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

Rens Hanewinckel
ACKNOWLEDGEMENTS

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

Prevalentie, risicofactoren en gevolgen van chronische polyneuropathie
De Rotterdam Studie

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*These authors contributed equally to the respective manuscript.*
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 is 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.\textsuperscript{2-4}

Neurological examination of a patient with polyneuropathy usually shows decreased or absent sensation of touch, pinprick 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).\textsuperscript{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

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Nerve conduction studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal polyneuropathy</td>
<td>Usually slowly progressive, distal symmetric sensory-predominant symptoms (numbness, tingling, pain). Muscle weakness occurs but often is relatively mild</td>
<td>Reduced or absent sensation of touch, vibration, pinprick, reduced or absent distal (Achilles) tendon reflexes, distal muscle weakness, sensory ataxia</td>
<td>Distal amplitudes: decreased Distal latency: normal Conduction velocity: normal Conduction block: absent Temporal dispersion: absent</td>
</tr>
<tr>
<td>Demyelinating polyneuropathy</td>
<td>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)</td>
<td>Proximal (or distal) muscle weakness, mild sensory deficits, absent tendon reflexes, sometimes cranial nerve deficits</td>
<td>Distal amplitudes: normal Distal latency: prolonged Conduction velocity: slowed Conduction block: present Temporal dispersion: present</td>
</tr>
</tbody>
</table>
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). 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. 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. 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. 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. These patients are generally diagnosed with chronic idiopathic axonal polyneuropathy (CIAP).

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. However, it is remarkable that only half of all diabetics develop polyneuropathy, suggesting that additional factors must be involved. 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. Similarly, these factors have increasingly been associated with CIAP in recent uncontrolled and case-controlled studies. Axonal degeneration currently is irreversible and therefore curative options do not (yet) exist. 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. 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
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. 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.
REFERENCES


