clinic-based studies found only a few or none participants with unobtainable sural SNAP amplitudes.[11-13, 15-17] In our study, sural SNAP amplitudes were abnormal in 9.9% of participants and absent in 6.8% of participants, and this proportion increased with age. We might even have underestimated this proportion: temperature is inversely related to NCS amplitudes, it is thus possible that participants with cold feet had artificially high amplitudes.[30] This is supported by the findings of our sensitivity analyses, showing a higher percentage of participants with abnormal values after excluding participants with cold feet (<29 degrees Celsius). Given this high frequency of abnormal NCS amplitudes in elderly without symptoms or signs of polyneuropathy, the results of such findings should be interpreted in combination with other findings of a neurological examination. On its own, a reduced sural SNAP amplitude might not be clinically relevant, similar to reduced or absent ankle reflexes or distal vibration sensation, which are also quite common findings in elderly without polyneuropathy.[31] Whether such observations, especially in elderly, should even be considered as abnormal is debatable.

Besides age, we found that several measures of body mass were independently related to lowered sural SNAP and peroneal CMAP amplitudes. It has been suggested that measuring NCS amplitudes is less reliable in heavy people due to attenuation of amplitudes by a thicker layer of subcutaneous tissue.[12, 32] An alternative explanation is that these lower amplitudes can be an early sign of peripheral nerve dysfunction. Given our findings of a relation with especially abdominal obesity (waist circumference and waist-to-hip ratio), the latter explanation might be more likely. Obesity has been linked to polyneuropathy and lowered intra-epidermal nerve fiber density in several studies, including our own recent study where we investigated the effect of different components of metabolic syndrome on polyneuropathy and nerve conduction values.[19, 33-36] Therefore, correcting NCS values for BMI as a confounding measurement seems not appropriate.[12, 14, 32]

We found that hypertension and kidney dysfunction independently related to abnormal sural SNAP amplitudes, but not with other NCS measures. Around 60-90% of patients with end-stage chronic kidney disease who require dialysis have an uremic neuropathy.[21] When this neuropathy exactly develops during the course of chronic kidney disease is not known, but it has been suggested that neuropathy is limited to patients with end-stage kidney disease, which means an eGFR <15 ml/min.[21] Interestingly, none of the participants in our study had such a low eGFR and only five participants had an eGFR below 30 ml/min. Even when excluding these participants, we found a similar association of mild to moderate kidney dysfunction with reduced sural nerve action potential amplitudes (results not shown). Whether peripheral nerve injury already starts in an early stage of kidney dysfunction needs to be further investigated.

We did not observe associations with lipid levels, smoking, or liver enzymes. Nor did we find associations with diabetes and alcohol use, even though excessive alcohol use and diabetes are known risk factors for polyneuropathy. There are several explanations for these findings. First, there were few participants who were overusing alcohol. Second, alcohol use was assessed by self-report, and underreporting of alcohol intake is common.[37] A surprising finding is that diabetes mellitus in this study did not relate to reduced sural SNAP or peroneal CMAP amplitudes. This is likely caused by the selection of participants for this study, as those with clinical symptoms or signs of neuropathy were excluded, because we were interested in what happened with nerve function prior to the onset of clinical polyneuropathy. Diabetics are often screened by their doctors and educated about the occurrence of complications like neuropathy. We suspect that these individuals are more likely to report symptoms and are more often and early on diagnosed with neuropathy, and thus excluded from this study. The remaining diabetics in our study sample may have too mild or early diabetes to show a significant effect on nerve dysfunction. Unfortunately, we did not have sufficient data to further study this.

The strengths of our study include the population-based design, which led to an unselected sample of the general population, the inclusion of a large sample of elderly persons, and the prospective and extensive data collection. The main limitation of our population-based study is that we could not preheat the legs before performing NCS. Although the results of our sensitivity analyses were similar to the main analyses, we cannot rule out this has influenced our results. A second limitation is that we had to use blood samples taken at a previous visit for a subset of the population. We adjusted the analyses for the time between NCS and blood sampling to take this into account, but since blood measurements can change over time, this may have influenced our results.

In conclusion, sural and peroneal nerve amplitudes gradually decline with advancing age. Increased body mass, and obesity are independently associated with reduced action potential amplitudes of these nerves. Moderate kidney dysfunction and hypertension might further contribute to impaired functioning of especially sensory nerves. These results suggest a gradual decline in peripheral nerve function in the presence of these potentially modifiable metabolic factors, even before symptoms or signs of polyneuropathy develop. Longitudinal studies are required to investigate whether these factors predispose for the development of polyneuropathy.

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Supplementary table 1. Determinants of abnormal nerve conduction parameters in individuals *without clinical suspicion* of polyneuropathy in the total sample of participants, and in the sample excluding limbs <29 degrees Celsius

	Abnormal sural NAP amplitude OR (95% C.I.)		Abnormal peroneal CMAP amplitude OR (95% C.I.)	
	All participants	<29 degrees excluded	All participants	<29 degrees excluded
Age, per SD	**3.81 (2.77;5.24)**	**4.01 (2.76;5.83)**	**1.77 (1.35;2.33)**	**1.58 (1.16;2.14)**
Female sex	1.75 (0.87;3.49)	**2.48 (1.14;5.40)**	1.26 (0.63;2.54)	1.43 (0.64;3.22)
Height, per SD	**1.89 (1.30;2.74)**	**2.23 (1.46;3.39)**	**1.49 (1.03;2.14)**	1.44 (0.93;2.22)
Weight, per SD	**1.62 (1.18;2.21)**	**1.58 (1.12;2.24)**	**1.47 (1.10;1.98)**	**1.56 (1.13;2.17)**
Body mass index, SD	**1.48 (1.14;1.93)**	**1.46 (1.09;1.95)**	**1.39 (1.09;1.78)**	**1.46 (1.11;1.92)**
Overweight[a]	**2.15 (1.20;3.84)**	**2.23 (1.18;4.23)**	1.59 (0.90;2.82)	1.73 (0.90;3.32)
Obese[a]	**2.75 (1.28;5.92)**	**2.43 (1.04;5.72)**	1.95 (0.93;4.08)	1.81 (0.78;4.19)
Waist circumference, per SD	**1.51 (1.16;1.95)**	**1.59 (1.16;2.17)**	1.19 (0.92;1.55)	1.22 (0.92;1.62)
Elevated waist circumference	**2.18 (1.20;3.93)**	**2.39 (1.22;4.67)**	1.16 (0.67;1.99)	1.35 (0.71;2.55)
Waist-to-hip ratio, per SD	**1.35 (1.03;1.78)**	**1.58 (1.09;2.28)**	1.07 (0.79;1.45)	1.11 (0.81;1.51)
Diabetes	0.93 (0.44;1.96)	0.94 (0.42;2.12)	0.40 (0.14;1.15)	0.50 (0.17;1.43)
Hypertension	**2.22 (1.23;4.02)**	**2.16 (1.15;4.03)**	1.04 (0.62;1.76)	1.19 (0.66;2.16)
HDL cholesterol, per SD	0.82 (0.62;1.09)	0.85 (0.63;1.16)	0.91 (0.69;1.20)	0.96 (0.71;1.30)
Triglycerides, per SD*	1.11 (0.87;1.42)	1.08 (0.83;1.40)	1.03 (0.81;1.32)	0.95 (0.72;1.26)
eGFR, per SD	0.96 (0.59;1.56)	1.16 (0.67;2.01)	0.94 (0.58;1.52)	0.88 (0.51;1.52)
AC-ratio, per SD*	1.20 (0.95;1.51)	1.22 (0.95;1.56)	1.00 (0.79;1.28)	1.04 (0.80;1.35)
Abnormal AC-ratio or eGFR[b]	1.17 (0.58;2.36)	1.11 (0.51;2.41)	1.01 (0.50;2.03)	1.06 (0.49;2.28)
Abnormal AC-ratio and eGFR[b]	**5.12 (1.55;16.85)**	**5.23 (1.48;18.46)**	3.08 (0.91;10.44)	3.00 (0.79;11.35)
Alanine transaminase, per SD*	0.89 (0.70;1.14)	0.81 (0.62;1.06)	0.95 (0.74;1.22)	1.02 (0.78;1.34)
Aspartate transaminase, per SD*	1.08 (0.82;1.42)	1.07 (0.80;1.44)	1.05 (0.82;1.36)	1.09 (0.84;1.41)
Bilirubin, per SD*	1.06 (0.82;1.36)	1.04 (0.79;1.37)	0.93 (0.72;1.19)	0.93 (0.70;1.24)
Alkaline phosphatase, per SD	0.97 (0.79;1.18)	0.96 (0.78;1.18)	1.03 (0.84;1.26)	1.00 (0.80;1.27)
Gamma-GT per SD*	0.95 (0.73;1.23)	0.89 (0.66;1.20)	0.95 (0.73;1.24)	0.98 (0.73;1.32)
Past smoking[c]	1.16 (0.67;1.99)	1.13 (0.62;2.04)	1.13 (0.64;1.99)	1.19 (0.63;2.23)
Current smoking[c]	0.85 (0.32;2.22)	1.12 (0.41;3.06)	1.90 (0.89;4.04)	1.80 (0.76;4.23)
Alcohol, per SD	1.00 (0.77;1.31)	1.05 (0.80;1.39)	0.77 (0.57;1.03)	0.70 (0.49;1.00)

Values represent odds ratios comparing odds on impairment in nerve conduction parameter per SD (continuous determinants) or per category (categorical determinants).

Adjusted for age, sex, height and time between laboratory assessment and NCS (if applicable)

[a] Compared to body mass index < 25

[b] Compared to normal eGFR and normal AC-ratio

[c] Compared to never smokers

* Log-transformed values

SD: standard deviation; eGFR: estimated glomerular filtration rate; AC-ratio: albumin-to-creatinine ratio

Supplementary table 2. Determinants of nerve conduction parameters in individuals *without clinical or electrophysiological suspicion* of polyneuropathy in the total sample of participants, and in the sample excluding limbs <29 degrees Celsius

	Change in sural SNAP amplitude, µV β (95% C.I.)		Change in peroneal CMAP amplitude, mV β (95% C.I.)	
	All participants	<29 degrees excluded	All participants	<29 degrees excluded
Age, per SD	**-2.29 (-2.61;-1.96)**	**-1.85 (-2.20;-1.49)**	**-0.55 (-0.74;-0.36)**	**-0.49 (-0.71;-0.27)**
Female sex	-0.30 (-1.16;0.56)	-0.68 (-1.62;0.25)	-0.18 (-0.69;0.33)	-0.25 (-0.84;0.34)
Height, per SD	**-1.63 (-2.07;-1.18)**	**-1.38 (-1.88;-0.89)**	-0.25 (-0.51;0.02)	-0.27 (-0.59;0.05)
Weight, per SD	**-0.49 (-0.85;-0.13)**	**-0.74 (-1.13;-0.36)**	-0.08 (-0.29;0.14)	-0.09 (-0.34;0.15)
Body mass index, per SD	**-0.42 (-0.72;-0.12)**	**-0.65 (-0.97;-0.33)**	-0.07 (-0.24;0.11)	-0.08 (-0.28;0.13)
Overweight[a]	0.10 (-0.55;0.76)	-0.21 (-0.92;0.49)	-0.19 (-0.57;0.20)	-0.22 (-0.66;0.22)
Obese[a]	**-1.39 (-2.26;-0.52)**	**-1.98 (-2.91;-1.06)**	-0.22 (-0.74;0.30)	-0.21 (-0.80;0.38)
Waist circumference, per SD	**-0.43 (-0.74;-0.11)**	**-0.57 (-0.93;-0.22)**	0.05 (-0.13;0.24)	0.01 (-0.20;0.22)
Elevated waist circumference	**-0.79 (-1.42;-0.15)**	**-0.99 (-1.67;-0.30)**	-0.06 (-0.44;0.32)	-0.16 (-0.60;0.28)
Waist-to-hip ratio, per SD	**-0.43 (-0.78;-0.07)**	-0.43 (-0.86;0.00)	0.19 (-0.02;0.40)	0.14 (-0.09;0.37)
Diabetes	-0.67 (-1.59;0.24)	-0.82 (-1.75;0.11)	-0.16 (-0.71;0.38)	-0.10 (-0.73;0.52)
Hypertension	-0.15 (-0.77;0.47)	-0.31 (-0.97;0.35)	0.14 (-0.23;0.51)	0.04 (-0.38;0.46)
HDL cholesterol, per SD	**0.35 (0.03;0.68)**	0.32 (-0.03;0.66)	-0.06 (-0.25;0.13)	-0.11 (-0.33;0.10)
Triglycerides, per SD*	0.08 (-0.22;0.38)	-0.06 (-0.37;0.25)	0.09 (-0.09;0.27)	0.13 (-0.08;0.33)
eGFR, per SD	-0.24 (-0.87;0.39)	0.03 (-0.64;0.70)	0.10 (-0.27;0.48)	0.02 (-0.41;0.45)
AC-ratio, per SD*	-0.10 (-0.41;0.51)	-0.15 (-0.47;0.17)	0.03 (-0.15;0.21)	0.01 (-0.19;0.22)
Abnormal AC-ratio or eGFR[b]	0.18 (-0.67;1.02)	-0.04 (-0.92;0.83)	-0.23 (-0.74;0.28)	-0.31 (-0.87;0.25)
Abnormal AC-ratio and eGFR[b]	-0.12 (-2.30;2.07)	-0.37 (-2.41;1.67)	-0.30 (-1.68;1.08)	-0.16 (-1.64;1.33)
Alanine transaminase, per SD*	0.04 (-0.26;0.35)	0.18 (-0.14;0.50)	-0.04 (-0.22;0.14)	-0.04 (-0.24;0.16)
Aspartate transaminase, per SD*	-0.06 (-0.37;0.24)	0.10 (-0.22;0.41)	-0.10 (-0.28;0.08)	-0.09 (-0.29;0.11)
Bilirubin, per SD*	-0.02 (-0.33;0.28)	-0.05 (-0.37;0.27)	-0.03 (-0.21;0.15)	-0.03 (-0.25;0.18)
Alkaline phosphatase, per SD	-0.26 (-0.56;0.04)	-0.20 (-0.49;0.09)	0.01 (-0.17;0.18)	0.05 (-0.14;0.24)
Gamma-GT per SD*	0.13 (-0.19;0.44)	0.22 (-0.12;0.55)	0.03 (-0.15;0.22)	-0.00 (-0.22;0.21)
Past smoking[c]	0.28 (-0.38;0.94)	0.64 (-0.06;1.34)	0.13 (-0.25;0.52)	0.07 (-0.37;0.50)
Current smoking[c]	-0.29 (-1.22;0.65)	-0.10 (-1.12;0.92)	0.10 (-0.46;0.65)	-0.02 (-0.66;0.61)
Alcohol, per SD	0.29 (-0.02;0.59)	0.32 (-0.02;0.66)	0.01 (-0.17;0.19)	-0.04 (-0.58;0.06)

Values represent the change in nerve conduction parameter per SD (continuous determinants) or per category (categorical determinants) difference of the characteristics shown.

Adjusted for age, sex, height and time between laboratory assessment and NCS (if applicable)

[a] Compared to body mass index < 25

[b] Compared to normal eGFR and normal AC-ratio

[c] Compared to never smokers

* Log-transformed values

SD: standard deviation; eGFR: estimated glomerular filtration rate; AC-ratio: albumin-to-creatinine ratio

4

Chapter 5

**The impact of polyneuropathy
and related disorders on daily life**

Chapter 5.1

Polyneuropathy relates to impairment in daily activities, worse gait and fall-related injuries

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ABSTRACT

Objective: To extensively investigate the association of chronic polyneuropathy with basic and instrumental activities of daily living (BADL and IADL), falls and gait.

Methods: 1445 participants of the population-based Rotterdam Study (mean age 71 years, 54% women) underwent a polyneuropathy screening involving a symptom questionnaire, neurological examination and nerve conduction studies. Screening yielded four groups: no, possible, probable and definite polyneuropathy. Participants were interviewed about BADL (Stanford Health Assessment questionnaire), IADL (Instrumental Activities of Daily Living scale) and frequency of falling in the previous year. In a random subset of 977 participants, gait was assessed with an electronic walkway. Associations of polyneuropathy with BADL and IADL were analyzed continuously with linear regression, and dichotomously with logistic regression. History of falling was evaluated with logistic regression and gait changes were evaluated with linear regression.

Results: Participants with definite polyneuropathy had more difficulty in performing BADL and IADL than participants without polyneuropathy. Polyneuropathy related to worse scores of all BADL (especially walking) and three IADL components (housekeeping, traveling, and shopping). Participants with definite polyneuropathy were more likely to fall, and these falls more often resulted in injury. Participants with polyneuropathy had worse gait parameters on the walkway, including lower walking speed and cadence, and more errors in tandem walking.

