

An epidemiologic study of diabetes-related foot ulcers

*Issues related to prevention and mortality
based on the Nord-Trøndelag Health Study (HUNT 2)*

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Paper II: Regularity of preventive foot care in persons with diabetes: results from the Nord-Trøndelag Health Survey

Erratum: Paper II

Paper III: The association between history of diabetic foot ulcer, perceived health and psychological distress: the Nord-Trøndelag Health Study

Paper IV: A history of foot ulcer increases mortality among persons with diabetes. 10 year follow-up of the Nord-Trøndelag Health Study, Norway

Appendix 1. Questionnaire 1 (Q1) used in the Nord-Trøndelag Health Study 2 (1995–1997)

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Scientific environment

This study was carried out at the Department of Public Health and Primary Health Care, Section of Nursing Science, University of Bergen during the period 2005-2009, with Professor Berit Rokne from the Section of Nursing Science as principal advisor and Professor Grethe S. Tell, Head of the Research Group on Lifestyle Epidemiology, Department of Public Health and Primary Health Care, University of Bergen as co-advisor. The research group also included co-advisor Professor Kristian Midthjell, Head of the diabetes substudy of the Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag) HUNT 2 at the HUNT Research Centre in Verdal, Nord-Trøndelag and co-advisor Professor Monica W. Nortvedt, Head of Center of Evidence Based Practice and Vice Dean at the Faculty of Health and Social Sciences at Bergen University College. Marjolein M. Iversen is employed as Assistant Professor at the Department of Nursing at Bergen University College and a PhD fellow at the University of Bergen.

Further, there was scientific collaboration during parts of the study with Associate Professor Marit Graue, Head of the Diabetes Research Group for Best Practice, Department of Nursing at Bergen University College; MD Sverre Uhlving, Head of the Department of Internal Medicine, at Stavanger University Hospital; Professor Torbjørn Moum of the Department of Behavioural Sciences in Medicine at the University of Oslo; and Professor Trond Riise, member of the Research Group for Lifestyle Epidemiology of the Department of Public Health and Primary Health Care at the University of Bergen. These scientists are co-authors of different parts of the study.

The study included a 10 month working period at Duke University in Durham, North Carolina in 2006-2007 at the invitation of Professor Truls Østbye, Vice-Chair of Research at the Department of Community and Family Medicine and the late Professor Elisabeth Clipp, Associate Dean for Research Affairs at the School of Nursing. During this period there was collaboration with statistician Rick Sloan from the Center for the Study of Aging and Human development, while collaboration with Truls Østbye has been an ongoing process throughout this scientific work. These scientists are also co-authors of various papers in the study.

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Summary

The prevalence of type 2 diabetes is increasing dramatically and type 1 diabetes moderately both in Norway and globally. As a result, long-term diabetes-related complications are also likely to increase. One long-term complication of diabetes is diabetes-related foot ulcers, which represent challenges for the individual and for the health care system. Awareness is growing that more attention should be given to this condition.

Aim: The main aim of this study was to obtain more knowledge about people with diabetes reporting a history of foot ulcer (HFU) in a large, unselected population sample in Norway. We wanted 1) to determine the proportion of self-reported foot ulcers that required more than 3 weeks to heal and investigate associated factors, 2) to examine preventive foot care practices for people with diabetes and identify factors associated with such ulcers, 3) to compare levels of anxiety and depression as well as psychological well-being and perceived health between people with diabetes with and without a history of foot ulcer and those who reported not having diabetes and 4) to estimate the mortality risk for people who reported a HFU, people with diabetes without a HFU and people without diabetes.

Methods: The study used a cross-sectional design in Papers I–III and a prospective design in Paper IV. During 1995 to 1997, the second health survey was conducted in Nord-Trøndelag County, Norway, the Nord-Trøndelag Health Study 2 (HUNT 2). Those who responded positively to the question, “Do you have or have you had diabetes?” were classified as having known diabetes ($n = 1972$) and were invited to participate in the diabetes substudy. Those responding affirmatively to the question “Have you had a foot ulcer that required more than 3 weeks to heal?” were classified as having a HFU ($n = 155$) and those responding negatively as having diabetes without a HFU ($n = 1339$). Some 63,632 participants reported not having diabetes. Measures of sociodemographic, lifestyle and clinical factors were available as well as perceived health and several aspects of psychological distress such as symptoms of anxiety, depression and psychological well-being. Participants with self-reported diabetes were well characterized with regard to their diabetes condition. All participants in HUNT 2 were followed for 10 years, with mortality as the end-point.