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

Journal of the Peripheral Nervous System, 2016
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.
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-
sequently 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-
<table>
<thead>
<tr>
<th>Article</th>
<th>Score</th>
<th>Symptoms/Exam</th>
<th>Administered by</th>
<th>Time required</th>
<th>Developed for</th>
<th>Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dyck, et al., 1980</em></td>
<td>NSS</td>
<td>Symptoms</td>
<td>Neurologist</td>
<td>++</td>
<td>Diabetes</td>
<td>Detection and grading of neuropathy</td>
</tr>
<tr>
<td><em>Freeman, et al., 1985</em></td>
<td>-</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>+</td>
<td>Peripheral neuropathy</td>
<td>Distinguish patients with peripheral neuropathy from those without</td>
</tr>
<tr>
<td><em>Dyck, et al., 1986</em></td>
<td>NSP</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>+++</td>
<td>Diabetes</td>
<td>Characterization and grading of symptoms</td>
</tr>
<tr>
<td><em>Beghi, et al., 1988</em></td>
<td>-</td>
<td>Symptoms</td>
<td>Physician</td>
<td>+</td>
<td>Polynuropathy</td>
<td>Diagnosis of polynuropathy</td>
</tr>
<tr>
<td><em>Grootenhuis, et al., 1994</em></td>
<td>DSC-Type 2</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>++</td>
<td>Diabetes</td>
<td>Detect and monitor diabetes complications</td>
</tr>
<tr>
<td><em>Ziegler, et al., 1995</em></td>
<td>TSS</td>
<td>Symptoms</td>
<td>Physician/nurse</td>
<td>+</td>
<td>Diabetes</td>
<td>Evaluate treatment effects on symptoms</td>
</tr>
<tr>
<td><em>Dyck, et al., 1997</em></td>
<td>NSC</td>
<td>Symptoms</td>
<td>Neurologist</td>
<td>+++</td>
<td>Diabetes</td>
<td>Monitor change in symptoms over time</td>
</tr>
<tr>
<td><em>McArthur, 1998</em></td>
<td>SPNS</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>+</td>
<td>HIV</td>
<td>Screen for neuropathy in HIV patients</td>
</tr>
<tr>
<td><em>Meijer, et al., 2002</em></td>
<td>DNS</td>
<td>Symptoms</td>
<td>Physician</td>
<td>+</td>
<td>Diabetes</td>
<td>Screen for diabetic polyneuropathy</td>
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<tr>
<td><em>Bastyr, et al., 2005</em></td>
<td>NTSS-6</td>
<td>Symptoms</td>
<td>Physician</td>
<td>++</td>
<td>Diabetes</td>
<td>Evaluate frequency and intensity of symptoms</td>
</tr>
<tr>
<td><em>Leonard, et al., 2005</em></td>
<td>-</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>++</td>
<td>Chemotherapy</td>
<td>Document incidence and type of neurotoxicity</td>
</tr>
<tr>
<td><em>Postma, et al., 2005</em></td>
<td>CIPN20</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>+</td>
<td>Chemotherapy</td>
<td>Assessment of chemotherapy-induced neuropathy</td>
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<td><em>Toftthagen, et al., 2011</em></td>
<td>CIPNAT</td>
<td>Symptoms</td>
<td>Self-administered</td>
<td>+</td>
<td>Chemotherapy</td>
<td>Evaluate occurrence and distress of chemotherapy-induced neuropathy</td>
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<td><em>Franklin, et al., 1990</em></td>
<td>-</td>
<td>Symptoms + signs</td>
<td>Physician/nurse</td>
<td>++</td>
<td>Diabetes</td>
<td>Screen for polyneuropathy in patients with diabetes</td>
</tr>
<tr>
<td><em>Chaudhry, et al., 1994</em></td>
<td>TNS</td>
<td>Symptoms + signs + tests</td>
<td>Physician</td>
<td>+++</td>
<td>Chemotherapy/ Diabetes</td>
<td>Detecting and quantifying peripheral neuropathy</td>
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<tr>
<td>Article</td>
<td>Score</td>
<td>Symptoms/Exam</td>
<td>Administered by</td>
<td>Time required</td>
<td>Developed for</td>
<td>Aim</td>
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<td>------------------------</td>
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<td>---------------</td>
<td>---------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Gentile, et al., 1995</td>
<td>-</td>
<td>Symptoms + signs</td>
<td>Physician</td>
<td>++</td>
<td>Diabetes</td>
<td>Screening for polyneuropathy</td>
</tr>
<tr>
<td>Bril, 2002</td>
<td>TCSS</td>
<td>Symptoms + signs</td>
<td>Neurologist</td>
<td>++</td>
<td>Diabetes</td>
<td>Detection and grading of neuropathy</td>
</tr>
<tr>
<td>Cherry, et al., 2005</td>
<td>BPNS</td>
<td>Symptoms + signs</td>
<td>Physician</td>
<td>++</td>
<td>HIV</td>
<td>Screen for neuropathy in HIV patients</td>
</tr>
<tr>
<td>Dyck, et al., 1980</td>
<td>NDS</td>
<td>Signs</td>
<td>Neurologist</td>
<td>++</td>
<td>Diabetes</td>
<td>Evaluation of neurological deficit</td>
</tr>
<tr>
<td>Valk, et al., 1992</td>
<td>CNE</td>
<td>Signs</td>
<td>Physician</td>
<td>+</td>
<td>Diabetes</td>
<td>Diagnosis of diabetic neuropathy</td>
</tr>
<tr>
<td>Dyck, et al., 1997</td>
<td>NIS(LL)(+)</td>
<td>Signs (+ tests)</td>
<td>Neurologist</td>
<td>+++</td>
<td>Diabetes</td>
<td>Quantification of neuropathic impairment</td>
</tr>
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<td>Feldman, et al., 1994</td>
<td>MDNS</td>
<td>Signs + tests</td>
<td>Neurologist</td>
<td>+++</td>
<td>Diabetes</td>
<td>Diagnosis of diabetic neuropathy</td>
</tr>
<tr>
<td>Meijer, et al., 2000</td>
<td>DNE</td>
<td>Signs</td>
<td>Physician</td>
<td>+</td>
<td>Diabetes</td>
<td>Diagnosis of diabetic neuropathy</td>
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<td>Merkies, et al., 2000</td>
<td>ISS</td>
<td>Signs</td>
<td>Neurologist</td>
<td>+</td>
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<td>Singleton, et al., 2008</td>
<td>UENS</td>
<td>Signs</td>
<td>Neurologist</td>
<td>+</td>
<td>Diabetes</td>
<td>Detect early sensory predominant polyneuropathy</td>
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<td>Zilliox, et al., 2015</td>
<td>ENS</td>
<td>Signs</td>
<td>Neurologist</td>
<td>+</td>
<td>Diabetes</td>
<td>Assess abnormalities of early neuropathy</td>
</tr>
</tbody>
</table>

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

*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
logical examination scores, neuropathological abnormality of the sural nerve and with multiple parameters of nerve conduction.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{14} An advantage of these extensive scales is that the questionnaires can be read by a computer that converts the responses into specific scores.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.\textsuperscript{21}

Several other validated but less widely used questionnaires have been developed. Examples include the Type 2 Diabetes Symptom Checklist\textsuperscript{22} and the Neuropathy Total Symptom Score-6\textsuperscript{23}, which were designed to detect or to follow complications of diabetes; the Subjective Peripheral Neuropathy Screen\textsuperscript{24} and the Brief Peripheral Neuropathy Screen\textsuperscript{25}, which were developed to detect neuropathy in patients with HIV; the Total Symptom Score\textsuperscript{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.\textsuperscript{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.\textsuperscript{29} Some scales were specifically designed for neuropathy, such as the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT)\textsuperscript{30}, the Chemotherapy-Induced
### Table 2. Overview of different assessment scales that include symptoms of polyneuropathy