Conclusions: Chronic polyneuropathy strongly associates with impairment in the ability to perform daily activities and relates to worse gait and an increased history of falling.

INTRODUCTION

The ability to walk and to perform daily activities is an important health indicator that strongly relates to the risk of future morbidity and mortality.[1, 2] Disability in activities of daily living (ADL) can result in loss of the ability to function independently in society, which ultimately leads to institutionalization and a reduced quality of life.[3, 4]

Proper functioning in ADL requires integration of input from various systems. The peripheral nervous system plays a key role in this integration by conducting important information from all body parts towards the central nervous system and vice versa. In persons with polyneuropathy this information throughput is disturbed, typically leading to sensory disturbances, balance problems and walking instability. Studies showed that polyneuropathy affects mobility and leads to a reduced quality of life.[5-11] Additionally, persons with polyneuropathy have an increased risk of falling, which is associated with significant morbidity, loss of independence and mortality.[12-14] It is thus not surprising that polyneuropathy can severely reduce a person's ability to perform ADL.[5, 13-16]

Still, several knowledge gaps remain. First, ADL consist of physical basic activities of daily living (BADL)[17, 18], and of cognitively more challenging instrumental activities of daily living (IADL)[19], each comprising different components that cover more than just mobility. Whether polyneuropathy-related impairment extends beyond purely physical activities has not been investigated in detail. Second, patients with chronic polyneuropathy have an increased risk of falls, but whether this also relates to an increased risk of fall-related injuries is less clear. Moreover, the role of falls in the association of polyneuropathy with ADL is undetermined. Third, although it is known that persons with polyneuropathy have gait difficulties due to proprioceptive and non-proprioceptive sensory loss and motor weakness, there is little data about which specific spatiotemporal aspects of gait are predominantly affected. Gait is a complex process, comprising several different gait domains, each capturing a certain independent aspect of gait.[20] Studies have shown different gait domains to be associated with variations in pathology, but the link with polyneuropathy is underexplored.

There are a few small studies that addressed some of these issues, but only in selected patient groups, mostly consisting of subjects with diabetes mellitus or those receiving chemotherapy, precluding generalization to the general population.[21-23] Polyneuropathy is a common disorder in the general population, especially among elderly.[24] Therefore, further research is required to address these knowledge gaps. We investigated the relation of polyneuropathy with ADL and its individual components. Additionally, we studied the relation of polyneuropathy with gait and with falls and related injuries in the large population-based Rotterdam Study.

METHODS

Study population

This study was embedded in the Rotterdam Study, a prospective, population-based cohort study initiated in 1990.[25] Participants of this study, individuals over 45 years, reside in a specific district of Rotterdam, the Netherlands. Every 3 to 4 years, participants visit the (single) research center of the Rotterdam Study where they undergo extensive interviews and examinations to facilitate the investigation of epidemiological characteristics of chronic diseases. In total, 14926 individuals agreed to participate (overall response rate 72%).

From 2013 onwards, a polyneuropathy screening was added to the core protocol of the Rotterdam Study. The current study includes all individuals that underwent this screening between June 2013 and January 2016. During this period, 1726 participants were randomly invited. Ninety-seven participants did not undergo the neuropathy screening and 165 participants were excluded because they were not sufficiently screened in order to complete the diagnostic process, mainly due to logistic reasons. Of the remaining 1464 participants, 19 had missing ADL data. The final study population for ADL- and fall-related analyses comprised 1445 participants, including a random subset of 977 persons with fully processed gait data.

Standard protocol approvals, registrations and patient consents

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Polyneuropathy screening

A detailed description of the polyneuropathy screening can be found elsewhere.[24] In brief, the screening consisted of three parts: a symptom questionnaire, neurological examination of the legs (vibration and pin sensibility, tendon reflexes, muscle strength), and nerve conduction studies (bilateral sural nerve and unilateral peroneal nerve). A team of well-trained examiners screened all participants using exactly the same protocol. Medical records were scrutinized in case of a self-reported diagnosis of polyneuropathy, and in case of an abnormal part of the screening, to identify participants who were already diagnosed with polyneuropathy. An expert panel categorized all participants case-by-case into no, possible, probable or definite polyneuropathy, depending on the estimated likelihood of the diagnosis. Definite polyneuropathy typically required abnormality in all three parts of the screening, or a previously made diagnosis

of polyneuropathy by a neurologist (which is considered superior to our screening, since this contains a complete work-up according to hospital guidelines). Participants with no abnormal parts of the screening were categorized as no polyneuropathy. The remaining participants were categorized as possible or probable polyneuropathy, depending on the level of abnormality of the screening.[24]

Assessment of daily functioning

Daily functioning was assessed with questionnaires on BADL and IADL. BADL was assessed using the Stanford Health Assessment Questionnaire.[17] This questionnaire consists of 20 items constituting eight components: dressing and grooming, arising, eating, walking, hygiene, grip, reach and activities. Items were scored from 0 to 3, with higher scores indicating worse ability (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to). Component scores were calculated as the highest scored item per component.[17] The BADL score was calculated by summing all components, obtaining a score from 0 to 24. A score of 0 to 8 reflects no to mild impairment, a score above 8 reflects moderate to very severe impairment.[18]

IADL was assessed with the Lawton and Brody Instrumental Activities of Daily Living scale.[19] This scale also consists of eight components: shopping, meal preparation, laundry, medication maintenance, management of finances, housekeeping, traveling alone and using a telephone. Consistent with BADL, these items were scored from 0 to 3. If participants reported that they did not perform certain activities, these items were scored as non-applicable (5.5% of the IADL variables). To prevent selective loss of data, these items were imputed by the mean of five imputations, based on age, sex, all BADL items and all other available IADL items. The IADL score was then calculating by summing the eight components, yielding a score from 0 to 24. Similar to BADL, a score from 0 to 8 was considered as no to mild impairment, and a score above eight was considered as moderate to very severe impairment.

Assessment of falls

Participants were asked whether they fell during the last twelve months. If so, participants were subsequently asked whether this (or these) fall(s) ever resulted in serious injuries, like fractures, head trauma, severe bruises or lacerations or sustained complaints of pain. Falls were dichotomized in no falls or any fall. Additionally, we divided participants who reported at least one fall in the last year into falls with and falls without self-reported injury.

Assessment of gait

Gait was assessed with a 5.79 meter electronic walkway (4.88 meter active area; GAITRite Platinum; CIR systems, USA). Details about the gait assessment have been published elsewhere.[20] In summary, gait was assessed in three walking conditions: normal walk

(walking at usual pace), turn (turning halfway) and tandem walk (heel-to-toe walking over a line). This assessment yielded 30 different spatiotemporal variables, which we summarized using principal component analysis with varimax rotation into seven inde-pendent domains: Rhythm (temporal variables such as single support time, cadence), Variability (variability in length and time among strides), Phases (double support time, swing time as a percentage of stride time), Pace (velocity, step length), Base of Support (stride width), Turning (turning time, turning step count) and Tandem (errors in heel-to-toe walking). The seven gait domains were z-standardized and averaged into Global gait. Lower values of gait can be considered "worse" gait. Gait data was available for participants that visited the research center between June 2013 and June 2015. During this period 977 participants underwent this assessment.

Covariates

We collected data about height and weight and we calculated body mass index (weight in kilograms divided by height squared in meters). Blood pressure was measured (mean of two consecutive readings) and use of antihypertensive and other medications was evaluated, including lipid lowering and antidiabetic medication. Blood samples were drawn to assess lipid levels and serum glucose. Diabetes mellitus was assessed as a fasting glucose ≥7.0 mmol/L, a non-fasting glucose ≥11.1 mmol/L, use of antidiabetic treatment or a previous diabetes mellitus diagnoses as identified through a link with general practitioner's records. Smoking was categorized as never, former, or current.

Statistical analyses

Associations between polyneuropathy and ADL were investigated in two ways. First, we applied linear regression to investigate the association of polyneuropathy with continuous BADL and IADL scores, using dummy variables. Second, BADL and IADL were dichotomized at a score of 8. Individuals with a score between 0 and 8 were con-sidered not impaired, and individuals with a score above 8 were considered impaired.[26] Logistic regression was used to investigate the association of polyneuropathy with impairment in ADL. These two analyses were repeated after exclusion of participants with diabetes mellitus to investigate whether associations were mainly attributable to diabetic neuropathy, or were also present in participants with polyneuropathy of other, mainly idiopathic, origin.[24] Linear and logistic regression were also used to investigate associations of polyneuropathy with separate BADL and IADL component scores. For the logistic regression, individuals with a score of 0 to 1 were considered not impaired, and above 1 impaired.

   The association of polyneuropathy with falls and self-reported fall-related injury was investigated with logistic regression and we explored to what extent the association between polyneuropathy and ADL was affected by a history of falling.

We investigated the association of polyneuropathy with gait using linear regression. Besides Global gait and the seven domains, we also included two of the most studied original gait variables (velocity and cadence) into the analyses.

Analyses were adjusted for age, sex, body mass index, diabetes mellitus, blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking. Analyses involving Tandem were additionally adjusted for step count and step length in tandem walking. All statistical analyses were performed using the IBM SPSS statistical package, version 21.0.0.1 for windows.

RESULTS

We included 1445 participants, mean age 70.7 years (standard deviation (SD) 9.7), of which 781 (54.0%) were women (Table 1). Possible, probable and definite polyneuropathy were present in 265 (18.3%), 111 (7.7%) and 81 (5.6%) participants respectively. The mean BADL score in the total sample was 3.1 (SD 3.3), the mean IADL score was 1.7 (SD 2.6), 115 (8.0%) participants had impairment in BADL and 46 (3.2%) had impairment in IADL. During the last twelve months, 336 (23.3%) participants at least fell once.

Table 1. Population characteristics

Characteristic	Total population (n=1445)
Age, years	70.7 (9.7)
Women, n	781 (54.0)
Polyneuropathy status	
No polyneuropathy, n	988 (68.4)
Possible polyneuropathy, n	265 (18.3)
Probable polyneuropathy, n	111 (7.7)
Definite polyneuropathy, n	81 (5.6)
Diabetes mellitus, n	209 (14.8)
Body mass index, kg/m^2	27.0 (3.9)
Systolic blood pressure, mmHg	137.3 (19.5)
Diastolic blood pressure, mmHg	77.6 (11.0)
Antihypertensive medication, n	603 (41.9)
Triglyceride levels, mmol/L	1.4 (0.7)
High-density lipoprotein cholesterol, mmol/L	1.5 (0.4)
Lipid lowering medication, n	423 (29.4)
Current smoking, n	181 (12.6)
Former smoking, n	794 (55.2)

Values represent number (%) or mean (standard deviation). Percentages were calculated without missing values.

Polyneuropathy and activities of daily living

A stronger likelihood of polyneuropathy associated with higher ADL scores (Table 2), indicating worse ability to perform these activities. Definite polyneuropathy associated with a 2.98 (95% confidence interval (CI) 2.29;3.68) points higher BADL score and 0.82 (95% CI 0.24;1.41) points higher IADL score than participants without polyneuropathy. Polyneuropathy also associated with more ADL impairment (Table 2). With increasing diagnostic certainty of polyneuropathy, the association with especially BADL impairment increased likewise. Participants with definite polyneuropathy were 6.41 (95% CI 3.19;12.88) times more likely to have impairment in BADL and 1.74 (95% CI 0.59;5.10) times more likely to have impairment in IADL, though the latter association was not statistically significant. After excluding participants with diabetes mellitus, associations were similar (Supplementary table 1).

Table 2. Association between the presence of polyneuropathy and impairment in activities of daily living

	Basic activities of daily living		Instrumental activities of daily living	
	Difference in score (95% CI)	BADL impairment OR (95% CI)	Difference in score (95% CI)	IADL impairment OR (95% CI)
Possible polyneuropathy	1.18 (0.77;1.60)	3.23 (1.92;5.45)	0.79 (0.44;1.13)	1.71 (0.75;3.90)
Probable polyneuropathy	1.72 (1.12;2.32)	3.56 (1.83;6.94)	0.63 (0.12;1.13)	2.24 (0.88;5.69)
Definite polyneuropathy	2.98 (2.29;3.68)	6.41 (3.19;12.88)	0.82 (0.24;1.41)	1.74 (0.59;5.10)

Values represent the difference in score or odds ratios of prevalent impairment in BADL or IADL (95% confidence intervals), compared to participants with no polyneuropathy. Higher scores reflect poorer functioning. Analyses were adjusted for age, sex, body mass index, diabetes mellitus, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking
BADL: basic activities of daily living; IADL: instrumental activities of daily living; OR: odds ratio; CI: confidence interval

Table 3. Association between the presence of polyneuropathy and history of falling

	Falls OR (95% CI)	Fall-related injury OR (95% CI)	
		Fall without injury	Fall with injury
Possible polyneuropathy	1.14 (0.81;1.60)	0.86 (0.56;1.32)	1.69 (0.72;3.96)
Probable polyneuropathy	1.30 (0.81;2.09)	1.17 (0.67;2.06)	2.30 (0.72;7.32)
Definite polyneuropathy	1.87 (1.10;3.16)	1.64 (0.89;3.02)	3.35 (1.02;10.97)

Values represent the odds ratios of falling (95% confidence intervals) compared to participants with no polyneuropathy.
Adjusted for age, sex, body mass index, diabetes mellitus, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking
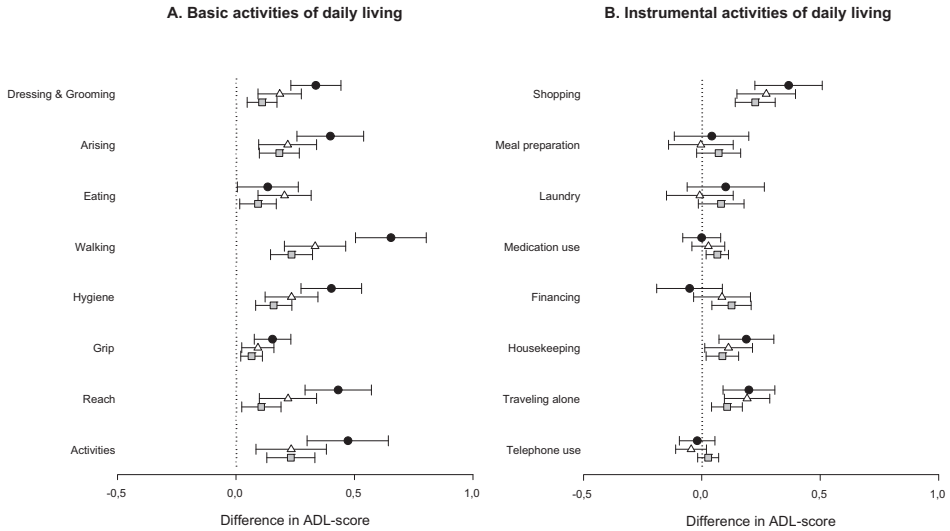OR: odds ratio; CI: confidence interval

Figure 1. Association between polyneuropathy and components of ADL. The symbols represent the difference in ADL-scores compared to participants with no polyneuropathy (dotted reference line). A higher score indicates poorer functioning. Black circles represent participants with a definite polyneuropathy, white triangles represent participants with a probable polyneuropathy and grey squares represent participants with a possible polyneuropathy. Error bars represent the 95% confidence interval around the difference. Analyses were adjusted for age, sex, body mass index, diabetes mellitus, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking. ADL: activities of daily living

Figure 1 shows the association of polyneuropathy with ADL component scores and Supplementary table 2 shows the association with impairment in ADL components. Polyneuropathy related to higher scores and more impairment in almost all BADL components (especially walking and hygiene) and in some IADL components (especially housekeeping and shopping).

Polyneuropathy and history of falling

Participants with polyneuropathy were almost two times more likely to have fallen in the preceding twelve months (OR 1.87, 95% CI 1.10;3.16, Table 3) and polyneuropathy especially related to falls that resulted in injury (OR 3.35, 95% C.I. 1.02;10.97). As with BADL, associations were stronger with increasing diagnostic certainty of polyneuropathy. Adjusting the analyses between polyneuropathy and ADL for falls had no effect on the associations reported in the previous section.