Results: The overall proportion of people with diabetes reporting a HFU was 10.4% [95% confidence interval (CI) 8.8%–11.9%]. Significant correlates of a HFU were male gender [1.5 (1.03–2.2)], age older than 75 years [odds ratio (OR) 1.8, 95% CI (1.2–2.8)], taller than the median (men >175 cm, women >161cm) [1.9 (1.3–2.8)], using insulin [1.6 (1.1–2.4)], and the presence of macrovascular complications [1.8 (1.2–2.6)] (Paper I).

Some 58.8% of people with diabetes without a HFU reported regular preventive foot care (Paper II). Almost 85% reported receiving regular clinical diabetes examinations, 31.7% reported regular foot inspection by health care personnel and 66.3% reported foot self-inspection. In addition, participants' reports of inspections by health care provider and their own inspections were strongly correlated ($P < 0.001$). Independent variables associated with reporting preventive foot care included female gender, long duration of diabetes (>10 years), insulin use and membership in the Norwegian Diabetes Association. Those who reported macrovascular complications were less likely to report regular preventive diabetes foot care.

In Paper III, we reported that anxiety and depression symptoms did not differ between those with diabetes reporting a HFU and those with diabetes without a HFU or those without diabetes. Among those with diabetes, perceived health was significantly worse among those reporting a HFU while psychological well-being did not differ. Perceived health and psychological well-being were significantly poorer among those with a HFU than among those without diabetes.

Participants who reported a HFU had an increased mortality rate compared with both the subjects who did not report diabetes (hazard ratio 2.29, 95% CI 1.82–2.88) and those who did report diabetes but not a HFU (hazard ratio 1.41, 95% CI 1.09–1.82). The excess risk persisted after adjusting for comorbidity and depression scores (Paper IV).

Conclusions: Overall, among community-dwelling people with known diabetes, 1 out of 10 reported a HFU. Characteristics associated with a HFU were male gender, age older than 75 years, taller than the median for each sex, insulin use and the presence of macrovascular complications. The clinical picture among people with diabetes reporting a HFU was complex, with several complications appearing at the same time. A HFU was associated with poorer perceived health. However, among people with diabetes a HFU was not associated with more anxiety or depression symptoms or poorer psychological well-being.

Reported regular preventive foot care practices were associated with female gender, insulin use and having had diabetes for more than 10 years. Those reporting macrovascular complications were less likely to report regular preventive diabetes foot care.

The findings in this study reinforce previous evidence of a link between diabetic foot ulceration and increased risk of death and extend knowledge concerning excess mortality beyond what was previously known about people with foot ulcers attending specialist health care clinics. The excess mortality risk of approximately 40% was only partly explained by older age, sex (male), a higher percentage of glycosylated hemoglobin (HbA_{1c}), current smoking, insulin use, microalbuminuria, cardiovascular disease and depression.

Our findings indicate the importance of identifying and monitoring people with foot ulcers at an early stage. The findings suggest that systematically implementing evidence-based guidelines in diabetes care and foot care may be very important for those with a HFU, who are particularly susceptible to adverse outcomes.

List of papers

The dissertation is based on the following four papers.

- I. Iversen MM, Midthjell K, Østbye T, Tell GS, Clipp E, Sloane R, Nortvedt MW, Uhlving S, Hanestad BR. History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trøndelag Health Study. *Scand J Publ Health*, 36:62–68, 2008.
- II. Iversen MM, Østbye T, Clipp E, Midthjell K, Uhlving S, Graue M, Hanestad BR. Regularity of preventive foot care in persons with diabetes: results from the Nord-Trøndelag Health Survey. *Res Nurs Health*, 31:226–237, 2008.
- III. Iversen MM, Midthjell K, Tell GS, Moum T, Østbye T, Nortvedt MW, Uhlving S, Hanestad BR. The association between history of diabetic foot ulcer, perceived health and psychological distress: the Nord-Trøndelag Health Study. *BMC Endocr Disord*, 9:18, 2009.
- IV. Iversen MM, Tell GS, Riise T, Hanestad BR, Østbye T, Graue M, Midthjell K. A history of foot ulcer increases mortality among persons with diabetes. 10 year follow-up of the Nord-Trøndelag Health Study, Norway. *Diabetes Care*, 32:2193–2199, 2009.