<table>
<thead>
<tr>
<th>Population</th>
<th>NSS(^7)</th>
<th>Freeman(^{27})</th>
<th>NSP(^{36})</th>
<th>Beghi(^3)</th>
<th>Franklin(^{28})</th>
<th>TNS(^{42})</th>
<th>MNSI(^{35})</th>
<th>DSC-type 2(^{22})</th>
<th>Gentile(^4)</th>
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<td>Neurologist</td>
<td>NSS and NIS(^b)</td>
<td>Neurologist, NCS, Mayo criteria(^f)</td>
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<td>NCS</td>
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<td>65(^f)</td>
<td>64(^c)</td>
<td>92(^c)</td>
<td>87(^d)</td>
<td>-</td>
<td>40(^g)</td>
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<td>87(^g)</td>
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<tr>
<td>Specificity</td>
<td>30(^a)</td>
<td>73(^f)</td>
<td>85(^c)</td>
<td>100(^c)</td>
<td>91(^d)</td>
<td>-</td>
<td>92(^g)</td>
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<td>60(^g)</td>
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</table>

### 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

\(^a,\) Not specified
\(^b,\) Clinical
\(^c,\) Neurologist
\(^d,\) NSS and NIS
\(^e,\) Neurologist, NCS, Mayo criteria
\(^f,\) Clinical
\(^g,\) NSS and NIS

Chapter 2.1
### Table 2. (continued)

<table>
<thead>
<tr>
<th></th>
<th>NSS⁷</th>
<th>Freeman⁷⁷</th>
<th>NSP³⁶</th>
<th>Beghi³</th>
<th>Franklin²⁸</th>
<th>TNS⁴²</th>
<th>MNSI³⁵</th>
<th>DSC-type 2²²</th>
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<tr>
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<td>-</td>
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<td>+</td>
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<tr>
<td>Stiffness</td>
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<tr>
<td>Tight feeling</td>
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</table>

+: present in scale; -: absent in scale

² Sensitivity and specificity of the NSS to detect polyneuropathy reported in a later validation study.⁶² 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.⁵⁵

ᵍ Sensitivity and specificity of the questionnaire part are not reported in original publication. These number are derived from a more recent study.⁶⁶

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
### Table 2. (continued)

<table>
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<tr>
<th>Population</th>
<th>TSS&lt;sup&gt;26&lt;/sup&gt;</th>
<th>NSC&lt;sup&gt;14&lt;/sup&gt;</th>
<th>SPNS&lt;sup&gt;14&lt;/sup&gt;</th>
<th>DNS&lt;sup&gt;19&lt;/sup&gt;</th>
<th>TCSS&lt;sup&gt;40&lt;/sup&gt;</th>
<th>NTSS-6&lt;sup&gt;23&lt;/sup&gt;</th>
<th>Leonard&lt;sup&gt;14&lt;/sup&gt;</th>
<th>CIPN20&lt;sup&gt;11&lt;/sup&gt;</th>
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## Table 2. (continued)

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</tbody>
</table>

+: 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.\(^{57}\)

\(^{d}\) 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).\(^{33}\)
Peripheral Neuropathy-20 (CIPN20)\textsuperscript{31, 32} and the Chemotherapy Induced Neurotoxicity Questionnaire (CINQ).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\%.\textsuperscript{36} The clinical part of the MNSI has been used throughout other studies.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42-47} Apart from symptoms and signs, the original TNS© includes a
Screening for polyneuropathy

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. 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. 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. 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. 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. The latter was also expanded with a range of additional examinations (vibration thresholds, nerve conduction studies, NIS-LL+7 tests). 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.

The extensive NDS was reduced into the 8-item Diabetic Neuropathy Examination (DNE), 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.

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. This scale includes pinprick and vibration sense on the
Table 3. Overview of different assessment scales that include a neurological examination for polyneuropathy

<table>
<thead>
<tr>
<th>Population</th>
<th>Diabetics</th>
<th>Diabetics</th>
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<th>Patients with IGT</th>
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<tbody>
<tr>
<td>Validation</td>
<td>NCS, biopsy</td>
<td>Vibration perception threshold</td>
<td>Mayo criteria</td>
<td>Mayo criteria</td>
<td>NSS and NIS</td>
<td>NCS</td>
<td>Monofilament</td>
<td>NCS and biopsy</td>
<td>QST and biopsy</td>
<td>NCS, QST, biopsy</td>
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<tr>
<td>Sensitivity</td>
<td>-</td>
<td>87%</td>
<td>80%</td>
<td>80% / 97%</td>
<td>-</td>
<td>94%</td>
<td>96%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>92%</td>
</tr>
<tr>
<td>Specificity</td>
<td>-</td>
<td>62%</td>
<td>95%</td>
<td>100% / 100%</td>
<td>-</td>
<td>92%</td>
<td>51%</td>
<td>-</td>
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</table>