Polyneuropathy and gait

In the subset of 977 participants with gait data available, 143 (14.6%) had possible polyneuropathy, 60 (6.1%) had probable polyneuropathy and 40 (4.1%) had definite

polyneuropathy. Definite polyneuropathy associated with worse Global gait (difference in z-score -0.76 95% CI -1.04;-0.48, see Figure 2). Rhythm (difference in z-score -0.46, 95% CI -0.77;-0.15), Phases (difference in z-score -0.38, 95% CI -0.66;-0.09) and Tandem (difference in z-score -0.57, 95% CI -0.90;-0.25) were the gait domains driving this as-
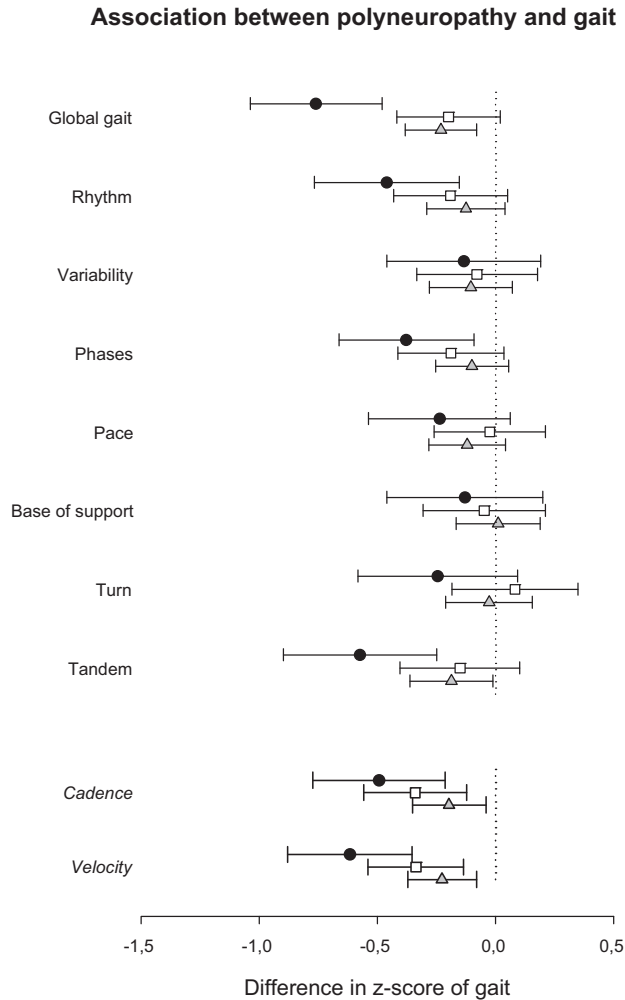
Association between polyneuropathy and gait

Figure 2. Association of polyneuropathy with gait. The symbols represent the difference (per standard deviation) in gait domains (bold) or original variables (italic) compared to participants with no polyneuropathy (dotted reference line). Negative values indicate worse gait. Black circles represent participants with a definite polyneuropathy, white triangles represent participants with a probable polyneuropathy and grey squares represent participants with a possible polyneuropathy. Error bars represent the 95% confidence interval around the difference. Analyses were adjusted for age, sex, body mass index, diabetes mellitus, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking. Tandem was additionally adjusted for step count and step length in tandem walking.

sociation. Participants with definite polyneuropathy also walked slower (11.3 centimeter per second slower, *p<0.01*) and with lower cadence (4.8 steps/minute less, *p<0.01*) than persons without polyneuropathy.

DISCUSSION

In this prospective population-based study, polyneuropathy strongly related to worse activities of daily living scores. Participants with polyneuropathy were six times more likely to have moderate to severe impairment in BADL, independent of comorbidities and falls. Besides walking difficulty, polyneuropathy also related to difficulty in arising, dressing, and even eating, among others. IADL were also affected by polyneuropathy, especially components that require much physical activity, like shopping and house-keeping. Polyneuropathy related to worse gait, mainly by interfering with the gait domains Rhythm, Phases and Tandem and participants with polyneuropathy were more likely to have fallen during the last twelve months.

Polyneuropathy is common in elderly, and its prevalence is expected to rise in the future because of an increased prevalence of diabetes mellitus, obesity and metabolic syndrome.[24] We showed that polyneuropathy is strongly related to impairment in walking and the ability to perform ADL, and to a higher probability of falling and related injuries. Impairment in the ability to walk and perform daily activities is associated with an increased risk of institutionalization.[3, 4] Despite the importance of polyneuropathy, the disease is often underreported and underdiagnosed.[14, 24]

A major strength of our study is that we quantified the effect of polyneuropathy on ADL, involving components of both basic and instrumental activities of daily living, while adjusting for comorbidities and falls. Additionally, our study was implemented in a large population-based study, in which all participants underwent an extensive polyneuropathy screening. This led to a reliable sample of the general population and a valid estimate of polyneuropathy and its effect on ADL. Of note, participants had to be able to visit the research center, which might be relatively healthy individuals. This could have resulted in an underestimation of the effect of polyneuropathy on ADL. Due to the cross-sectional design of our study we were not able to investigate a causal relationship, longitudinal studies are required to investigate the relation of polyneuropathy with incident ADL impairment.

Chronic axonal polyneuropathy, especially when idiopathic, is often considered a relatively mild condition that leads to only minor disability.[27] In our study, participants with definite polyneuropathy had BADL scores that were more than twice as high as participants with no polyneuropathy. Additionally, participants with definite polyneuropathy were more than 6 times more likely to have moderate to severe impairment in

BADL. These associations were independent of age, cardiovascular risk factors and falls. Associations were similar when excluding participants with diabetes mellitus, indicating that associations are not only driven by diabetic neuropathy, but also exists in other, mainly idiopathic, polyneuropathies. In our population-based study approximately half of the participants with polyneuropathy is newly diagnosed and it is likely that we diagnose participants in an earlier stage than in clinic-based studies.[24] Therefore, the effect of polyneuropathy on ADL might be even stronger in more advances stages of the condition. Our findings show that, although the clinical phenotype of (idiopathic) polyneuropathy may be relatively mild, patients may still experience much difficulty in performing basic daily activities.

We also showed that participants with polyneuropathy had more difficulty in IADL. One database-driven study also showed that individuals with polyneuropathy had more difficulty in IADL, but different components were not investigated.[13] In our study, polyneuropathy independently associated with more difficulty in the IADL domains shopping, housekeeping and traveling, which are the components that highly rely on mobility. Components that depend less on sensorimotor function, like laundry and management of finances and medication use, were not affected. Of the BADL components, polyneuropathy was also most strongly related with walking. Several studies showed that persons with polyneuropathy have impaired balance and motor performance, and low physical functioning scores, which probably explains most of these associations.[5-10, 15, 16, 28-30] However, we also found that polyneuropathy related to impairment in BADL components like dressing and grooming, eating and hygiene. This indicates that difficulty in performing ADL is not only caused by lower extremity dysfunction, but also by impairment in more subtle and precise movements of the upper extremities.[11]

We further investigated the association of polyneuropathy with walking using an objective, electronic gait assessment. Participants with definite polyneuropathy had worse Global gait, concurring with the self-reported difficulty in walking assessed in BADL. Gait domains that were affected most were Rhythm, Phases and Tandem. Additionally, participants with polyneuropathy had lower velocity and cadence. Different gait domains reflect different abilities, such as balance, physical strength and fine motor speed. Physical strength is most strongly related to the domains Rhythm and Pace.[26] Hence, reduced muscle strength, which can occur in polyneuropathy, may lead to worse Rhythm and Pace, providing an explanation for the associations with Rhythm, cadence and velocity. An alternative explanation is that individuals with polyneuropathy may adopt a more conservative gait pattern, with decreased walking speed, cadence and an increased double support time (Phases), to feel more secure during walking.[31] Balance and fine motor speed, often altered in polyneuropathy, are more closely related to Tandem, explaining the association found between polyneuropathy and Tandem.[26]

Chronic polyneuropathy is a disabling disorder that can lead to significant morbidity. Recognition of polyneuropathy and associated disability is therefore very important in order to inform, support and possibly treat patients, and prevent future falls and dependence in daily functioning.

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5

Supplementary table 1. Association between the presence of polyneuropathy and impairment in activities of daily living, *excluding participants with diabetes mellitus*

	Basic activities of daily living		Instrumental activities of daily living	
	Difference in score (95% CI)	BADL impairment OR (95% CI)	Difference in score (95% CI)	IADL impairment OR (95% CI)
Possible polyneuropathy	1.15 (0.71;1.59)	3.28 (1.83;5.87)	0.61 (0.25;0.97)	1.62 (0.62;4.28)
Probable polyneuropathy	1.68 (1.02;2.33)	3.75 (1.76;8.01)	0.56 (0.02;1.11)	2.64 (0.92;7.57)
Definite polyneuropathy	3.59 (2.75;4.42)	7.95 (3.51;17.96)	1.05 (0.35;1.74)	2.79 (0.82;9.52)

Values represent the difference in score or odds ratios of prevalent impairment in BADL or IADL (95% confidence intervals), compared to participants with no polyneuropathy. Higher ADL scores reflect poorer ADL. Analyses were adjusted for age, sex, body mass index, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking
BADL: basic activities of daily living; IADL: instrumental activities of daily living; OR: odds ratio; CI: confidence interval

Supplementary table 2. Polyneuropathy and odds ratios on impairment in activities of daily living

	Possible polyneuropathy OR (95% CI)	Probable polyneuropathy OR (95% CI)	Definite polyneuropathy OR (95% CI)
BADL			
Dressing & grooming	2.22 (0.86;5.75)	2.18 (0.61;7.84)	4.66 (1.35;16.01)
Arising	2.84 (1.65;4.88)	3.21 (1.64;6.27)	4.66 (2.25;9.62)
Eating	1.95 (1.07;3.54)	2.79 (1.33;5.84)	2.52 (1.05;6.08)
Walking	2.50 (1.56;4.02)	3.63 (2.02;6.51)	6.64 (3.55;12.39)
Hygiene	2.23 (1.12;4.47)	3.74 (1.68;8.36)	4.98 (2.12;11.69)
Grip	1.95 (0.49;7.74)	4.53 (0.95;21.69)	1.50 (0.15;14.78)
Reach	1.54 (0.83;2.84)	1.92 (0.87;4.27)	3.77 (1.72;8.23)
Activities	2.71 (1.74;4.22)	2.32 (1.26;4.25)	3.77 (1.98;7.19)
IADL			
Shopping	2.79 (1.67;4.67)	3.24 (1.68;6.23)	4.07 (1.99;8.32)
Meal preparation	1.16 (0.69;1.96)	0.99 (0.48;2.02)	1.29 (0.61;2.74)
Laundry	1.19 (0.72;1.96)	0.75 (0.36;1.55)	1.15 (0.55;2.39)
Medication use	2.26 (0.91;5.59)	1.33 (0.35;5.00)	0.71 (0.14;3.52)
Financing	2.06 (1.24;3.43)	1.37 (0.65;2.89)	0.80 (0.30;2.14)
Housekeeping	0.62 (0.22;1.73)	1.59 (0.58;4.33)	1.36 (0.41;4.50)
Traveling alone	2.72 (1.13;6.52)	4.21 (1.58;11.22)	2.73 (0.83;8.99)
Telephone use	1.31 (0.53;3.27)	0.43 (0.09;2.03)	0.54 (0.11;2.78)

Values represent the odds ratios for impairment in specific BADL and IADL components (95% confidence intervals) compared to persons with no polyneuropathy.
Adjusted for age, sex, body mass index, diabetes mellitus, diastolic blood pressure, systolic blood pressure, antihypertensive medication, triglyceride level, high-density lipoprotein cholesterol level, lipid lowering medication and smoking
BADL: basic activities of daily living; IADL: instrumental activities of daily living; OR: odds ratio; CI: confidence interval

Chapter 5.2

Gait characteristics in older adults with diabetes and impaired fasting glucose: the Rotterdam Study.

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ABSTRACT

Aims: To investigate the association of diabetes mellitus and impaired fasting glucose with gait in the general middle-aged and elderly population.

Methods: We performed a cross-sectional study on 3019 participants from the population-based Rotterdam Study (aged >45 years, 54% women). The presence of diabetes mellitus and impaired fasting glucose was evaluated by measuring serum glucose levels and by documenting anti-diabetic treatment. Participants underwent gait analysis using an electronic walkway. Over 30 gait variables were summarized into five independent gait domains for normal walking (*Rhythm*, *Variability*, *Phases*, *Pace* and *Base of Support*), one for turning (*Turning*) and one for walking heel to toe (*Tandem*), which were averaged into *Global Gait*. Linear regression analyses were performed to determine the association of diabetes, impaired fasting glucose and continuous glucose levels within the normal range with gait.

Results: Diabetes mellitus was associated with worse *Global Gait* (Z-score difference -0.19, 95% Confidence Interval (CI) -0.30;-0.07), worse *Pace* (-0.20, 95% CI -0.30;-0.10) and worse *Tandem* (-0.21, 95% CI -0.33;-0.09), after adjusting for age, sex, height and weight. The association with *Tandem* remained significant after additional adjustment for cardiovascular risk factors. Impaired fasting glucose and continuous glucose levels within the normal range were not associated with any of the gait domains.

Conclusion: In our population-based study diabetes mellitus was associated with worse *Global Gait*, which was mostly reflected in *Pace* and *Tandem*. These associations were partly driven by other cardiovascular risk factors, emphasizing the importance of optimal control of cardiovascular risk factor profiles in patients with diabetes.

INTRODUCTION

Diabetes mellitus is common in the elderly population and is a serious threat to an older person's quality of life. Complications such as polyneuropathy, retinopathy and peripheral artery disease can already be present at the moment of diagnosis of the disease.[1] This suggests that microvascular as well as macrovascular changes already occur in early stages of diabetes and perhaps even in a state before overt diabetes develops, which is often referred to as prediabetes.[2] These complications directly (neuropathy, peripheral artery disease) or indirectly (muscle weakness, ulcerations, cerebrovascular disease) lead to walking instability, falls, and fall-related injuries.[3-10] To detect the impact of diabetes on walking and lower limb performance in an early stage, extensive assessment of gait in different walking conditions may be useful.[10]

Gait is a complex concept that is increasingly recognized as a marker of general health.[11, 12] Gait is influenced by different organ systems, including the central and peripheral nervous system, central and peripheral circulation and the musculoskeletal system, all of which can be affected by diabetes mellitus. Dysfunction in any of these systems may lead to gait impairment, which in turn is associated with an increased risk of falling and higher mortality.[13, 14] Gait can be measured using many different spatiotemporal variables, which can be summarized into seven independent gait domains (Figure 1): *Rhythm* (cadence, stride time), *Variability* (variability in stride length and stride time), *Phases* (double support percentage of gait cycle), *Pace* (stride length, velocity), *Base of Support* (stride width and stride width variability) *Tandem* (number of side steps in walking heel to toe) and *Turning* (number of steps and turning time).[12, 13]

Previous case-control studies reported lower walking speed and cadence in individuals with diabetes[10, 15], but population-based data about the relation between diabetes and the gait pattern is lacking. In addition, since microvascular pathology can be present already early in the course of the disease[1], we hypothesized that subtle changes in specific gait domains can not only be found in participants with diabetes, but also in persons having only impaired fasting glucose or even a glucose level in the high range of normal.

Therefore, we aimed to investigate the association of diabetes mellitus and prediabetes (impaired fasting glucose) with gait and its separate domains in a community-dwelling population.
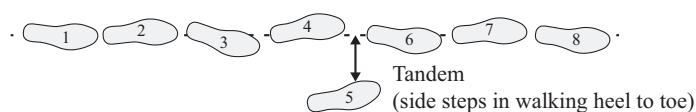
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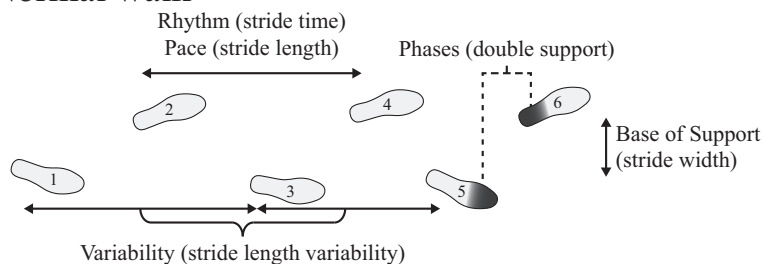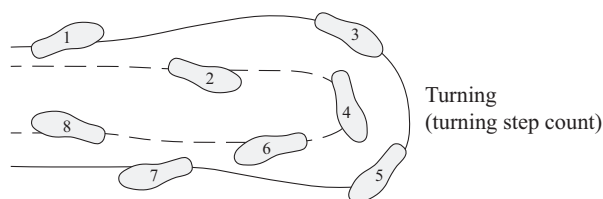
Figure 1. The three walking conditions. Gait assessment yielded seven gait domains, including five domains for normal walk (*Rhythm*, *Variability*, *Phases*, *Pace*, and *Base of Support*), one for the turn (*Turning*), and one for tandem walk (*Tandem*).