Abbreviations

BMI	Body mass index
CI	Confidence interval
GAD	Glutamic acid decarboxylase
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale, anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale, depression subscale
HbA1c	Glycosylated hemoglobin
HFU	History of foot ulcer
HUNT	Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)
ICD-10	International Classification of Diseases, 10th revision
OR	Odds ratio

1. Introduction and literature review

The prevalence of type 2 diabetes is increasing dramatically and type 1 diabetes moderately in both Norway and globally [1, 2]. The prevalence for all age groups worldwide was projected to rise from 2.8% in 2000 to 4.4% in 2030. The total number of people who have diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The most important contributor to the rise in diabetes prevalence globally appears to be the increase in the proportion of old people. However, given the increasing prevalence of obesity, these figures probably underestimate the future diabetes prevalence [1]. In Norway, about 90,000 to 120,000 people have been diagnosed with diabetes, and for each person diagnosed with diabetes an undiagnosed person is expected to have diabetes [3]. Norway has a high prevalence of type 1 diabetes [4, 5]. The prevalence of type 2 diabetes has also been increasing [6], and the latest data indicate that this increase will continue, particularly among men [7].

Diabetes is a chronic illness requiring continual health care and patient self-management education to prevent the development of acute complications and reduce the risk of long-term complications [8]. As the prevalence of diabetes increases, the prevalence of long-term diabetes-related complications is also likely to increase [9]. The ‘diabetic foot’ has been considered the “Cinderella” complication of diabetes care, and the International Diabetes Federation dedicated the year 2005 to foot care of people with diabetes in order to raise awareness of foot disease among people with diabetes. No large epidemiological studies on diabetes-related foot ulcers have been conducted in Norway.

Diabetes-related foot ulcers represent challenges for the individual and for the health care system, as they increase the demand for specialized health care. Even though preventive strategies have been shown to be cost-effective [10], meeting this demand in the health care system remains an enormous challenge from the financial and workforce perspectives [11, 12]. The rapid increase of people with diabetes requires having a solid epidemiological knowledge base and developing high-quality health care services and effective preventive strategies. Thus, the overall aim of this study was to gain more knowledge about people with diabetes who reported a history of foot ulcer (HFU) in a large, unselected population in Norway. Knowledge obtained from this study concerning preventing foot ulcers and the

mortality associated with a HFU may contribute to the future development of health care strategies that enhance the quality of care for people with diabetes.

1.1 Diabetes and foot ulcers

People with diabetes are more likely to develop foot ulcers than people without diabetes [13]. Moreover, a HFU or current ulceration is the most important risk factor for new ulceration [14]. People with diabetes fear foot ulceration, which represents a challenge for the health care system [15, 16]. Awareness is growing that more attention should be given to this condition [17].

The International Consensus on the Diabetic Foot defined a diabetic foot ulcer as a full-thickness wound below the ankle in a person with diabetes, irrespective of duration [18]. Several risk classification schemes have been developed to facilitate communication between health care providers and to help guide diabetic foot assessment and management decisions [19, 20]. The most commonly used classification system internationally is Wagner's, which consists of five stages [21]. The University of Texas expanded this classification system with an additional four stages [22]; in the SAD (size (area and depth)) system, neuropathy has been added [19]. Finally, the International Working Group on the Diabetic Foot has developed a classification system (PEDIS) that has recently been restructured [23].

Neuropathy and ischemia most often lead to the development of the foot at risk, although ulcers may frequently occur as a consequence of an interaction between specific pathologies in the lower limb and environmental factors [19, 24-26]. Diabetic foot ulcers may be divided into two groups: neuropathic ulcers and neuroischemic ulcers, the crucial difference between them being the absence or presence of ischemia. The purely ischemic foot is rare. Peripheral neuropathy is the most important causal pathway leading to foot ulceration and often leads to sensory deficit with the loss of protective pain sensation. Ischemia, on the other hand, results from atherosclerotic peripheral vascular disease, which usually affects the distal vessels of the lower limb [19]. Infection can complicate any type of diabetic foot ulcer and is one of the most common causes of hospital admission among people with diabetes.