Contents of the scale

<table>
<thead>
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<th>Upper/lower extremities</th>
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<th>Lower</th>
<th>Lower</th>
<th>Both</th>
<th>Lower</th>
<th>Both</th>
<th>Both</th>
<th>Lower</th>
<th>Lower</th>
<th>Lower</th>
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<td>Symptoms</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Cranial nerves</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Foot inspection</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<td>Pin prick</td>
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<td>+</td>
<td>-</td>
<td>+</td>
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<td>-</td>
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<td>Light touch</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Position sense</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
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<td>+</td>
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<td>Temperature sense</td>
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<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>+</td>
<td>(+)</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>
### Table 3. Overview of different assessment scales that include a neurological examination for polyneuropathy (continued)

<table>
<thead>
<tr>
<th></th>
<th>NDS / NIS</th>
<th>CNE(^a)</th>
<th>MNSI(^b)</th>
<th>MDNS(^d)</th>
<th>TNS(^e)</th>
<th>Gentile(^f)</th>
<th>DNE(^g)</th>
<th>ISS(^h)</th>
<th>TCSS(^i)</th>
<th>BPNS(^j)</th>
<th>UENS(^k)</th>
<th>ENS(^l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon reflexes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>(-)(^{\circ})</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>studies</td>
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<td>Quantitative</td>
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<td></td>
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<tr>
<td>sensory testing</td>
<td>(+)(^{\circ})</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>(-)(^{\circ})</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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</tr>
</tbody>
</table>

+: 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. 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. 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 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. Moreover, distal sensory loss can also be found in healthy people without other signs of polyneuropathy, especially in elderly. 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. 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. The choice of the reference test can also bias the diagnostic accuracy of a test. This is referred to as inappropriate reference standard bias. 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. 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. 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. 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. 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. 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. 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)

Rens Hanewinckel, Marieke van Oijen, Ingemar S.J. Merkies, Nicolette C. Notermans, Alexander F.J.E. Vrancken, M. Arfan Ikram, Pieter A. van Doorn

Submitted
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

*European Journal of Epidemiology, 2016*
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 patient 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
door-to-door survey studies\textsuperscript{11-21}, seven case-control studies\textsuperscript{22-28} and eleven cohort studies (seven cohort studies and four database studies).\textsuperscript{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.\textsuperscript{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

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

Survey studies reporting prevalence of polyneuropathy. If reported, prevalence of polyneuropathy subtypes is also shown.

*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.*

*Protocol not specified, most likely WHO protocol*

*Screening for all neuropathies, but only prevalence of diabetic neuropathy reported*

*Including hypothyroidism, uremic and hepatic neuropathy*

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

*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. When only elderly are studied, prevalence ranges from 18.8 to 200 per 1000 persons (1.9-20%). 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 and Saudi Arabia. In these studies only 4-11% of the population is over the age of 50 years. In contrast, in European countries such as Spain, where polyneuropathy affects 7.3 per 1000 people, and in Albania, 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. 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 and of 18.6 per 1000 (crude 18.8 per 1000) in Tanzania.

**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). In four of these studies, persons known with diabetes or impaired glycemia were identified from medical databases and invited to participate in the study. A random sample of controls was selected from the same community or practice and matched to the diabetes patients on age, sex, and ethnicity. The three remaining case-control studies included participants from population-based surveys, where diabetes was assessed by self-report or by an oral glucose tolerance test. 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.
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

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

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

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

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

* Probable and definite polyneuropathy are both considered polyneuropathy.

OGTT: oral glucose tolerance test; DM: diabetes mellitus; IG: 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). 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. 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. Two database studies used hospital registries to identify patients with polyneuropathy from a specific community. The other two additionally used medical records and notes from general practices. 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. 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) and one study investigating only idiopathic polyneuropathy in Gulf war veterans.