METHODS

Study setting, study design and study population

The study was embedded in the Rotterdam Study, a population-based cohort in the Netherlands that started in 1990. At the start of the study in 1990 and again in 2000, all people living in the Ommoord district of Rotterdam, aged 55 years and older were selected from the municipal population records and invited to participate in the study. In 2006 the cohort was extended with individuals that moved into the study area, aged 45 years and older. Residential area (ZIP code) and age were the only eligibility criteria used for inclusion of participants. In total, 14926 out of 20744 invited persons agreed to participate in the study (overall response rate 72%). At baseline and every 3-4 years of follow-up, all participants undergo a home interview and extensive medical examinations at the research center.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sports of the Netherlands,

implementing the "Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)". A written informed consent to participate in the study and to obtain information from their treating physicians was obtained from all participants.[16]

From March 2009 onwards, gait assessment was implemented in the core protocol of the study. The current study includes all participants that underwent gait assessment between March 2009 and March 2012. During this period 3666 persons were invited for gait measurements; after exclusion of 600 persons (207 persons were excluded due to physical health reasons, 296 because of technical problems, 46 participants did not follow or complete the entire protocol, 34 persons had fewer than 16 steps available for analyses, 15 had a repeated assessment and 2 persons were excluded for other reasons), 3066 participants were eligible for the study; 3019 of them had information about diabetes mellitus available. These 3019 participants were included in the analyses.

Diabetes mellitus and impaired fasting glucose assessment

Presence of diabetes mellitus and impaired fasting glucose was evaluated using laboratory data derived from blood sampling performed at the research center and with data on medication use. Medication use was assessed by self-report and by going through the medication cabinets in the home of the participants during the home interview. Diabetes was defined as a fasting glucose level ≥7.0 mmol/L, a non-fasting glucose level ≥11.1 mmol/L (if fasting samples were not available) or use of anti-diabetic therapy.[17] Impaired fasting glucose was defined according to the ADA 2010 diagnostic criteria as a fasting glucose level between 5.6 mmol/L and 6.9 mmol/L in the absence of diabetes.[2]

Gait assessment

Gait was assessed using a 5.79 meter long electronic walkway (4.88 meter of active area; GAITRite Platinum; CIR systems, Sparta, NJ, USA), that has been validated before.[18-20] Three walking conditions were recorded: normal walk, turning and tandem walk. In normal walk, participants were asked to walk across the electronic walkway at their own pace. In the turn, people walked across the walkway, turned halfway, and returned to their starting position. In tandem walk, participants walked heel-to-toe over a line visible on the walkway.

The walkway software was used to generate 30 different spatiotemporal gait variables; 25 for normal walk, 2 for turning and 3 for tandem walk. Principal components analysis (PCA) was used to summarize these 30 gait variables into independent gait domains, while capturing the largest amount of variance. Varimax rotation was used to make sure that the gait domains were mutually independent. The PCA resulted in seven independent domains: *Rhythm*, *Variability*, *Phases*, *Pace*, *Base of Support*, *Tandem* and *Turning*. Among others, *Rhythm* represents cadence and stride time; *Phases* represent double support time and double support as a percentage of the gait cycle;

Variability represents variability in stride length and stride time; *Pace* represents velocity and stride length; *Base of Support* represents stride width and stride width variability; *Tandem* represents errors in tandem walking; and *Turning* represents the number of turning steps and turning time (see Supplementary Table 1 and Figure 1). More details about the principal component analyses can be found elsewhere.[12, 13] These domains were standardized and, when necessary, inverted so that lower values indicate "worse" gait. Additionally, *Global Gait* was calculated by averaging the seven independent gait domains into one standardized Z-score.

Assessment of covariates

The home interview comprised questionnaires about smoking (current cigarette smoking versus non-smoking) and alcohol consumption (converted to grams per day). Examinations at the research center included measurement of height (in cm), weight (in kg) and mean systolic and diastolic blood pressure from two consecutive measurements (in mmHg). Total cholesterol and HDL-cholesterol were measured in serum (mmol/L). Use of lipid lowering medication (statins, ezetimibe, or fibrates) and antihypertensive medication (diuretics, calcium-channel blockers, ACE-inhibitors or beta-blockers) was also documented during the home interview.

Statistical analysis

We used multivariable linear regression analyses to investigate the association of diabetes with *Global Gait* and specific gait domains. Next, we performed analyses of impaired fasting glucose. Additionally, we investigated the association of continuous glucose levels on gait in individuals with a glucose level within the normal range and in individuals with a normal or an impaired fasting glucose combined. All analyses were performed using two models. The first model was adjusted for age, sex, height and weight; the second model was additionally adjusted for cardiovascular risk factors and medication use (mean systolic and mean diastolic blood pressure, smoking, alcohol use, total cholesterol, HDL-cholesterol, antihypertensive medication and lipid lowering medication). Analyses involving *Tandem* were additionally adjusted for step length and step count in the tandem walk.[13] Effect modification by sex was tested by adding an interaction term into the models. We applied Bonferroni correction for seven tests (reflecting the seven independent gait domains) to correct for multiple testing (p-value < 0.007). We assessed potential non-linear associations for the continuous glucose levels with gait using splines regression in R version 3.2.0. All other reported statistical analyses were performed using the SPSS statistical package, version 21 for Windows (IBM Corp., Armonk, NY).

RESULTS

We compared population characteristics between participants and non-participants. Results of these analyses can be found in Supplementary Table 2. There were more females and more people being treated for hypertension in the non-participants, and non-participants were on average older.

In our sample of 3019 participants, 1782 participants (59.0%) had a plasma glucose within the normal range, 921 participants (30.5%) had impaired fasting glucose and 316 participants (10.5%) had diabetes. Participants with normoglycemia were on average younger than participants with impaired fasting glucose or diabetes. In the normoglycemia group 60.9% was female, while this was 45.2% and 43.4% in the impaired fasting glucose and diabetes group respectively. Normoglycemic participants had a lower weight and systolic blood pressure and fewer people used lipid-lowering or antihypertensive medication compared to participants with impaired fasting glucose and diabetes (Table 1).

Diabetes mellitus was associated with worse *Global Gait* (difference in Z-score -0.19, 95% Confidence Interval (CI) -0.30;-0.07) compared to normoglycemic persons after adjustment for age, sex, height and weight. Specifically, participants with diabetes had

Table 1. Population Characteristics

Characteristic	Normoglycemia N = 1782	Impaired fasting glucose N = 921	Diabetes N = 316
Age, years	66.1 (9.2)	68.6 (8.7)*	70.0 (8.2)[*,†]
Female sex, n	1085 (60.9)	416 (45.2)*	137 (43.4)*
Height, cm	168.6 (9.3)	169.9 (9.4)	169.5 (9.0)
Weight, kg	75.3 (13.1)	82.0 (14.4)*	84.9 (14.5)[*,†]
Current cigarette smoking, n	284 (16.0)	135 (14.7)	43 (13.6)
Alcohol, grams per day	6.1 (6.7)	8.1 (8.4)*	5.8 (7.5)[†]
Diastolic blood pressure, mmHg	82.9 (11.0)	85.4 (11.0)*	84.6 (10.9)
Systolic blood pressure, mmHg	138.2 (21.7)	145.5 (21.9)*	148.2 (21.8)*
Antihypertensive medication, n	502 (28.2)	404 (43.9)*	215 (68.3)[*,†]
Total cholesterol, mmol/L	5.6 (1.1)	5.5 (1.0)	4.8 (1.1)[*,†]
HDL-cholesterol, mmol/L	1.5 (0.4)	1.4 (0.4) *	1.3 (0.4)[*,†]
Lipid lowering medication, n	367 (20.6)	266 (28.9)*	172 (54.6)[*,†]
Glucose, mmol/L	5.1 (0.4)	6.0 (0.4) *	8.1 (2.3)[*,†]

Values are mean (SD) or number (%). Percentages were calculated without missing values. Missing values occurred in less than 1%.

* p-value < 0.05, impaired fasting glucose and diabetes compared to normoglycemia, age- and sex adjusted (if applicable)

[†] p-value < 0.05, diabetes compared to impaired fasting glucose, age- and sex adjusted (if applicable)
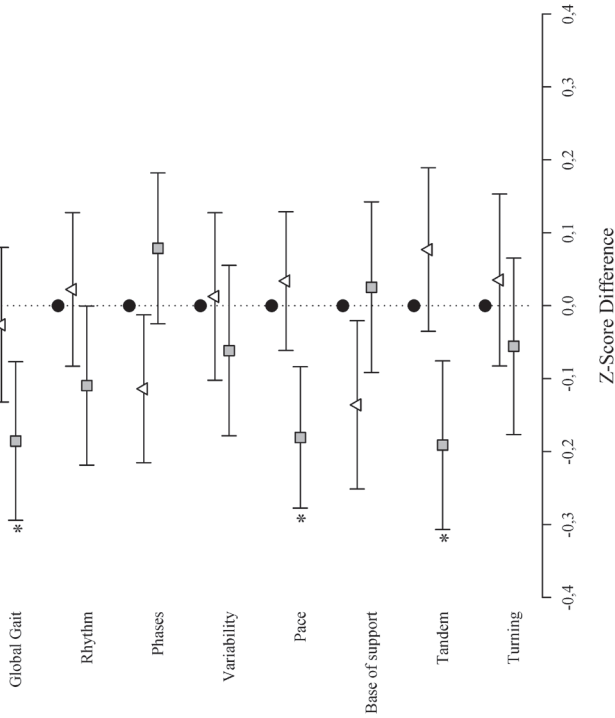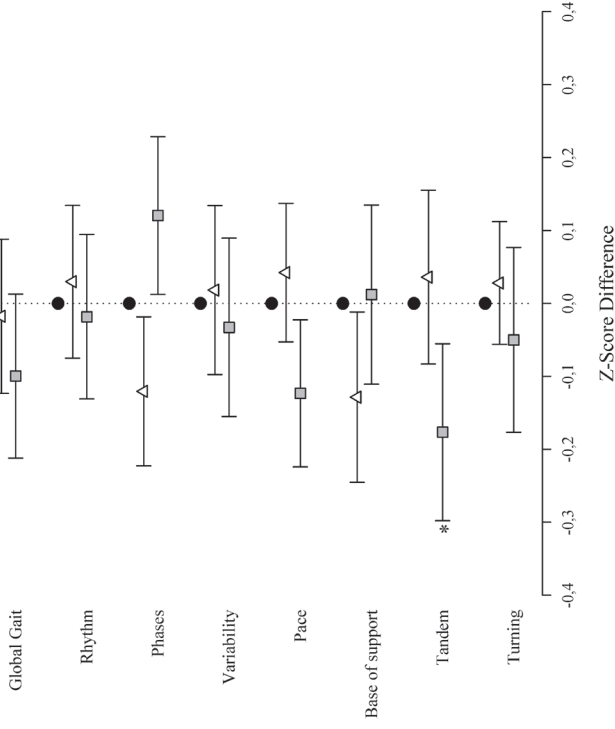
Figure 2. Difference in Z-scores of global gait and gait domains across different glycemic stages. The symbols represent the difference in Z-score of gait for participants with diabetes (grey squares) and impaired fasting glucose (white triangles) compared to normoglycemia (black circles, reference). Error bars represent the 95% confidence intervals around the difference. Asterisks mark the associations that survived Bonferroni correction for 7 tests (p < 0.007). Model 1 is adjusted for age, sex, height, weight. Model 2 is additionally adjusted for smoking, alcohol, mean diastolic blood pressure, mean systolic blood pressure, antihypertensive medication, total cholesterol, HDL-cholesterol, lipid lowering medication.

Table 2. Difference in Z-score of gait per mmol/L change in glucose level in people without diabetes

Gait domains	Normoglycemia (serum glucose <5.6 mmol/L) N = 1766		Normoglycemia and impaired fasting glucose (serum glucose <7.0 mmol/L) N = 2675	
	Model 1	Model 2	Model 1	Model 2
Global gait	0.05 (-0.06;0.16)	0.04 (-0.07;0.15)	0.02 (-0.04;0.08)	0.01 (-0.06;0.07)
Rhythm	0.05 (-0.06;0.16)	0.03 (-0.08;0.14)	0.03 (-0.03;0.09)	0.02 (-0.05;0.08)
Phases	0.09 (-0.01;0.20)	0.10 (-0.01;0.20)	0.06 (-0.00;0.12)	0.06 (-0.00;0.12)
Variability	-0.02 (-0.13;0.09)	-0.03 (-0.15;0.08)	-0.04 (-0.11;0.03)	-0.05 (-0.12;0.02)
Pace	-0.07 (-0.17;0.02)	-0.10 (-0.20;-0.01)	-0.05 (-0.10;0.01)	-0.06 (-0.12;-0.01)
Base of Support	0.03 (-0.08;0.14)	0.04 (-0.07;0.16)	0.06 (-0.01;0.13)	0.06 (-0.01;0.13)
Tandem[a]	-0.03 (-0.14;0.08)	-0.03 (-0.14;0.08)	-0.04 (-0.11;0.03)	-0.04 (-0.11;0.03)
Turning	0.08 (-0.04;0.20)	0.10 (-0.02;0.22)	0.03 (-0.04;0.10)	0.03 (-0.04;0.11)

Values represent the difference in Z-score of gait with 1 mmol/L change in glucose level
Model 1: age, sex, height, weight
Model 2: model 1+ smoking, alcohol, mean diastolic blood pressure, mean systolic blood pressure, antihypertensive medication, total cholesterol, HDL-cholesterol, lipid lowering medication
None of the results survived Bonferroni adjustment for 7 tests (p-value 0.007)
[a] Additionally adjusted for step length and step count in tandem walk

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worse *Pace* (difference in Z-score -0.20, 95% CI -0.30;-0.10) and *Tandem* (difference in Z-score -0.21, 95% CI -0.33;-0.09) than participants with normoglycemia (Figure 2). After additional adjustment for cardiovascular risk factors and medications, only *Tandem* remained worse (difference in Z-score -0.20, 95% CI -0.33;-0.07) in participants with diabetes compared to participants with normoglycemia (Figure 2). The attenuation of the association with *Pace* and *Global Gait* was mainly driven by the inclusion of antihypertensive medication and total cholesterol into the analyses.

Impaired fasting glucose was not associated with *Global Gait*, nor with any of the specific gait domains. However, for several domains the effect estimates for impaired fasting glucose were between those of diabetes and normoglycemia. This was especially noticeable for the domains *Pace* and *Tandem* (Figure 2).

Higher glucose levels were not associated with gait within participants with normoglycemia nor within individuals with normoglycemia or impaired fasting glucose combined (Table 2). There were some indications for a non-linear relation of glucose with *Rhythm*, *Turning* and *Global Gait*, but these associations did not survive correction for multiple testing. We did not observe a consistent pattern of effect modification by sex in any of the analyses.

DISCUSSION

In this population-based study diabetes mellitus was associated with worse *Global Gait*, which was mainly accounted for by worse *Pace* and *Tandem*. The association for *Tandem* remained significant after adjustment for cardiovascular risk factors. In persons with impaired fasting glucose or a glucose level below the threshold for diabetes there was no association with gait.

The strengths of our study include the large population-based sample, assessment of both diabetes mellitus and earlier stages of diabetes, defined as impaired fasting glucose, and the extensive and objective assessment of gait in different walking conditions using an electronic walkway. Our study also has some limitations. The analyses are cross-sectional, making it difficult to draw firm conclusions on causality. Gait was assessed in persons that visited the research center, which might have prevented persons with severe physical disability to participate, leading to a relatively healthy study population. We did not have data on impaired glucose tolerance, which is also part of the definition of prediabetes. Impaired glucose tolerance may be stronger associated with complications of diabetes, especially neuropathy, than impaired fasting glucose.[2] We were not able to assess how different diabetes treatment types and diabetes duration would affect our results. This would be interesting, since both insulin treatment and diabetes duration have been associated with mobility impairment.[21] Another limitation is that we did not evaluate the presence of polyneuropathy, peripheral artery disease, diabetic feet and retinopathy and therefore were not able to assess how these conditions influence the associations.

Gait is a complex motor function that depends on the interplay of multiple systems, such as intact structure and functioning of the central and peripheral nervous system, the vestibular system, intact vascularization of both the brain and the extremities and intact functioning of the musculoskeletal system. All of these systems can be affected by diabetes. We found that participants with diabetes had significantly worse *Global Gait*, *Pace* and *Tandem* compared to persons with normoglycemia. Previous, smaller studies that investigated the association of diabetes with spatiotemporal variables of gait found an association with a decrease in cadence (constituting the domain *Rhythm*)[15, 22, 23] and with lower gait velocity and shorter stride length (both constituting the domain *Pace*).[6, 7, 9, 10, 15, 23-27] In our study, we also found an association with *Pace*, which might result from damage to the vasculature of the legs or feet or be due to damage of the proprioceptive system in case of neuropathy. After adjusting for cardiovascular risk factors the association with *Pace* attenuated, mainly due to inclusion of total cholesterol and antihypertensive medications. Adjusting for cardiovascular risk factors also attenuated the association of diabetes with *Global Gait*, suggesting that a large part of the effect of diabetes on gait is due to vascular comorbidity.