Foot ulceration presents a troubling picture [27]. One in every seven individuals with diabetes has a foot ulcer during their lifetime [12, 28], and it has recently been suggested that the lifetime risk of a person with diabetes developing a foot ulcer could be as high as 25% [25]. Foot ulcers precede about 85% of all diabetic lower-extremity amputations [29]. It is argued that the use of the term “diabetic foot ulcer” may be misleading, as diabetic foot ulceration is very heterogeneous, whereby several pathophysiological mechanisms may be involved [30].

Reported annual incidence rates (new onset) varied between 1.2% and 3.0% [12, 14, 31]. Among studies with community-based samples, a large study in the United Kingdom reported a 2.2% (291 of 6613) annual incidence of foot ulcers after two years for survivors [14]. In a study in the Netherlands, [31] the annual incidence of foot ulceration varied from 1.2% to 3.0% (mean 2.1%, 95% confidence interval (CI) 1.52–2.28) during the 3-year study period. Incidence rates in two clinically based studies in the United States were 1.9% and 2.2%, respectively [12, 32].

During the past two decades, various studies have reported estimates of the prevalence of having a HFU. A cross-sectional community survey among people with type 1 and type 2 diabetes reported that 7.4% (95% CI 5.8–9.0%) had past or present foot ulceration [13]. Another study from three districts in the United Kingdom reported that 5.3% of those with type 2 diabetes had past or present foot ulcers [33]. Further, in a primary care-based survey of patients with clinical diabetes, 12% reported previous foot ulceration in Trinidad and Tobago [34], while data analyzed from the 2000–2002 Behavioral Risk Factor Surveillance System showed that 11.8% of United States adults with diabetes reported foot ulcers that did not heal for more than 4 weeks [35]. Only 2.1% of people with type 2 diabetes reported a HFU in a cross-sectional study in Australia.

In conclusion, although international evidence on the epidemiology of diabetic foot ulcers is growing, little is known about the extent of this diabetes-related complication in Norway.

1.2 Risk factors associated with foot ulcers

Prospective studies have found that neuropathy, deformity and previous HFU are important risk factors for foot ulceration [14, 36, 37]. Many studies have investigated other potential

risk factors such as old age, male gender, low education, duration of diabetes, poor glycemic control, renal disease or microalbuminuria, poor vision, poor footwear, cigarette smoking, social deprivation and isolation, but the results are inconclusive [13, 32, 33, 37-42]. Height and waist circumference have been associated with neuropathy, but the direct impact of height and waist circumference on foot ulceration has been more uncertain [41, 43, 44]. Studies have used various methods and study populations as well as different potential risk factors and have arrived at different conclusions in predicting complications. In addition, the risk of diabetic foot ulceration in community settings has been less thoroughly explored than in cohorts from hospital diabetes clinics and dedicated foot clinics [45].

Further, ethnicity has been reported to affect the prevalence of foot ulcer. Abbott et al. [46] found that foot ulceration is more common among Caucasians than among Asians of Indian subcontinent origin, while Lavery et al. [47] have shown that ulceration is more common among Hispanic-Americans and in Native Americans than in non-Hispanic whites.

It was thus of interest to examine the factors associated with a HFU in relation to demographic characteristics, lifestyle factors, diabetes-specific variables and comorbidity in a large unselected population-based study in Norway.

1.3 Anxiety, depression, psychological well-being and perceived health

An overall aim of diabetes care in Norway is that people should be able to live a good life despite having diabetes. In recent years, interest has increased in subjective patient-reported outcomes as a supplement to objective measures in research. Several somatic diseases, such as diabetes, commonly coexist with anxiety and depression [48], and these mental disorders are often comorbid. This picture becomes even more complex, as evidence suggests a bidirectional association between depression and diabetes [49-51]. The comorbidity of major depression and anxiety disorders is often associated with barriers to seeking treatment and a greater chance of the recurrence of mental disorders [48, 52]. Among people with diabetes, anxiety, depression and low subjective well-being are suggested to be of concern because these conditions may negatively affect self-management, glycemic control and diabetes-related complications [52-54]. However, whether a HFU is associated with more anxiety and

depression symptoms or with poorer psychological well-being is unclear. As perceived health is thought to reflect the severity of the underlying disease burden [55], reports of perceived health among people with a HFU may contribute to greater knowledge about associations between HFU and perceived health in everyday life.