**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. Crude sex-specific prevalence rates are less consistent; most authors reported a higher prevalence in females, with a ratio of 1.5-2:1. Two of these studies reported age-standardized, sex-specific prevalence rates and showed
<table>
<thead>
<tr>
<th>Study and study period</th>
<th>Population</th>
<th>Age of the study population</th>
<th>Assessment protocol</th>
<th>Definition of polyneuropathy</th>
<th>Prevalence of polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beghi(^{29}) Italy 1990-1993</td>
<td>4191 patients seen in GP’s office consultations for any reason</td>
<td>All &gt;55 years</td>
<td>Questionnaire followed by examination (strength, sensation, reflexes) when ≥2 symptoms</td>
<td>Possible: ≥1 abnormal item of exam Probable: ≥2 abnormal items</td>
<td>Crude: 3.6% (^{a}) Adjusted: 3.5% (^{b}) - Diabetes: 44% - Neoplasm: 10% - Alcohol: 6%</td>
</tr>
<tr>
<td>Nakashima(^{30}) Japan 1991</td>
<td>Database of 7685 residents of Daisen Town</td>
<td>All ages included, about 45% &gt;50 years</td>
<td>Medical records of hospitals, GPs and other sources</td>
<td>Not specified</td>
<td>Crude: 3.3 per 1000 Adjusted: 2.2 per 1000 (^{c})</td>
</tr>
<tr>
<td>MacDonald(^{31}) Norway 1999</td>
<td>Database of 27657 subjects from 3 GP practices in London</td>
<td>All ages included, about 28% &gt;50 years</td>
<td>Medical records and notes from GPs and referral hospital</td>
<td>Clinical objective signs in the presence of an established cause, such as diabetes. Alternatively, an EMG diagnosis was required</td>
<td>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})</td>
</tr>
<tr>
<td>Mygland(^{32}) Norway 1999</td>
<td>Database of 155464 inhabitants of Vest-Agder</td>
<td>All ages</td>
<td>Database of all patients with polyneuropathy referred to the only neurology center in the county</td>
<td>Clinically and electrophysiologically classified</td>
<td>Crude: 1.2 per 1000 - Idiopathic: 26% - Diabetes: 19% - Hereditary: 12% - Alcohol: 10% - CIDP: 8%</td>
</tr>
<tr>
<td>Mold(^{33}) USA 1999-2000</td>
<td>795 non-institutionalized subjects recruited from 9 GP practices</td>
<td>All &gt;65 years</td>
<td>Symptom questionnaire, fine touch, position and vibration sensation and ankle reflexes</td>
<td>1 or more complete bilateral peripheral neurologic deficits</td>
<td>Crude: 30.9%</td>
</tr>
<tr>
<td>Eisen(^{34}) USA 1999-2001</td>
<td>1061 deployed and 1128 non-deployed Gulf war veterans</td>
<td>Mean age 31-33 years</td>
<td>Neurologic examination and nerve conduction studies</td>
<td>Idiopathic distal sensory, motor or sensorimotor polyneuropathy based on exam and/or NCS (^{f})</td>
<td>Crude: Deployed: 4.8% Non deployed: 5.9%</td>
</tr>
<tr>
<td>Baldereschi(^{35}) Italy 1992-1993</td>
<td>4500 participants of the Italian Longitudinal Study on Aging (ILSA): population-based cohort study</td>
<td>65-84 years</td>
<td>Screening: self-reported diagnosis, symptoms, ankle reflexes, heel gait, touch and pain sensation</td>
<td>Full neurological exam, history and record review when positive on any of the screening items Diagnosis: clinical judgment</td>
<td>Crude: 7.4% Adjusted: 7.0% (^{g}) - Diabetes: 39.2% - Idiopathic:51.5%</td>
</tr>
</tbody>
</table>
### Table 3. (continued)

<table>
<thead>
<tr>
<th>Study and study period</th>
<th>Population</th>
<th>Age of the study population</th>
<th>Assessment protocol</th>
<th>Definition of polyneuropathy</th>
<th>Prevalence of polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruce56 Canada 2003</td>
<td>467 nonpregnant community members of the Sandy Bay First Nation</td>
<td>All &gt;18 years &gt;50y: 18%</td>
<td>10-g Monofilament on 10 sites of the foot</td>
<td>Unable to sense monofilament on one or more sites</td>
<td>Crude: 7.3% Incidence: 7.9 per 1000/yr</td>
</tr>
<tr>
<td>Lin37 China 2009</td>
<td>5385 subjects from the She population of China</td>
<td>All &gt;20 years, mean age 47 years</td>
<td>Toronto Clinical Neuropathy Scoring System (TCSS)</td>
<td>TCSS ≥ 6</td>
<td>Crude: 12.6%</td>
</tr>
<tr>
<td>Lu38 China 2011-2012</td>
<td>2035 nonpregnant Han community members without type 1 diabetes or renal failure</td>
<td>All &gt;25 years</td>
<td>Modified Neuropathy Deficit Score (NDS) and Neuropathy Symptom Score (NSS)</td>
<td>NDS ≥ 6, or NDS ≥ 3 and NSS ≥ 5</td>
<td>Crude: 4.0%</td>
</tr>
<tr>
<td>Visser39 Netherlands 2010</td>
<td>Adult population of the province of Utrecht: 953110</td>
<td>All ≥18 years</td>
<td>New cases that are registered in databases of all hospitals in the proximity of the province of Utrecht during a period of 1 year</td>
<td>Local guidelines: combination of symptoms and deficits compatible with polyneuropathy and diagnostic work-up for etiological diagnosis</td>
<td>Only incidence: Crude: 0.7/1000/yr Adjusted: 0.5/1000/yr</td>
</tr>
</tbody>
</table>