Our study is among the first to investigate the effect of diabetes mellitus on tandem walk in a community-dwelling population. We found a strong independent association of diabetes with errors in tandem walking. Tandem walk represents a complex heel-to-toe type of walk that requires very fine and precise motor function, preserved balance and integration of various other systems, including the eyes, in order to be performed correctly. Even subtle changes in the feet and lower limbs, as well as ocular pathology that can occur due to diabetes mellitus may affect successful performance in tandem walk.

In our study, there was no association of diabetes with *Rhythm*. The most likely explanation for this is that in our study cadence (*Rhythm*) is made independent from stride length (*Pace*) with the principle component analysis. Hence, associations with cadence in previous studies may have been (partly) driven by an association with stride length, which in our study is a component of *Pace*. Moreover, we adjusted the analyses for several cardiovascular risk factors, which is not performed in most studies that found an effect on cadence (part of the domain *Rhythm*). The results of these studies might have been due to confounding. We did not find an association of diabetes with *Variability*, which is the domain from the normal walk that is most strongly related to falls.[12, 13] Previous studies that reported this association could only find an effect while walking in challenging circumstances or on irregular surface, which makes comparison with our study difficult.[10, 15] A perhaps surprising result was the inverted association of diabetes with *Phases*, even though it did not survive correction for multiple testing. Post-hoc analysis revealed that this was possibly due to overadjustment for weight, which is a strong determinant of both diabetes and *Phases*. Indeed, if we ran models without weight as covariate, the effect size of diabetes for *Phases* was -0.17 (95% CI -0.29;-0.04). This suggests that the association of diabetes with "better" gait was likely a spurious result. Whether our findings of gait impairment are specific to diabetes, or specific to certain complications of diabetes such as polyneuropathy, needs to be further investigated.

Since microvascular pathology occurs early in the development of diabetes we hypothesized that this already leads to subtle changes in gait characteristics in patients with earlier stages of diabetes. However, in our study gait was not significantly different in participants with impaired fasting glucose than in participants with normoglycemia, though we did find a pattern of the strength of the associations with impaired fasting glucose being in between those of normoglycemia (reference) and diabetes. This suggests an early decline in gait when moving away from the normal glucose range and was especially noticeable in the domains *Pace* and *Tandem*. Yet, a counterargument against this reasoning is the finding that a glucose level within the normal range was not associated with gait domains when investigated continuously.

To conclude, in our community-dwelling population, the presence of diabetes mellitus was associated with worse *Global Gait*, *Pace* and *Tandem*. This relationship is

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mainly mediated by cardiovascular risk factors. Impairment in gait seems to occur early in the process of developing diabetes mellitus. It may be beneficial to detect and treat abnormal fasting glucose levels and diabetes in early stages in order to prevent future gait impairment in middle-aged and elderly people. Furthermore, within diabetes care, tight regulation of blood pressure and cholesterol levels might be important to prevent or reduce the development of gait problems.

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Supplementary table 1. Correlation of all gait variables with their corresponding gait domain

Gait Domain	Gait variable	Correlation	Mean (SD)
Rhythm			
	Single Support Time, s	-0.958	0.42 (0.04)
	Swing Time, s	-0.958	0.42 (0.04)
	Step Time, s	-0.943	0.55 (0.05)
	Stride Time, s	-0.943	1.10 (0.10)
	Cadence, steps/min	0.939	109.58 (9.64)
	Stance Time, s	-0.837	0.68 (0.08)
Phases			
	Single Support (%GC)	0.973	38.60 (1.91)
	Swing (%GC)	0.973	38.60 (1.91)
	Stance (%GC)	-0.972	61.40 (1.91)
	Double Support (%GC)	-0.969	23.03 (3.83)
	Double Support Time, s	-0.851	0.26 (0.06)
Variability			
	Stride Length SD	-0.877	4.58 (1.68)
	Step Length SD	-0.865	2.85 (0.95)
	Stride Velocity SD	-0.861	5.90 (1.98)
	Stride Time SD	-0.767	0.03 (0.02)
	Step Time SD	-0.749	0.02 (0.01)
	Stance Time SD	-0.761	0.03 (0.02)
	Swing Time SD	-0.650	0.02 (0.01)
	Single Support Time SD	-0.650	0.02 (0.01)
	Double Support Time SD	-0.512	0.02 (0.01)
Pace			
	Stride Length, cm	0.857	130.43 (18.52)
	Step Length, cm	0.856	65.02 (9.27)
	Velocity, cm/s	0.718	118.96 (20.48)
Base of Support			
	Stride Width SD	-0.734	2.40 (0.85)
	Stride Width, cm	0.663	10.34 (4.05)
Tandem			
	Sum of Feet Surface	-0.914	0.33 (0.65)
	Sum of Step Distance	-0.904	9.68 (17.28)
	Double Step	-0.563	0.07 (0.30)
Turning			
	Turning Step Count, steps	-0.921	4.95 (0.91)
	Turning Time, s	-0.851	2.84 (0.63)

Factors were inverted so that lower values represent "worse" gait. The numbers shown represent correlations after the inversion.

SD: standard deviation; %GC: as a percentage of the gait cycle time, the cycle time equals the stride time.

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Supplementary table 2. Population characteristics of participants and non-participants

	Participants	Non-participants	P-value
Age, years	67.3 (9.1)	73.3 (10.3)	<0.01
Female sex, n	1638 (54.3)	385 (59.5)	0.01
Height, cm	169.1 (9.3)	167.0 (9.6)	0.69
Weight, kg	78.4 (14.2)	77.5 (14.6)	0.03
Current cigarette smoking, n	462 (15.3)	64 (12.0)	0.56
Alcohol, grams per day	6.7 (7.4)	5.9 (7.2)	0.70
Diastolic blood pressure, mmHg	83.8 (11.0)	83.8 (11.0)	0.16
Systolic blood pressure, mmHg	141.5 (22.2)	146.0 (22.5)	0.06
Antihypertensive medication, n	1121 (37.1)	274 (52.4)	0.01
Total cholesterol, mmol/L	5.5 (1.1)	5.3 (1.1)	0.06
HDL cholesterol, mmol/L	1.5 (0.4)	1.4 (0.4)	<0.01
Lipid lowering medication, n	805 (26.7)	166 (25.7)	0.50
Glucose, mmol/L	5.7 (1.2)	5.8 (1.3)	0.89
Diabetes, n	316 (10.5)	71 (14.8)	0.13
Impaired fasting glucose, n	921 (30.5)	143 (29.8)	0.19

Values represent number (%), or mean (SD). P-values are age- and sex adjusted (if applicable).

Chapter 6

General discussion

This thesis focusses on the epidemiology of chronic axonal polyneuropathy. The main aims were to describe the prevalence of chronic (idiopathic) axonal polyneuropathy in the general population, to study the impact of chronic polyneuropathy on a person's daily life, and to describe the effect of known and new risk factors for chronic polyneuropathy and for chronic idiopathic axonal polyneuropathy (CIAP) in particular. In this chapter, the main findings of the studies described in this thesis will be outlined and discussed with regard to previous studies. Subsequently, methodological considerations regarding the work described in this thesis and potential clinical implications will be discussed. Finally, directions for future research will be provided.

MAIN FINDINGS

Screening methods for polyneuropathy

Polyneuropathy is a common disease in both general and neurological practice.[1] Yet, large, comprehensive epidemiological studies investigating this disease are scarce, hence the exact prevalence in the population is unknown. The first step in the investigation of the prevalence of a disease is to develop a screening protocol that can accurately detect the disease. Herein probably lies the main reason why large epidemiological studies on chronic polyneuropathy are lacking. Polyneuropathy is a heterogeneous disease and there is not one gold standard test for polyneuropathy. In neurological practice, polyneuropathy usually is a clinical diagnosis that can be made after careful history taking and neurological examination, which can be further complemented with nerve conduction studies (NCS) and electromyography (EMG).[2] Besides NCS and EMG, there are several other laboratory tests that can aid the diagnostic process, such as computerized sensory testing instruments and skin- or nerve biopsies. These tests have often been criticized to be too time-consuming, invasive or costly, and therefore inappropriate and not feasible for utilization in large epidemiological field studies.[3-9] Several simplified methods have been developed to be able to estimate the prevalence of polyneuropathy.[9-20] These simplified methods are reviewed in chapter 2.1. In this literature overview, questionnaires, scoring systems for neurological signs and scoring systems that combined both symptoms and signs, all developed with the aim to detect polyneuropathy in high-risk patient groups, such as in patients with diabetes mellitus, are summarized. Although these tools can be useful to screen high-risk individuals in clinical practice, it is unknown whether these techniques also produce accurate prevalence estimates when used in a general low-risk population. Moreover, the diagnostic accuracy, as measured with the sensitivity and specificity, of these simplified screening methods is often suboptimal. Likewise, estimating the prevalence of polyneuropathy with a single simple test, such as a monofilament or a tuning fork is also inaccurate.[21, 22]

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Screening procedures that combine symptoms with a neurological examination focused on sensory alterations seem to have the best discriminative ability for chronic axonal polyneuropathies.[9] Motor symptoms are often only present in more advanced stages of polyneuropathy, and are therefore less sensitive for screening. Therefore, when initiating an epidemiological study focused on chronic polyneuropathy it is important to not only use symptoms, but also incorporate an assessment of at least sensory modalities into the screening protocol.

In chapter 2.2 we further examined the discriminative ability of individual symptoms of polyneuropathy and we described the development of a new simple questionnaire that may aid the diagnosis of polyneuropathy. Numbness and tingling sensations in the feet were the most sensitive symptoms (87% and 85% respectively), as these symptoms were experienced by most polyneuropathy patients. Allodynia (pain due to a stimulus that normally does not provoke pain) and a feeling as if walking on cotton wool had the highest specificity (90% and 77% respectively). These four symptoms, together with balance problems and tingling hands were included in the new, validated Erasmus Polyneuropathy Symptom Score (E-PSS), a tool that can be used to discriminate persons with polyneuropathy from persons without polyneuropathy. This 14-point scoring system was based on a logistic regression model and incorporated the frequency of occurrence of each symptom (never, sometimes, and (almost) continuously), as well as the individual diagnostic value of each of the six symptoms. The discriminative ability, as assessed by the area under the receiver operating characteristics curve, of this score was very good (0.92), but further studies are required to assess the utility of this score in clinical practice. As with the other questionnaires that have been discussed in chapter 2.1, the Erasmus Polyneuropathy Symptom Score may have to be complemented with other tests to further improve the diagnostic accuracy.

Prevalence of polyneuropathy

Most of the scoring systems have been used to investigate the prevalence and incidence of polyneuropathy in high-risk groups, in particular in patients with diabetes mellitus. The amount of studies investigating the prevalence of polyneuropathy in a low-risk, general population is very limited. In chapter 3.1, data from studies that report on the prevalence of polyneuropathy in the general population are reviewed. These studies differed greatly in study design, study size, age distribution of the study population, employed methodology and polyneuropathy definitions. None of these studies used an extensive-in person screening that included assessment of symptoms, signs and nerve conduction. Some studies defined polyneuropathy as the presence of merely one bilateral neurological deficit (such as numbness or abnormal ankle reflexes), while in other studies only persons with electrophysiology confirmed polyneuropathy (based on medical records in database studies) were included in the case definition. Consequently,

prevalence estimates across these studies also differed substantially, ranging from 0.1% to 12.6% when considering the total adult population[23, 24], and from 1.9% to 30.9% when only considering an elderly population.[25, 26] Based on this literature review, we estimated the prevalence of chronic polyneuropathy (in developed countries) at approximately 1% in the total population, and at approximately 7% in elderly. Further population-based studies had to confirm these estimates.

Chapter 3.1 also delineates the most common risk factors for chronic polyneuropathy. This data was extracted from hospital-based studies, as population-based data was not available. Hospital-based studies identified diabetes mellitus, toxic factors (like alcohol abuse and chemotherapy), inflammatory factors and systemic diseases as the most common risk factors for polyneuropathy. Despite extensive diagnostic investigations, in approximately 25% of polyneuropathy cases no known risk factor can be identified. These cases are diagnosed with CIAP. We did not identify studies that described the prevalence of CIAP in the general population.

Prevalence of chronic polyneuropathy in the Rotterdam Study

We developed an extensive in-person screening protocol for polyneuropathy which we implemented in the population-based Rotterdam Study. This screening protocol consists of three parts: 1) a questionnaire that evaluates the presence of neuropathic symptoms; 2) a neurological examination with a focus on sensory modalities; and 3) nerve conduction studies, which were focused on distal action potential amplitudes of the peroneal (motor) and sural (sensory) nerve (Table 1). All participants of the Rotterdam Study undergo this screening procedure. Among 1310 middle-aged and elderly participants the prevalence of 'definite' polyneuropathy, a relatively strict definition requiring

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Table 1. Polyneuropathy screening in the Rotterdam Study

Symptom questionnaire	Neurological examination	Nerve conduction studies
Tingling/prickling feet	Bilateral assessment of:	Bilateral assessment of:
Burning feet	- Pin prick (wooden pin)	- Sural nerve (sensory)
Walking on cotton-wool feeling	- Vibration (Rydel-Seiffer tuning fork)	Unilateral assessment of:
Muscle cramps in legs or feet	- Knee and ankle tendon reflexes	- Peroneal nerve (motor)
Muscle pain in legs or feet	- Muscle strength (dorsiflexion feet)	
Stabbing pain in legs or feet	- Ability to walk on heels	
Muscle weakness in legs or feet		
Numb feet		
Tightness of the legs		
Allodynia in legs or feet		

Polyneuropathy screening used in the population-based Rotterdam Study. All collected data from each individual participant is discussed by an expert panel. The panel categorizes each participant into no, possible, probable or definite polyneuropathy.

abnormality in all three parts of the screening (questionnaire, neurological examination and nerve conduction studies) or a previous neurologist's diagnosis of polyneuropathy, was 5.5% (chapter 3.2). Applying a less strict definition, requiring abnormality in only two parts of the screening protocol ('probable' and 'definite' polyneuropathy combined), yielded a prevalence of 13.1%. These estimates fall in the same range as those reported in the literature review described in chapter 3.1 (polyneuropathy prevalence in elderly ranging from 1.9% to 30.9%). Since we used a rigorous definition of polyneuropathy in a large and random sample of the general population (only selected on residential area and age), our estimates likely are the most accurate to date.

Prevalence of definite polyneuropathy was slightly higher in males than in females (6.7% compared to 4.5%) and drastically increased with age from 1.2% in persons aged 50-60 years to 13.2% in persons aged 80 years and over. To take the age distribution of our study sample into account, we age-standardized the prevalence to the population of the Netherlands. This yielded a standardized (definite) polyneuropathy prevalence of 4.0%, indicating that elderly were slightly overrepresented in our sample. Assuming polyneuropathy under the age of 50 years (the lower limit of our age-range) is relatively uncommon, this prevalence translates to approximately 260 000 persons in the Netherlands suffering from chronic polyneuropathy.[27] If age-specific prevalence of polyneuropathy does not change in the future, this number will rise to approximately 400 000 persons in 2040, purely due to aging of the population.[27] However, given the worldwide increase in the prevalence and incidence of risk factors for polyneuropathy such as diabetes mellitus, obesity, chronic kidney disease and cancer (with its related treatments), it may be unlikely that the (age-specific) prevalence of polyneuropathy will remain stable.[28-34] Therefore, this projection is likely underestimating the true burden that polyneuropathy will pose in the future.