#### Cohort studies reporting prevalence of polyneuropathy in a general population

- Average probable polyneuropathy prevalence from two regions
- Age- and sex-standardized to the 1990 Italian population
- Age- and sex-standardized to the 1990 Japanese population
- Age- and sex-standardized to the 1991 United Kingdom population
- Incidence was calculated with data from 13 general practices, covering a population of 100230 patients
- Only idiopathic or unexplained neuropathy. Alcohol abuse, HIV, hypothyroidism, diabetes and medication excluded
- Age- and sex-standardized to the 1992 Italian population
- Age- and sex-standardized to the WHO world standard population
that this female predominance is not confounded by age.\textsuperscript{20, 35} Other studies found no difference\textsuperscript{27, 38}, or a slight opposite result with a female:male ratio of about 1:1.4.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 disabiling symptom, occurring in 40-60\% of patients
<table>
<thead>
<tr>
<th>Study</th>
<th>George</th>
<th>Lin</th>
<th>Johannsen</th>
<th>Mygland</th>
<th>VergheSE</th>
<th>Rosenberg</th>
<th>Vrancken</th>
<th>Rudolph</th>
<th>Visser</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>UK</td>
<td>Taiwan</td>
<td>Denmark</td>
<td>Norway</td>
<td>USA</td>
<td>Netherlands</td>
<td>Netherlands</td>
<td>Norway</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Population</td>
<td>Patients referred for NCS</td>
<td>Patients referred for NCS</td>
<td>Patients referred to neurologist</td>
<td>Patients referred for NCS</td>
<td>Patients at outpatient department</td>
<td>Multicenter study of patients with a diagnostic work-up for PNP</td>
<td>Patients referred to neurologist</td>
<td>New hospital-registered cases</td>
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</tr>
<tr>
<td>Number of patients</td>
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<td>520</td>
<td>147</td>
<td>192</td>
<td>231</td>
<td>171</td>
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<td>137</td>
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<tr>
<td>Age</td>
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<td>-</td>
<td>18-70</td>
<td>-</td>
<td>65-75</td>
<td>≥75</td>
<td>26-93</td>
<td>≥18</td>
<td>9-92</td>
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<td>Associated risk factor (%)</td>
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<tr>
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<td>- Inflammatory</td>
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<td>- Alcohol</td>
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### Table 4. (continued)

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<th>Lin\textsuperscript{b}</th>
<th>Johannsen\textsuperscript{c}</th>
<th>Mygland\textsuperscript{d}</th>
<th>Verghese\textsuperscript{e}</th>
<th>Rosenberg\textsuperscript{f}</th>
<th>Vrancken\textsuperscript{g}</th>
<th>Rudolph\textsuperscript{h}</th>
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\textsuperscript{a} Including vitamin B1 and vitamin B12 deficiency
\textsuperscript{b} Infection includes borrelia infection, leprosy and other unspecified infections
\textsuperscript{c} 2% unspecified metabolic disorder. Thyroid dysfunction not reported
\textsuperscript{d} HIV referral center
\textsuperscript{e} Largest center is a CIAP referral center
\textsuperscript{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
\textsuperscript{g} Toxic medication and alcohol abuse are combined in this study and accounts for 14%
\textsuperscript{h} Thyroid dysfunction and renal function are combined in this study and accounts for 4%
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. 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. The relative risk of polyneuropathy in chronic alcoholics is estimated at 3.9 (95% confidence interval 1.5-9.0). 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. 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. 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. Mutations in genes encoding major structural proteins of myelin, axonal transport and mitochondrial metabolism have been described. 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
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 syndrome61 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. 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. Quantitative sensory testing may show abnormal temperature and vibration thresholds. Diagnostic criteria have been developed to improve recognition and diagnosis of CIAP.

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. Studies showed that the metabolic syndrome is an independent risk factor for macro- and microvascular complications such as retinopathy, nephropathy and neuropathy in patients with diabetes. Studies also showed that the metabolic syndrome is more prevalent in patients with CIAP. 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. 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, and prevalence of diabetes is lower, especially in Africa.

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.

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. 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%. 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%, which is much higher than the rates found in the door-to-door surveys, which are close to 1%. 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. 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. 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. 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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*Shared last author

Neurology, 2016
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

Rens Hanewinckel, Judith Drenthen, Symen Ligthart, Abbas Dehghan, Oscar H. Franco, Albert Hofman, M. Arfan Ikram, Pieter A. van Doorn

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. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), together commonly called prediabetes, might also increase the risk of polyneuropathy. With the globally increasing prevalence of both diabetes and prediabetes, incidence of polyneuropathy and its consequences is also expected to increase. 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. Results from studies that did investigate the association between prediabetes and neuropathy using a control group have been inconsistent. The uncontrolled nature, often retrospective study design, lack of appropriate adjustments and potential referral bias of most of these studies have previously been indicated.

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. Obesity, another global epidemic, is one of these factors. Hyperglycemia and obesity are central components of the metabolic syndrome (MetS). 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. 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 and several components of this syndrome have also been implicated in the development of neuropathy in patients with diabetes. A few case-control studies even suggested an association between MetS and idiopathic polyneuropathy, but more well-developed, extensive epidemiological studies are necessary to confirm this association.

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

**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 components: OR 2.64, 95% CI 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

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

Values represent number (%) or mean (SD).

* 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

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

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

Metabolic syndrome and polyneuropathy (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.
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 and in case-control studies of patients with idiopathic neuropathy. A recent population-based study,
Table 4. Association of MetS with nerve conduction parameters in males and females categorized as no polyneuropathy

<table>
<thead>
<tr>
<th>Glycemic state</th>
<th>Peroneal CMAP amplitude, mV</th>
<th>Sural SNAP amplitude, µV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.27 (-1.18;0.64)</td>
<td>0.01 (-0.80;0.82)</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>-0.33 (-1.16;0.49)</td>
<td>-0.11 (-1.02;0.79)</td>
</tr>
</tbody>
</table>

MetS

Total sample

| ≥3 criteria of MetS          | -0.84 (-1.44;-0.23)          | 0.44 (-0.06;0.94)          | -0.99 (-1.75;-0.22) | -1.24 (-2.28;-0.21) |
| ≥4 criteria of MetS          | -0.92 (-1.68;-0.16)          | 0.44 (-0.24;1.11)          | -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 | -0.78 (-1.44;-0.13)          | 0.03 (-0.55;0.61)          | -0.42 (-1.24;0.40) | -0.64 (-1.83;0.54) |
| Elevated triglycerides      | 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     | 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     | 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    | -0.48 (-1.12;0.16)           | 0.17 (-0.35;0.68)          | -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)          | 0.39 (-0.15;0.94)          | -1.13 (-1.97;-0.30) | -1.30 (-2.38;-0.23) |
| ≥4 criteria of MetS          | -1.03 (-1.90;-0.17)          | 0.48 (-0.31;1.27)          | -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) | 0.94 (-2.56;4.43)  |

| Elevated waist circumference | -0.74 (-1.46;-0.03)          | 0.03 (-0.58;0.64)          | -0.46 (-1.34;0.42) | -0.57 (-1.78;0.64) |
| Elevated triglycerides      | 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     | -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     | 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    | -0.50 (-1.20;0.19)           | 0.26 (-0.31;0.82)          | -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)

* Additionally adjusted for the other components of MetS

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{4-8}, or did not control for age, which is strongly related to both polyneuropathy and (pre)diabetes.\textsuperscript{10, 34, 35} One controlled study did show an association of impaired glucose tolerance and neuropathy\textsuperscript{9}, while the majority of controlled studies, especially the studies that took the confounding effect of age into account, found no association.\textsuperscript{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. 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.
Metabolic syndrome and polyneuropathy

REFERENCES


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

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

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
Chapter 4.2

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

Rens Hanewinckel, M. Arfan Ikram, Oscar H. Franco, Albert Hofman, Judith Drenthen, Pieter A. van Doorn

*Journal of the Peripheral Nervous System, 2017*
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

Rens Hanewinckel, Judith Drenthen, Vincentius J.A. Verlinden, Sirwan K.L. Darweesh, Jos N. van der Geest, Albert Hofman, Pieter A. van Doorn, M. Arfan Ikram

Neurology, 2017
Chapter 5.2

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


* Authors contributed equally

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 diabetes10, 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 disease1, 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.
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.\textsuperscript{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 $\geq 7.0$ mmol/L, a non-fasting glucose level $\geq 11.1$ mmol/L (if fasting samples were not available) or use of anti-diabetic therapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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;
Chapter 5.2

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

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.
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.