In chapter 3.2 the presence of putative causes of polyneuropathy was also described. Diabetes mellitus was present in about a third of all definite cases, which corresponds with the findings from hospital-based studies.[35-37] In contrast, the proportion of participants with definite polyneuropathy with no known risk factor (these persons are diagnosed with CIAP in clinical practice) was higher in our population-based study than in previous hospital-based studies: 46% in our study compared to approximately 25% in hospital-based studies. This indicates that, on population level, CIAP is much more prevalent than was previously estimated, translating to roughly 120 000 persons in the Netherlands.[27] There are at least three reasons that may explain this discrepancy. First, the probability of finding an underlying etiology when a person is diagnosed with polyneuropathy decreases with age.[35] The study population consisted of middle-aged and elderly participants, with an age range from 50 to 95 years, and we slightly oversampled elderly, as discussed earlier. Therefore the proportion of elderly with polyneuropathy is probably higher in our study than in hospital-based studies. Second, it is likely that

we detected cases of polyneuropathy in persons who are only mildly affected. These persons may be less likely to visit their general practitioner or be referred to a neurologist, especially when symptoms are not very bothersome and the disease course is slow. Hence, these mildly affected persons are missed in hospital-based studies. Since chronic idiopathic axonal polyneuropathy (CIAP) often is a relatively mild disease, these mildly affected persons may more often have idiopathic polyneuropathy.[38] Third, although the presence of several known risk factors (diabetes mellitus, vitamin deficiencies (B1 and B12), thyroid dysfunction and monoclonal gammopathies) was routinely evaluated in patients with definite polyneuropathy, we did not routinely investigate for very unlikely causes of chronic axonal polyneuropathy, we had to rely on medical records for a history of systemic diseases, we did not have information about a possible family history of hereditary neuropathies and we might have been unable to distinguish mild forms of inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy. However, since hereditary and demyelinating neuropathies are rare in the general population, this probably only marginally influenced our estimates.[39, 40]

A last, but also important finding described in chapter 3.2 is the finding that 49% of polyneuropathy cases was not yet diagnosed. This emphasizes that underreporting or underdiagnosing is a common problem in polyneuropathy. An even higher proportion (85%) was reported by a previous population-based study, conducted in Italy, approximately 20 years ago.[4] Apparently, there has been some improvement in the awareness and recognition of polyneuropathy during the last decades, but polyneuropathy still is an underacknowledged disease.

Emerging cardiovascular and metabolic risk factors of polyneuropathy

Diabetes mellitus is present in about a third of polyneuropathy cases. This makes diabetes mellitus the most frequently identified, and most important risk factor for polyneuropathy, especially since its prevalence is reaching epidemic proportions worldwide.[29, 33] However, although diabetes mellitus can cause polyneuropathy, it does not cause polyneuropathy in all diabetic patients as approximately 50% will eventually develop neuropathy during the course of the disease.[41] Apparently, some individuals are more susceptible to the effects of diabetes mellitus on peripheral nerves than others. According to Rothman's theory of causation, a sufficient cause inevitably leads to disease in everyone in whom this cause is present.[42] Since diabetes mellitus does not lead to polyneuropathy in all patients, by definition it cannot be considered as a sufficient cause of polyneuropathy. This indicates that other factors, or component causes, are likely also required to cause polyneuropathy. This is further supported by the observation that strict glucose control is not efficacious in reducing the development of polyneuropathy in patients with type 2 diabetes.[41] Factors that have been associated with the development or the presence of polyneuropathy in patients with diabetes mellitus
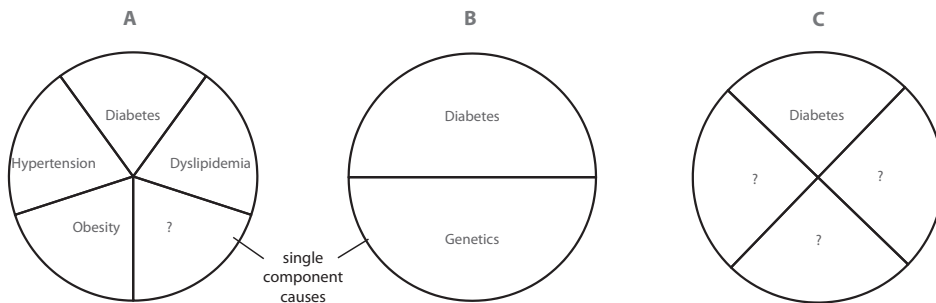
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Figure 1. Causal mechanisms for polyneuropathy in persons with diabetes mellitus. The figure shows three hypothetical causal mechanisms (sufficient causes) through which diabetes mellitus can cause poly-neuropathy. Diabetes mellitus itself is not a sufficient cause: there is no causal pie that only includes diabetes as component, it needs other (unknown) component causes to lead to polyneuropathy. Pie A illustrates an example that includes cardiometabolic factors, which have been associated with polyneuropathy in patients with diabetes mellitus, and a yet unknown, perhaps genetic component. Genetic susceptibility may also be the only extra component that is necessary to form a sufficient cause in diabetics (pie B). It is likely that there are more causal mechanisms that include yet unknown components (pie C).

include cardiometabolic factors such as obesity, dyslipidemia and hypertension.[41, 43-46] These factors may be the other component causes that are required to form a complete causal mechanism in patients with diabetes mellitus. See Figure 1 for an illustration of this theory of causation.

There are several mechanisms through which these cardiometabolic factors may promote the development of polyneuropathy. In diabetes mellitus, hyperglycemia causes enhanced formation and deposition of advanced glycation end products that initiate inflammatory pathways that generate oxidative stress, impair the biological function of cellular proteins and increase the rate of atherosclerosis which can lead to occlusion of vessels and thus to hypoxia of peripheral nerves.[41, 47] Hyperglycemia and insulin resistance also lead to dysregulation of several metabolic pathways that result in mito-chondrial dysfunction, inflammation and further oxidative stress. All these processes can eventually lead to nerve ischemia and cytotoxicity.[41] Dyslipidemia can further enhance neuronal damage via several mechanisms. First, free fatty acids can injure Schwann cells directly, and also promote inflammatory pathways that lead to oxidative stress. Second, high levels of oxidized low-density lipoprotein can also trigger mitochondrial dysfunction and increase oxidative stress. Abdominal obesity plays an important role in these processes since it leads to increased concentrations of free fatty acids and systemic inflammation, which further contributes to insulin resistance and nerve ischemia.[41, 47, 48]

An increasing body of evidence implicates the same cardiometabolic factors in the pathophysiology of chronic idiopathic axonal polyneuropathy (CIAP), but population-based evidence in unselected samples was required to further strengthen this hypothesis.[48-52] In chapter 4.1 the role of diabetes mellitus, prediabetes and metabolic syndrome

in relation to polyneuropathy was investigated. Metabolic syndrome refers to a clustering of interrelated risk factors for cardiovascular diseases.[53] These factors include hypertension, abdominal obesity, elevated triglyceride levels, reduced high-density lipoprotein cholesterol levels and elevated glucose levels. In the study described in chapter 4.1, we found that participants with diabetes mellitus were three times more likely to have polyneuropathy than participants without diabetes mellitus. Participants with metabolic syndrome were two times more likely to have polyneuropathy and this relation was stronger as more factors of metabolic syndrome were present. Abdominal obesity and elevated triglycerides were the most important individual factors contributing to this association. The associations with metabolic syndrome, especially abdominal obesity, were present in the total study sample, as well as in the non-diabetic sample. This strengthens the hypothesis that these cardiometabolic factors are not only important in the pathophysiology of polyneuropathy in patients with diabetes mellitus, but indeed also in persons without diabetes mellitus, of which the vast majority is diagnosed with chronic idiopathic axonal polyneuropathy (as described in chapter 3.2). In contrast to some other, mostly uncontrolled studies, our findings do not support the hypothesis that prediabetes is related to polyneuropathy, but our study likely was underpowered to show a small effect.[3, 54-56]

The important role of these conventional cardiovascular risk factors in the pathophysiology of polyneuropathy is further supported by the finding that in patients with type 2 diabetes, polyneuropathy is related to an increased risk of cardiovascular events (myocardial infarction, transient ischemic attack, stroke), which is probably explained by the shared etiology.[57, 58] Similarly, in a case-control study of patients with chronic idiopathic axonal polyneuropathy (CIAP), cases had more often experienced a transient ischemic attack or stroke and more often had ischemic heart disease than controls.[59] Investigating the association between polyneuropathy and vascular diseases in the Rotterdam Study yielded similar results (Table 2). Participants with polyneuropathy more

Table 2. Polyneuropathy and vascular disease

	Clinical cerebrovascular disease		MRI defined brain infarcts		Coronary heart disease	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
No PNP	5.5	1.00	7.9	1.00	6.6	1.00
Possible PNP	10.0	1.37 (0.79;2.40)	11.4	1.15 (0.69;1.90)	8.1	0.97 (0.54;1.76)
Probable PNP	13.3	1.60 (0.80;3.18)	15.3	1.09 (0.55;2.17)	12.6	1.35 (0.67;2.72)
Definite PNP	19.5	2.75 (1.39;5.45)	20.3	1.92 (0.98;3.77)	17.1	1.66 (0.79;3.48)

Odds ratios (OR) with 95% confidence intervals (CI) comparing the presence of clinically defined cerebral vascular disease (stroke or transient ischemic attack), imaging defined brain infarcts (lacunar or cortical infarcts on magnetic resonance imaging, MRI) and coronary heart disease (myocardial infarction or coronary revascularization) between participants with possible, probable or definite polyneuropathy (PNP), compared to participants with no polyneuropathy. Odds ratios are adjusted for age and sex

often had cerebrovascular disease (both by a clinical definition of stroke or transient ischemic attack and by an imaging-based definition of lacunar or cortical infarcts) and coronary heart disease (history of myocardial infarction or coronary revascularization) than participants with no polyneuropathy. However, not all associations were statistically significant, which is probably due to a lack of power. Nonetheless, these findings support the hypothesis of a shared underlying etiology.

Preclinical changes in peripheral nerves

In chapter 4.1 we provided further support for a potential causal role of cardiometabolic factors in the development of polyneuropathy, by showing that the presence of these factors also related to impaired peripheral nerve function in persons yet without polyneuropathy. Participants with metabolic syndrome had lower sural sensory nerve action potential (SNAP) amplitudes and lower peroneal nerve compound muscle action potential (CMAP) amplitudes than persons without metabolic syndrome. Moreover, this association was stronger when more factors of metabolic syndrome were present. This association was even stronger in participants without diabetes mellitus than in the total sample of participants. This again emphasizes that these factors may not only be important for the development of polyneuropathy in persons with diabetes mellitus, but also in persons without diabetes mellitus.

The effect of demographic, anthropometric and other metabolic determinants on peripheral nerve function in participants without polyneuropathy is described in chapter 4.2. In order to study the deteriorating effect of these factors on peripheral nerve function, it is first important to understand normal aging effects on peripheral nerve function. Therefore, the relation between age and sural SNAP and peroneal CMAP amplitudes was investigated first. Both the sural SNAP and the peroneal CMAP amplitude linearly declined with increasing age. Furthermore, even in participants (yet) without polyneuropathy, abnormal amplitudes were a common finding, especially in old age groups. Sural SNAP amplitudes were abnormal in 1% of participants under 60 years, compared to 23% of participants over 80 years. Similarly, the proportion of abnormal peroneal CMAP amplitudes increased from 4% to 13%. These are important findings, which show that age must be taken into account when interpreting nerve conduction studies. It is possible that once these persons with impaired nerve function live long enough, they will eventually develop a chronic polyneuropathy. Aside from age, a person's height also was an important determinant of nerve action potential amplitudes, with a taller height relating to a lower amplitude. Potentially modifiable factors that related to especially worse sural SNAP amplitudes, were increased values of body weight (total weight, body mass index, waist circumference, waist-to-hip ratio) and chronic kidney dysfunction. Interestingly, none of the persons with chronic kidney disease that participated in our study met the criteria for end-stage kidney disease. Generally, polyneuropathy is

only described in patients with end-stage kidney disease.[60] Our results however suggest that changes in peripheral nerves already occur in an earlier stage of mild to moderate kidney dysfunction. This is an interesting observation that requires further investigation.

Polyneuropathy related disability

As already mentioned, polyneuropathy poses a large burden on society. In chapter 5 the impact of polyneuropathy on an individual is discussed. Besides bothersome complaints of numbness and pain, previous studies showed that polyneuropathy can lead to mobility impairment and a reduced quality of life.[61-63] In chapter 5.1 we further described the impact polyneuropathy has on an individual by investigating the effect of polyneuropathy on the ability to perform daily activities, history of falls, and the gait pattern. Persons with polyneuropathy were much more likely to experience difficulty in several complex mobility related tasks, such as walking, housekeeping and shopping, but even in very basic, simple tasks involving eating, hygiene, dressing and grooming. Participants with polyneuropathy were also more likely to fall, and these falls often resulted in injury, which in turn can further contribute to disability. The ability to perform activities of daily living is very important in order to function independently in society. Loss of this ability may lead to institutionalization.[64] With advancing age the ability to perform daily activities already decreases, until a point is reached where institutionalization may be necessary. Population aging will thus considerably increase the demand on health care.[65] This process will be further enhanced by a growing prevalence of age-related diseases that also affect daily functioning, such as polyneuropathy. Chronic polyneuropathy thus poses a large burden on both the society and the individual patient, which makes polyneuropathy an important health concern.

In chapter 5.1 we also discussed how gait patterns of participants with polyneuropathy differed from participants without polyneuropathy. Participants with polyneuropathy walked with lower gait velocity and lower cadence. This may be a direct consequence of polyneuropathy, for example due to muscle weakness or balance problems, but may also be because these participants adopt a more conservative gait pattern to achieve greater stability. Polyneuropathy also associated with more errors in tandem walking, which illustrates the problems with stability, balance and coordination. Importantly, errors in tandem walking is strongly related to an increased risk of falling, which may partly explain the increased risk of falling associated with polyneuropathy. In chapter 5.2, gait patterns of participants with diabetes mellitus were compared to gait patterns of participants without diabetes mellitus. This study showed similar findings as discussed in chapter 5.1. Diabetes mellitus associated with worse Pace (constituting velocity and step length), and also with more errors in tandem walking. Besides polyneuropathy, peripheral arterial disease may be another potential cause of gait disturbances in persons with diabetes mellitus. Peripheral arterial disease is characterized by pain that occurs

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during walking (intermittent claudication), which may lead to gait alterations. A previous study showed that peripheral arterial disease leads to similar spatiotemporal gait abnormalities as polyneuropathy.[66] These changes in gait could already be observed before the onset of pain, suggesting other mechanisms than pain are involved. Proposed mechanisms involve myopathy and axonal polyneuropathy secondary to mitochondrial dysfunction and chronic ischemia.[66] It is therefore not surprising that changes in gait observed as a consequence of peripheral arterial disease are similar to that observed in polyneuropathy. Unfortunately, data on polyneuropathy was not available for the participants of the study described in chapter 5.2 and no data was collected about peripheral arterial disease.

METHODOLOGICAL CONSIDERATIONS

Study design

The studies discussed in this thesis were conducted in the Rotterdam Study, a large, longitudinal population-based cohort study, designed to study determinants and prognosis of chronic diseases in the elderly.[67] One of the major advantages of this study is the repeated measurement and wide collection of data on numerous different exposures and outcomes, resulting in a wealth of data that enables in-depth cross-sectional and longitudinal analyses. The polyneuropathy screening protocol was only implemented in the beginning of 2013 and before this date, information about polyneuropathy was not available. Therefore, the amount of screened individuals is still relatively limited, and no repeated measurements have yet been performed. This prevents the investigation of potential small associations due to a lack of power, and restricts the investigation of potential risk factors to cross-sectional analyses. Results of these cross-sectional analyses should be interpreted cautiously with respect to causality. Hopefully, longitudinal studies will follow in the future.

Another major advantage of the Rotterdam Study over hospital-based studies is the population-based study design, in which participants can be considered as a random sample of the general middle-aged and elderly population. This greatly reduces the possibility of selection bias and therefore improves the generalizability of the results. Still, the population of this study is relatively homogeneous, mostly consisting of middle-class Caucasians, so results may therefore only be generalizable to similar populations. One other form of selection bias, known as the healthy volunteer effect, may still have been present in this study. Participation in the study is voluntary and participants have to visit the research center to complete the assessment of most exposures. This may prevent frail, disabled, or otherwise less healthy persons to participate. Polyneuropathy is a disease that results in mobility limitations, hence prevalence of polyneuropathy

may have been higher among these non-participants. Additionally, cardiovascular risk factors and diseases may have been more prevalent among non-participants. Therefore, the prevalence of polyneuropathy reported in chapter 3.2, as well as the associations with cardiovascular risk factors described in chapter 4 and with impairment in daily life reported in chapter 5, might have been underestimated.

Misclassification of polyneuropathy status

The diagnosis of polyneuropathy cannot be made by a single test. Several tests need to be combined in order to make a reliable polyneuropathy diagnosis. As discussed in chapter 3.1, there is a large inter-study variation with respect to the prevalence of poly-neuropathy, which was mainly due to differences in methodology. In several studies there probably was a large amount of misclassification due to inaccurate screening methods. In our study, we tried to minimize misclassification of polyneuropathy status by apply-ing a rigorous polyneuropathy definition which involved the presence of symptoms, bilateral abnormalities on neurological examination of the legs and bilaterally abnormal nerve conduction studies, but we cannot rule out that some misclassification remained, since it is not a full neurological and neurophysiological examination. The Rotterdam Study is an extensive population-based study involving multiple medical specialties. Therefore, there were several limitations we had to take into account when designing the screening protocol, especially concerning time, costs, invasiveness and burden for participants. The screening had to be a non-invasive protocol that could be performed within 20 minutes, was minimally cumbersome for participants, and could be executed by trained personnel working at the research center. Still, this protocol needed to result in reliable information about symptoms, signs (especially sensory, see chapter 2.1), and preferably also nerve conduction studies, since these greatly adds to the specificity.[68]

These limitations somewhat restricted the completeness of the diagnostic work-up and may have resulted in some bias due to misclassification of disease status. Misclassi-fication could have occurred in any of the three components of the screening (question-naire, examination, nerve conduction studies), but for each part we tried to minimize this possibility. First, instead of a live interview, polyneuropathy symptoms were evaluated using a questionnaire. The use of a questionnaire prevents the possibility to distinguish polyneuropathy-related symptoms from symptoms that result from diseases that may resemble some of the complaints of polyneuropathy (i.e. osteoarthritis, radiculopathy, fibromyalgia). Additionally, there is the possibility of recall bias. However, given that we assessed the presence of symptoms over the last three months, and given that these symptoms are often experienced daily, recall bias probably is very limited. Second, as polyneuropathy usually is a length-dependent disease that starts distally in the feet, the neurological examination was purely focused on the lower legs and consisted of assessment of vibration sensation on the big toes (large fibers), pin prick of the lower

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legs (small fibers), reflexes of both the knee and Achilles tendons, and muscle strength of the feet. Besides polyneuropathy, these modalities can also be affected by other (neurological) disorders, such as radiculopathies and mononeuropathies. To reduce misclassification, all items were assessed bilaterally, and only when multiple items were bilaterally abnormal, the neurological examination was considered abnormal. Still, we did not conduct a full neurological examination and for example did not assess sensation of touch, coordination and joint position sense. These items normally are included in the neurological examination of a patient who is suspected of polyneuropathy. However, we do not expect that information about these items would have led to important different conclusions. Third, although nerve conduction studies were performed according to internationally used guidelines, we were unable to preheat the legs of the participants. Cold feet may yield artificially high action potential amplitudes, possibly leading to a (false) classification of normal.[69] This might have led to an underestimation of the prevalence of polyneuropathy. Additionally, our nerve conduction studies were limited and did not include the full range of diagnostic tests that are advised for the diagnosis of polyneuropathy.[68] The sural and peroneal nerve taken together are the most sensitive for detecting a polyneuropathy, but these may not be very specific.[68] As shown in chapter 4.2, abnormal nerve conduction amplitudes also occur in elderly without polyneuropathy, indicating the necessity to combine nerve conduction studies with other tests to make a final diagnosis of polyneuropathy.[70, 71] Therefore, we used all three parts of the screening when forming an overall polyneuropathy conclusion. To further reduce bias in the polyneuropathy definition, an experienced expert panel categorized each participants into one of 4 groups (no, possible, probable and definite polyneuropathy), reflecting the diagnostic uncertainty. The amount of misclassification in the group of participants classified as definite polyneuropathy is therefore most likely very minimal.

Interpretation of associations

In this thesis several associations of cardiometabolic factors with polyneuropathy or peripheral nerve dysfunction and of polyneuropathy with impairment in gait and daily functioning are described. Aside from being true effects, these associations may also be introduced by selection bias, information bias (misclassification) and confounding. As already discussed in this chapter, selection bias is probably not much of an issue in our population-based studies and misclassification of polyneuropathy status is likely also minimal. Misclassification of cardiometabolic determinants due to measurement error may have been present in chapter 4. Similarly, misclassification may have occurred when assessing daily functioning in chapter 5. Daily functioning is assessed with questionnaires, and although validated, questionnaires are subjective and therefore more prone to information bias, either participant-related, such as recall bias and response bias, or researcher-related, such as interviewer bias. However, this misclassification is not directly

related to the presence of polyneuropathy and is therefore probably non-differential and thus not affecting the associations of interest or, if any, leading to an underestimation of the true effects. Finally, associations may be due to confounding. We tried to minimize this confounding by using multivariable modeling, thus adjusting for several potential confounding factors, but we cannot rule out that there is residual confounding that influenced some of our results. Much is unknown about polyneuropathy, so it is likely that other, unknown and unmeasured factors played a role in several associations.

Proportion of cases attributable to certain risk factors

In chapter 3.1 and chapter 3.2 the presence of putative causes in participants with polyneuropathy was described. In the study described in chapter 3.2, twenty-two participants (31%) with definite polyneuropathy had diabetes mellitus. In clinical practice, but also in most polyneuropathy-related research, a person who has both diabetes mellitus and a chronic distal polyneuropathy is considered to have diabetic polyneuropathy. Although this is clinically useful, from an etiological point of view this is not fully correct. This assumption ignores the fact that some patients with diabetes mellitus develop polyneuropathy irrespective of the presence of diabetes mellitus, and that a patient with diabetes mellitus also requires other (component) causes to give rise to the disease (as discussed before, see also Figure 1). Therefore, it is incorrect to state that 31% of polyneuropathy cases is due to diabetes mellitus. An alternative, more appropriate way to describe the proportion that can be attributed to a certain risk factor is by calculating the population attributable fraction.[72] The population attributable fraction can be calculated with the following formula:

$$\text{Population attributable fraction} = P(E|D) \, \frac{(RR - 1)}{RR}$$

In this formula $P(E|D)$ denotes the proportion of persons with the disease exposed to the risk factor, and RR denotes the relative risk of the disease associated with the exposure. In our study, the proportion of participants with polyneuropathy exposed to diabetes mellitus was 33% (22 out of 67 participants with data about diabetes mellitus available) and the relative risk, as estimated using the odds ratio, of definite polyneuropathy (compared to no polyneuropathy as reference) associated with diabetes mellitus was 3.3. Introducing these numbers in the formula yields an attributable fraction of 23%. This means that 23% of polyneuropathy cases can 'truly' be attributed to diabetes mellitus and can theoretically be prevented by completely eliminating this risk factor from the population. This computation also shows that there is a proportion of persons with diabetes mellitus and polyneuropathy, in which diabetes itself is not the cause of the polyneuropathy, but just a bystander. This example is a simple computation using the crude estimation of the relative risk, but this formula can also be applied using

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adjusted odds ratios, and several statistical programs are capable of calculating population attributable fractions. The age and sex-adjusted population attributable fraction for diabetes mellitus is 20%. Similarly, for metabolic syndrome (which includes diabetes mellitus among others) the age- and sex-adjusted population attributable fraction is 32%. This method preferentially should be used more often in polyneuropathy research. For proper use however, it requires extensive data collection on exposures among both cases and controls and also a large sample size. Currently, the sample size of our study is still relatively small and therefore yields wide confidence intervals, hampering us to study the population attributable fraction of the described risk factors in detail.

CLINICAL IMPLICATION AND FUTURE PERSPECTIVES

In this thesis, we described the prevalence of polyneuropathy in the general population, risk factors for polyneuropathy and the impact of polyneuropathy on daily functioning. There are several areas of health care in which this data is very useful.

Knowledge about the frequency of the disease is necessary to assess the burden of the disease on society (which is important for policy makers and funding agencies among others), but is also necessary in clinical practice. The prevalence determines the prior probability (before any testing has been done) that someone suffers from a specific disease. This is not only important for neurologists, but also and perhaps especially for general practitioners. A general practitioner has to think about polyneuropathy when a patient presents with numb feet or even when a patient presents with nonspecific leg complaints, purely because polyneuropathy is so common, especially in elderly. In our study, a large proportion of participants, although these participants had clinically overt polyneuropathy, was not previously diagnosed with this disease. Hopefully, the data described in this thesis will contribute information that will lead to an improved recognition and awareness of this disease.

This thesis also provided evidence that traditional cardiovascular risk factor may play an important role in the development of polyneuropathy, but longitudinal studies are required to further strengthen the hypothesis that this association is indeed causal. Besides assessment of diabetes mellitus, vascular factors are not routinely investigated in the diagnostic work-up of polyneuropathy. It may be recommended that future polyneuropathy guidelines implement measurement of lipid levels and blood pressure and encourage weight reduction when appropriate. However, it is currently unknown whether patients who are already diagnosed with polyneuropathy may benefit from treatment of these risk factors. Even if such treatments are able to halt progression, it will probably not cure the disease since irreversible damage may already have accumulated over a period of years. Therefore prevention may be most important. Unfortunately,

we performed a cross-sectional observational study and were not able to investigate whether such an intervention indeed helps. Trials are necessary to investigate the true potential of strict treatment of these factors on the development and progression of polyneuropathy. When designing a clinical trial that evaluates the effect of such an intervention, knowledge about the impact of polyneuropathy on daily life and the risk of falls is very important, especially when deciding on the appropriate outcome measures.[73] Information about the impact of polyneuropathy on daily life is also very useful for clinical practice. Clinicians can use this data to inform and counsel patients with polyneuropathy at diagnosis and during follow-up.

This thesis provides important information about chronic axonal polyneuropathy, but much of the etiology of this disease remains unknown. Currently, the Rotterdam Study is one of the very few population-based studies focusing on chronic axonal poly-neuropathy. This is unfortunate, since collaborative consortia greatly increases sample size, and thus increases the chance to find small effects. This would especially also be useful for the investigation of genetic polymorphisms in polyneuropathy. Still, when more participants of the Rotterdam Study have been screened, we will hopefully be able to further elucidate at least a part of the genetic background of chronic – yet idiopathic – axonal polyneuropathy. Besides the discussed cardiovascular risk factors and genetic factors, the search for other risk factors of (idiopathic) polyneuropathy still continues. Other interesting topics for new research include the investigation of inflammatory factors and markers of small vessel disease. As discussed before, inflammation, hypoxia and ischemia likely play an important role in the pathophysiology of polyneuropathy. One way to further study this association can be to study the association between changes in easily accessible vessel beds, such as the microvasculature of the retina, and poly-neuropathy. Retinal vessels can be visualized non-invasively, and are thought to be a representative reflection of systemic microvasculature.[74, 75] The eyes can also be used to study peripheral nerves non-invasively, using optical coherence tomography or corneal confocal microscopy, both relatively new and promising techniques that may be able to detect neurodegenerative changes already at an early stage.[76] The potential of these new techniques requires further investigation.

In conclusion, in this thesis, in which we described the first results of a study on polyneu-ropathy in the Rotterdam Study, we found that chronic (idiopathic) axonal polyneuropa-thy is a common, disabling, but underdiagnosed disease, that disproportionately affects elderly. Aside from diabetes mellitus, other cardiometabolic factors, especially dyslipid-emia, obesity and kidney dysfunction, are important in chronic axonal polyneuropathy, including chronic idiopathic axonal polyneuropathy. Future studies are necessary to investigate whether optimal prevention and treatment of these risk factors leads to a reduction in incidence or progression of chronic polyneuropathy.

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Chapter 7

Summary / Samenvatting

SUMMARY

Chronic axonal polyneuropathy is the most common age-related disease of the peripheral nervous system. The disease is characterized by slowly progressive symmetrically distributed sensory disturbances such as numbness, tingling and neuropathic pain, and motor symptoms, such as cramps and muscle weakness. Initially, most symptoms are restricted to distal body parts, but symptoms may ascend during the course of the disease, which is mostly over a period of several years. The symptoms are caused by irreversible length-dependent axonal degeneration of peripheral nerves. The most common cause of this axonal degeneration is diabetes mellitus. Other known causes of axonal polyneuropathy include alcohol abuse, nutritional deficiencies, hereditary factors, systemic diseases and use of certain medications, such as chemotherapy. Despite an extensive diagnostic work-up, the cause of axonal polyneuropathy remains unknown in 25-30% of cases. These patients are diagnosed with 'chronic idiopathic axonal polyneuropathy', or CIAP.

Due to the complexity of the diagnosis of chronic polyneuropathy, which includes assessment of symptoms, signs, and nerve conduction, little population-based data about the prevalence and risk factors of chronic axonal polyneuropathy, and in particular CIAP, was available. The scientific work described in this thesis addressed these knowledge gaps. The aims of the studies were to describe the prevalence of chronic (idiopathic) axonal polyneuropathy in the general population, to investigate the (early) effects of known risk factors on polyneuropathy and peripheral nerve function and to identify new risk factors for polyneuropathy. Most studies in this thesis were embedded in the Rotterdam Study, a large prospective population-based study among people 45 years of age and older, residing in Ommoord, a district of Rotterdam, the Netherlands.

In chapter 2 several screening methods for chronic polyneuropathy are described. Chapter 2.1 outlines screening questionnaires and scoring systems for neurological examination that have previously been developed especially for the detection of polyneuropathy in high-risk individuals, such as persons with diabetes mellitus. A screening that combines the assessment of symptoms with an evaluation of sensory modalities has the best discriminative ability for polyneuropathy. Scoring systems that only assess the presence of symptoms perform less well. Several questionnaires include multiple non-specific symptoms such as fatigue, muscle pain, or cramps and most do not incorporate the frequency of occurrence of these symptoms into the questionnaire, although this may contribute important information about the likelihood of the disease. Therefore, it is likely that the diagnostic accuracy of a questionnaire can be optimized. In the study described in chapter 2.2, we extensively interviewed polyneuropathy patients about their complaints, to investigate which symptoms are most informative for the presence

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of a polyneuropathy. The six most informative symptoms – numb feet, tingling feet, allo-dynia of the feet (pain due to a stimulus that normally does not provoke pain), a feeling as if walking on cotton wool, balance problems and tingling hands – were included in a new symptom scoring tool: the Erasmus Polyneuropathy Symptom Score (E-PSS). This tool proved to be highly accurate in detecting the presence of a polyneuropathy across several populations. The practical utility of this tool for the use in research settings and in clinical practice needs to be further investigated.

Chapter 3 focuses on the prevalence of polyneuropathy in the general population. Chapter 3.1 first summarizes previous studies that have attempted to report on the prevalence of polyneuropathy. Because of the complexity of the diagnostic procedure and the lack of a simple standard test to diagnose chronic polyneuropathy, there was a large inter-study variation with regard to the applied methodology to diagnose poly-neuropathy. Consequently, the reported prevalence among elderly ranged from around 2% to over 30%. Most studies had several limitations and most importantly, none used a rigorous screening that involved both assessment of symptoms and signs together with nerve conduction studies, which is recommended for the diagnosis of this disease.

In order to provide a more reliable estimate of the prevalence of chronic polyneu-ropathy, we implemented an extensive screening protocol for polyneuropathy in the population-based Rotterdam Study, that aside from assessment of symptoms and signs, also included nerve conduction studies. Among 1310 participants, the crude prevalence of polyneuropathy was 5.5%, and the age-standardized prevalence to the population of the Netherlands was 4.0%. (chapter 3.2) This translates to approximately 260 000 persons in the Netherlands with chronic polyneuropathy. In almost half (46%) of the participants of the Rotterdam Study with polyneuropathy no known risk factor was present (CIAP), a proportion that is much larger than was estimated based on hospital-based studies (25-30%). Additionally, almost half (49%) of the participants with polyneuropathy were not previously recognized as having polyneuropathy. These results show that chronic polyneuropathy, and in particular CIAP, is a common, but underdiagnosed health prob-lem, that deserves more public attention.

In chapter 4, potential risk factors of chronic (idiopathic) axonal polyneuropathy and peripheral nerve dysfunction are described. Chapter 4.1 focuses on the presence of diabetes mellitus and metabolic syndrome, a clustering of interrelated risk factors for cardiovascular diseases. The presence of thee out of five risk factors (abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, hypertension, and elevated fasting glucose) defines the presence of metabolic syndrome. Participants with diabetes mellitus were three times more likely to have polyneuropathy. Similarly, par-ticipants with metabolic syndrome were two times more likely to have polyneuropathy,

independent of the presence of diabetes mellitus. The presence of more components of metabolic syndrome related to a higher probability of having polyneuropathy. Abdominal obesity and elevated triglycerides contributed most to this association.

The important role of these cardiometabolic risk factors was further emphasized by showing that the presence of metabolic syndrome also related to worse peripheral nerve function (lower sural sensory nerve action potential amplitude and lower peroneal compound muscle action potential amplitude) in participants yet without polyneuropathy. Additionally, in chapter 4.2 we show that a high weight, obesity and the presence of moderate kidney dysfunction also relate to worse peripheral nerve function in persons without any symptoms or signs of polyneuropathy. These results suggest that the presence of cardiometabolic risk factors and kidney dysfunction leads to a gradual decline in peripheral nerve function and may predispose for the development of polyneuropathy.