<table>
<thead>
<tr>
<th>Gait domains</th>
<th>Normoglycemia (serum glucose &lt;5.6 mmol/L) N = 1766</th>
<th>Normoglycemia and impaired fasting glucose (serum glucose &lt;7.0 mmol/L) N = 2675</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Global gait</td>
<td>0.05 (-0.06;0.16)</td>
<td>0.04 (-0.07;0.15)</td>
</tr>
<tr>
<td>Rhythm</td>
<td>0.05 (-0.06;0.16)</td>
<td>0.03 (-0.08;0.14)</td>
</tr>
<tr>
<td>Phases</td>
<td>0.09 (-0.01;0.20)</td>
<td>0.10 (-0.01;0.20)</td>
</tr>
<tr>
<td>Variability</td>
<td>-0.02 (-0.13;0.09)</td>
<td>-0.03 (-0.15;0.08)</td>
</tr>
<tr>
<td>Pace</td>
<td>-0.07 (-0.17;0.02)</td>
<td>-0.10 (-0.20;0.01)</td>
</tr>
<tr>
<td>Base of Support</td>
<td>0.03 (-0.08;0.14)</td>
<td>0.04 (-0.07;0.16)</td>
</tr>
<tr>
<td>Tandem*</td>
<td>-0.03 (-0.14;0.08)</td>
<td>-0.03 (-0.14;0.08)</td>
</tr>
<tr>
<td>Turning</td>
<td>0.08 (-0.04;0.20)</td>
<td>0.10 (-0.02;0.22)</td>
</tr>
</tbody>
</table>

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)
* Additionally adjusted for step length and step count in tandem walk.
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. 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. 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
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.
REFERENCES


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

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

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

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

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. 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). 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.

Several simplified methods have been developed to be able to estimate the prevalence of polyneuropathy. 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.
Screening procedures that combine symptoms with a neurological examination focused on sensory alterations seem to have the best discriminative ability for chronic axonal polyneuropathies. 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\textsuperscript{23, 24}, and from 1.9% to 30.9% when only considering an elderly population\textsuperscript{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

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

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. 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.

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. 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. 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. 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. 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. Factors that have been associated with the development or the presence of polyneuropathy in patients with diabetes mellitus
include cardiometabolic factors such as obesity, dyslipidemia and hypertension.\textsuperscript{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.\textsuperscript{41, 47} Hyperglycemia and insulin resistance also lead to dysregulation of several metabolic pathways that result in mitochondrial dysfunction, inflammation and further oxidative stress. All these processes can eventually lead to nerve ischemia and cytotoxicity.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. 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.

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. 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. Investigating the association between polyneuropathy and vascular diseases in the Rotterdam Study yielded similar results (Table 2). Participants with polyneuropathy more

<table>
<thead>
<tr>
<th>Clinical cerebrovascular disease</th>
<th>MRI defined brain infarcts</th>
<th>Coronary heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>No PNP</td>
<td>5.5 1.00</td>
<td>7.9 1.00</td>
</tr>
<tr>
<td>Possible PNP</td>
<td>10.0 1.37 (0.79;2.40)</td>
<td>11.4 1.15 (0.69;1.90)</td>
</tr>
<tr>
<td>Probable PNP</td>
<td>13.3 1.60 (0.80;3.18)</td>
<td>15.3 1.09 (0.55;2.17)</td>
</tr>
<tr>
<td>Definite PNP</td>
<td>19.5 2.75 (1.39;5.45)</td>
<td>20.3 1.92 (0.98;3.77)</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.\textsuperscript{51-63} 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.\textsuperscript{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.\textsuperscript{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
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. 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. 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. 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 polyneuropathy, 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 applying 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. Misclassification could have occurred in any of the three components of the screening (questionnaire, 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
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. 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. The sural and peroneal nerve taken together are the most sensitive for detecting a polyneuropathy, but these may not be very specific. 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. The sural and peroneal nerve taken together are the most sensitive for detecting a polyneuropathy, but these may not be very specific. 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. 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 participant 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
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. 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 polyneuropathy. 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 polyneuropathy. Retinal vessels can be visualized non-invasively, and are thought to be a representative reflection of systemic microvasculature. 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. 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 polyneuropathy in the Rotterdam Study, we found that chronic (idiopathic) axonal polyneuropathy is a common, disabling, but underdiagnosed disease, that disproportionately affects elderly. Aside from diabetes mellitus, other cardiometabolic factors, especially dyslipidemia, 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.
REFERENCES

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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
of a polyneuropathy. The six most informative symptoms – numb feet, tingling feet, allostynia 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 polyneuropathy. 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 polyneuropathy, 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 problem, 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, participants 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-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.
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 hiat 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 evalueren 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
Samenvatting

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 klachten 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 werden 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 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.
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 men 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 droeg 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.
Chapter 8

Dankwoord

PhD portfolio

List of publications

About the author
DANKWOORD

Inmiddels zijn er ruim vier jaar verstreken sinds ik begon aan mijn promotie onderzoek. Deze tijd is voorbij gevlogen en heeft geresulteerd in het proefschrift dat nu voor u ligt. Via dit dankwoord wil ik graag iedereen bedanken die mij heeft gesteund, geholpen, begeleid of anderszins heeft bijgedragen aan de totstandkoming van dit proefschrift. Een aantal mensen wil ik in het bijzonder noemen.

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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

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**LIST OF PUBLICATIONS**


*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).