Chapter 5 of this thesis is dedicated to the impact of polyneuropathy on daily life. In chapter 5.1 the effect of polyneuropathy on the ability to perform daily activities was investigated. Participants with polyneuropathy were much more likely to experience difficulty in performing basic activities, such as walking, eating, dressing and arising, and also in more complex activities such as housekeeping and shopping. Additionally, gait pattern, as assessed with an electronic walkway, of participants with polyneuropathy showed a lower gait velocity, lower cadence, and a longer double support time. Moreover, participants with polyneuropathy made more errors when walking heel-to-toe over a line visible on the walkway. Especially the latter finding might predispose to an increased risk of falls in patients with polyneuropathy. In our study, we found that participants with polyneuropathy were two times more likely to fall, and these falls often resulted in injury, such as fractures, head trauma or severe bruising. In chapter 5.2 we investigated the gait pattern of participants with diabetes mellitus. Here we found that participants with diabetes mellitus exhibit similar gait abnormalities as participants with polyneuropathy. This is a logical observation, since polyneuropathy is a very common complication of diabetes mellitus.

The final chapter (chapter 6) provides an extensive discussion of the main findings, methodological considerations, clinical implications and future directions.

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SAMENVATTING

Chronische axonale polyneuropathie is de meest voorkomende leeftijdsafhankelijke aandoening van het perifere zenuwstelsel. Het ziektebeeld wordt gekenmerkt door langzaam progressieve symmetrische klachten van het gevoel, zoals doofheid, tintelingen en neuropathische pijn, en klachten van de motoriek, zoals kramp en spierzwakte. Aanvankelijk bevinden deze klachten zich vooral in de voeten, maar later in het beloop van de aandoening, meestal over een periode van meerdere jaren, kunnen deze klachten opstijgen in de benen en ook ontstaan in de handen en armen. De klachten worden veroorzaakt door irreversibele axonale degeneratie van perifere zenuwen. De meest voorkomende oorzaak van deze axonale degeneratie is diabetes mellitus (suikerziekte). Andere bekende oorzaken van axonale polyneuropathie zijn alcohol misbruik, tekorten aan bepaalde voedingsmiddelen, erfelijke factoren, systeemziekten en het gebruik van bepaalde medicijnen zoals chemotherapie. Ondanks uitgebreid aanvullend onderzoek blijft de oorzaak van polyneuropathie onbekend in 25-30% van alle polyneuropathie gevallen. Deze patiënten worden gediagnosticeerd met 'chronische idiopathische axonale polyneuropathie', ook wel CIAP.

Doordat het stellen van de diagnose chronische polyneuropathie een complexe procedure betreft, bestaande uit een evaluatie van symptomen, een neurologisch onderzoek en een zenuwgeleidingsonderzoek, zijn er erg weinig populatie studies naar de prevalentie (voorkomen) en de risicofactoren van chronische axonale polyneuropathie, en in het bijzonder CIAP, verricht. De studies die zijn beschreven in dit proefschrift richten zich op dit hiaat in de wetenschappelijke kennis. Het doel van deze studies was te beschrijven hoe vaak chronische (idiopathische) axonale polyneuropathie in de algemene bevolking voorkomt, te onderzoeken wat het effect is van bekende risicofactoren op polyneuropathie en perifere zenuw functie, en om nieuwe factoren te kunnen identificeren die betrokken zijn bij het ontstaan van polyneuropathie. De meeste studies die beschreven zijn in dit proefschrift zijn verricht in de Rotterdam Studie, een groot prospectief bevolkingsonderzoek onder inwoners van de wijk Ommoord in Rotterdam, van 45 jaar en ouder.

In hoofdstuk 2 worden verschillende screeningsmethoden voor chronische polyneuropathie beschreven. In hoofdstuk 2.1 zijn vragenlijsten en score instrumenten voor het neurologisch onderzoek samengevat die in eerdere studies zijn gebruikt om polyneuropathie op te sporen bij mensen met een hoog risico op polyneuropathie, zoals mensen met diabetes mellitus. Een screening protocol dat de aanwezigheid van klachten, in combinatie met sensibele stoornissen evalueert lijkt het meest geschikt om mensen met polyneuropathie te kunnen onderscheiden van mensen zonder polyneuropathie. Het gebruik van een vragenlijst alleen is minder accuraat, mogelijk omdat in de meeste vragenlijsten ook naar de aanwezigheid van verschillende aspecifieke klachten wordt

gevraagd, zoals moeheid, kramp en spierpijn. Daarnaast wordt vaak niet meegenomen hoe vaak klachten optreden, wat wellicht belangrijke informatie geeft over de waarschijnlijkheid van de diagnose. Mogelijk kunnen deze vragenlijsten dus verder worden geoptimaliseerd. In de studie beschreven in hoofdstuk 2.2 hebben we patiënten met polyneuropathie uitgebreid ondervraagd over het optreden van hun klachten, om zo te onderzoeken welke symptomen het meest informatief zijn voor de diagnose polyneuropathie. De zes meest informatieve symptomen – dove voeten, tintelende voeten, overgevoeligheid van de voeten, het gevoel op watten te lopen, balans problemen en tintelende handen – hebben we opgenomen in een nieuw score instrument voor symptomen van polyneuropathie: de "Erasmus Polyneuropathy Symptom Score" (E-PSS). Dit instrument was erg accuraat in het detecteren van de aanwezigheid van polyneuropathie in verschillende populaties. De bruikbaarheid van dit instrument voor wetenschappelijk onderzoek en in de klinische praktijk moet nog verder worden onderzocht.

Hoofdstuk 3 richt zich op het voorkomen van polyneuropathie in de algemene bevolking. In hoofdstuk 3.1 worden eerder verrichtte studies naar de prevalentie van polyneuropathie samengevat. Wegens de complexe diagnostische procedure en de afwezigheid van een simpele test om de diagnose chronische polyneuropathie te stellen, is er een grote variatie tussen deze studies met betrekking tot de toegepaste methodiek om de diagnose te stellen. Dit heeft als gevolg dat ook de resultaten erg uiteenlopen, variërend van een prevalentie onder ouderen van rond de 2% tot boven de 30%. De meeste van deze studies hadden verschillende beperkingen, en geen van alle studies gebruikte een strenge definitie van polyneuropathie, bestaande uit de combinatie van symptomen, afwijkingen bij het neurologisch onderzoek en afwijkingen bij het zenuwgeleidingsonderzoek, wat wel aanbevolen wordt bij het stellen van de deze diagnose.

Om een meer betrouwbare schatting van de prevalentie van polyneuropathie te verkrijgen, hebben we een uitgebreid polyneuropathie screening protocol geïmplementeerd in de Rotterdam Studie. Dit protocol bestaat uit een evaluatie van symptomen, afwijkingen bij neurologisch onderzoek en een zenuwgeleidingsonderzoek. Van de 1.310 onderzochte deelnemers had 5.5% een polyneuropathie (hoofdstuk 3.2). Wanneer we dit vertalen naar de Nederlands bevolking was dit 4.0%. Dit betekent dat er in Nederland ongeveer zo'n 260.000 mensen een chronische polyneuropathie hebben. In ongeveer de helft (46%) van de deelnemers aan de Rotterdam Studie waarbij er een polyneuropathie werd vastgesteld, kon geen bekende risicofactor gevonden worden (CIAP). Dit is een stuk vaker dan eerder werd geschat op basis van studies verricht in ziekenhuizen (25-30%). Bovendien vonden we dat bijna de helft (49%) van deze mensen nog niet eerder was gediagnosticeerd met polyneuropathie. Deze resultaten laten zien dat chronische polyneuropathie, met name ook CIAP, erg vaak voorkomt, maar vaak niet goed wordt herkend. Er moet dus meer aandacht komen voor polyneuropathie.

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In hoofdstuk 4 zijn potentiele risicofactoren voor chronische (idiopathische) axonale polyneuropathie en dysfunctie van perifere zenuwen onderzocht. In hoofdstuk 4.1 is het verband tussen de aanwezigheid van diabetes mellitus, het metabool syndroom en polyneuropathie beschreven. Het metabool syndroom is een benaming voor de aanwezigheid van een combinatie van meerdere risicofactoren voor hart- en vaatziekten. Bij de aanwezigheid van drie van vijf factoren (abdominale obesitas, verhoogde triglyceride, verlaagd HDL-cholesterol, hoge bloeddruk en verhoogd nuchter glucose) spreekt met van metabool syndroom. Deelnemers met diabetes mellitus hadden drie keer zo vaak een polyneuropathie. Deelnemers met metabool syndroom hadden twee keer zo vaak een polyneuropathie en dit was onafhankelijk van de aanwezigheid van diabetes mellitus. De kans op polyneuropathie was groter wanneer er meer factoren van metabool syndroom aanwezig waren. Abdominale obesitas en verhoogde triglyceride waarden droegen het meeste bij aan dit verband.

De belangrijke rol van deze cardio-metabole risico factoren werd verder benadrukt door aan te tonen dat de aanwezigheid van metabool syndroom gerelateerd was aan een slechtere perifere zenuwfunctie (verlaagde amplitudes bij zenuwgeleidingsonderzoek) bij mensen bij wie de diagnose polyneuropathie niet kon worden gesteld. Daarnaast laten we in hoofdstuk 4.2 ook zien dat een hoog gewicht, obesitas en de aanwezigheid van gematigd nierfalen gerelateerd zijn aan een verminderde zenuwfunctie bij mensen zonder symptomen of andere klinische kenmerken van polyneuropathie. Hieruit kunnen we concluderen dat de aanwezigheid van deze cardio-metabole factoren mogelijk leidt tot een geleidelijke afname van perifere zenuwfunctie, en mogelijk het risico op het ontwikkelen van een polyneuropathie vergroot.

Hoofstuk 5 van dit proefschrift gaat over de impact van polyneuropathie op het dagelijks leven. In hoofdstuk 5.1 is het effect van polyneuropathie op de mogelijkheid tot het uitvoeren van allerlei dagelijkse activiteiten onderzocht. Deelnemers met polyneuropathie bleken veel vaker moeilijkheden te hebben met het uitvoeren van simpele activiteiten zoals lopen, eten, aankleden, opstaan, maar ook met het uitvoeren van meer complexe activiteiten zoals boodschappen doen en het huishouden doen. Met behulp van een elektronische loopmat vonden we dat mensen met polyneuropathie een ander looppatroon hadden dan mensen zonder polyneuropathie: ze liepen langzamer en met een lagere cadans. Daarnaast maakten mensen met polyneuropathie meer zijstappen wanneer zij voetje-voor-voetje over een lijn moesten lopen. Deze bevindingen spelen een belangrijke rol bij het risico op vallen. Wij vonden dat mensen met polyneuropathie twee keer zo vaak vielen dan mensen zonder polyneuropathie. Een dergelijke val leidde ook vaker tot verwondingen zoals botbreuken, hoofdwonden, of kneuzingen. In hoofdstuk 5.2 wordt het looppatroon van mensen met diabetes mellitus beschreven. In deze studie vonden we dat het looppatroon bij mensen met diabetes op dezelfde manier is

veranderd als bij mensen met polyneuropathie. Dit is een logische bevinding, aangezien polyneuropathie een veel voorkomende complicatie van diabetes mellitus is.

In het laatste hoofdstuk (hoofdstuk 6) worden in een uitgebreide discussie de belangrijkste resultaten, methodologische overwegingen, klinische implicaties en onderwerpen voor toekomstig onderzoek beschreven.

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Chapter 8

Dankwoord

PhD portfolio

List of publications

About the author

DANKWOORD

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PhD PORTFOLIO

Name PhD Student:	Rens Hanewinckel
Erasmus MC Department:	Epidemiology
Research School:	NIHES
PhD Period:	January 2013 – October 2016
Supervisors:	Prof. dr. M.A. Ikram, Prof. dr. P.A. van Doorn

1. PhD training	Year	ECTS
Research skills		
Master of Science in Clinical epidemiology, NIHES	2013-2015	70
Integrity in Science (Erasmus MC)	2014	0.3
International conferences		
Peripheral Nerve Society Biennial Meeting, Saint-Malo, France: oral presentation	2013	1.6
Inflammatory Neuropathy Consortium, Düsseldorf, Germany: Attended	2014	1.0
Peripheral Nerve Society Biennial Meeting, Quebec City, Canada: 2 poster presentations	2015	1.3
American Academy of Neurology Annual Meeting, Vancouver, Canada: 2 poster presentations	2016	1.3
In depth courses, seminars and workshops		
Weekly research seminars, department of epidemiology, Erasmus MC	2013-2016	4.0
Boerhaave Prinses Beatrix Spierfonds symposium on neuromuscular diseases	2014-2016	1.0
Muscles2Meet, young talent symposium on neuromuscular diseases: organizing committee	2016	3.0
Spierziektencongres for patients: 2013-2015 posters, 2016 oral presentation	2013-2016	2.0

2. Teaching activities		
Teaching assistant		
Biostatistics 1, NIHES, Rotterdam, The Netherlands	2015-2016	2.0
Practice of epidemiologic analysis, NIHES, Rotterdam, The Netherlands	2015-2016	2.0
Teaching 3rd year medical students at Erasmus MC, Rotterdam, The Netherlands	2014-2016	1.0
Supervisor		
Master thesis of M. Terwiel: Nerve conduction parameters in restless legs syndrome	2013-2014	4.0

3. Other		
Reviewer		
Reviewing activities for various journals	2015- present	1.0

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LIST OF PUBLICATIONS

Hanewinckel R, van Oijen M, Merkies ISJ, Notermans NC, Vrancken AFJE, Ikram MA, van Doorn PA. Diagnostic value of symptoms in chronic polyneuropathy: The Erasmus Polyneuropathy Symptom Score (E-PSS). *Submitted.*

Hanewinckel R, Drenthen J, Verlinden VJA, Darweesh SKL, van der Geest JN, Hofman A, van Doorn PA, Ikram MA. Polyneuropathy relates to impairment in daily activities, worse gait and fall-related injuries. *Neurology*. In Press.

Hanewinckel R, Ikram MA, Franco OH, Hofman A, Drenthen J, van Doorn PA. High body mass and kidney dysfunction relate to worse nerve function, even in adults without polyneuropathy. *Journal of the Peripheral Nervous System.* In Press

Hanewinckel R, Drenthen J, Ligthart S, Dehghan A, Franco OH, Hofman A, Ikram MA, van Doorn PA. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: a prospective population-based cohort study. *Journal of Neurology, Neurosurgery and Psychiatry*. 2016;87(12):1336-1342

Hanewinckel R, Drenthen J, van Oijen M, Hofman A, van Doorn PA*, Ikram MA*. Prevalence of polyneuropathy in the general middle-aged and elderly population. *Neurology*. 2016;87:1892-1898.

Hanewinckel R, Ikram MA, van Doorn PA. Peripheral Neuropathies. In: Rosano C, Ikram MA, Ganguli M. eds. *Handbook of clinical neurology: Neuroepidemiology*. Elsevier. 2016;138:263-282.

Hanewinckel R, Ikram MA, van Doorn PA. Assessment scales for the diagnosis of polyneuropathy. *Journal of the Peripheral Nervous System*. 2016;21:61-73.

Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. *European Journal of Epidemiology*. 2016;31:5-20.

Maksimovic A*, **Hanewinckel R***, Verlinden VJA, Ligthart S, Hofman A, Franco OH, van Doorn PA, Tiemeier H, Dehghan A, Ikram MA. Gait characteristics in older adults with diabetes and impaired fasting glucose: the Rotterdam Study. *Journal of Diabetes and Its Complications*. 2016;30:61-66.

Hanewinckel R, Maksimovic A, Verlinden VJA, van der Geest JN, Hofman A, van Doorn PA, Boon AJ, Tiemeier H, Ikram MA. The impact of restless legs syndrome on physical functioning in a community-dwelling population of middle-aged and elderly people. *Sleep Medicine*. 2016;16:399-405.

Hanewinckel R, Jongman HP, Wallis LA, Mulligan TM. Emergency medicine in Paarl, South-Africa: a cross-sectional descriptive study. *International Journal of Emergency Medicine*. 2010;3:143-150.

*These authors contributed equally to the respective manuscript.

ABOUT THE AUTHOR

Rens Hanewinckel was born on October 16th, 1986 in Rotterdam, the Netherlands and grew up in Hellevoetsluis. After graduating at G.S.G. Helinium in Hellevoetsluis in 2004, he started his medical education at the Erasmus University in Rotterdam. In November 2010, Rens obtained his medical degree. Subsequently, he worked as a resident at the department of Neurology at the Sint Franciscus Gasthuis in Rotterdam, under supervision of dr. S.L.M. Bakker.

In January 2013, Rens started working at the department of Epidemiology on the project described in this thesis under supervision of prof. dr. M.A. Ikram (department of Epidemiology) and prof. dr. P.A. van Doorn (department of Neurology). In August 2015, he obtained a Master of Health Sciences in Clinical Epidemiology at the Netherlands Institute for Health Sciences. As of October 2016, Rens is working as a resident at the department of Neurology at the Erasmus Medical Center (head: prof. dr. P.A.E. Sillevis Smitt).

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