1.3.1 Anxiety

Earlier studies that have investigated anxiety among people with diabetes have used various instruments and/or methods. In clinical research, anxiety disorders are normally assessed using structured or semistructured diagnostic interviews and are diagnosed according to the criteria specified in the International Classification of Diseases (ICD-10) [56], or the *Diagnostic and statistical manual of mental disorders* of the American Psychiatric Association (DSM-IV) [57], which are standard classifications of mental disorders. Studies using diagnostic interviews include only clinical cases that meet the required criteria. However, this method is not suitable for use at the population level. In health surveys and/or screening, the Hospital Anxiety and Depression Scale (HADS) has been recognized as a valid instrument for measuring anxiety and depression symptoms. Studies using this questionnaire also include subclinical cases that do not meet all required DSM-IV criteria (possible cases measured by HADS ≥ 8 and probable cases by HADS ≥ 11) [58-60].

A systematic review estimated the prevalence of generalized anxiety disorders among people with diabetes to be 14% and that up to 40% had elevated symptoms of anxiety [61]. This review included all available studies before 2001. All studies, except one, were hospital based. A recent study with a large sample of people with diabetes recruited from both hospital and primary care settings in Ireland reported a prevalence of anxiety symptoms of 32% (measured by HADS ≥ 8) [60].

The literature on anxiety among people with diabetes-related foot ulcers is limited. Ragnarson Tennvall & Apelqvist [62] reported that people with primary healed ulcers had less anxiety than those with current ulcers. Carrington et al. [63] did not find differences in anxiety symptoms between people with a diabetic foot ulcer, amputation and diabetic controls ($n = 52$) (HADS ≥ 8). However, complications of diabetes such as cardiovascular disease and retinopathy have been shown to be the most important predictors for more anxiety symptoms among people with diabetes [60, 64]. A meta-analysis showed an

association between hyperglycemia and anxiety (using diagnostic interview) in type 1 and type 2 diabetes [65].

Although studies from hospital-based settings may indicate an association between anxiety and diabetes-related complications, little was known about the prevalence of anxiety symptoms among people with diabetes and a HFU in community-based samples.

1.3.2 Depression

Depression is more prevalent among people with diabetes than among people without diabetes [66]. Depression is associated with outcomes such as poor glycemic control [67] and long-term complications [64, 68]. In the HUNT 2 population, Engum et al. [69] found that comorbid chronic diseases among people with diabetes were associated with depression in type 2 diabetes. This is in accordance with the results of Pouwer et al. [70], in which one of every five people with diabetes and comorbid disease had depression.

Some evidence indicates that diabetes related foot ulceration is associated with depression. A prospective study that recruited patients from foot clinics showed that one third of those who had a diabetic foot ulcer for the first time had clinical depression [71]. In addition, Carrington et al. showed that people with chronic foot ulceration reported significantly more symptoms of depression than controls with diabetes who had never had foot ulcers (measured using HADS) [63]. Depressive symptoms are reported to be associated with impaired healing and the recurrence of ulcers among older people with type 2 diabetes [72].

The associations between foot ulceration and depression may be bidirectional: either that difficulty associated with foot ulceration might result in elevated feelings of depression or that depression might result in reduced foot-self care and the development of a foot ulcer. However, among people with their first foot ulcer, Ismail et al. [71] found no difference between diabetes self-care scores among people who were depressed and not depressed. Lin et al. [73] also found no association between depression and poorer preventive foot self-care.

Although evidence suggests an association between a current diabetic foot ulcer and a higher risk of depression, whether depression is a problem among those who have had a foot ulcer is less clear.

1.3.3 Psychological well-being

Psychological well-being refers to individuals' subjective evaluation of their lives. The construct usually embraces a cognitive component of life satisfaction and two affective components: the presence of positive affect and the absence of negative affect [74, 75]. Little is known about psychological well-being and a HFU. However, in quality of life measurements, psychological well-being is often addressed as one domain reflecting mental health, as in the SF-36 Health Survey [76, 77], a commonly used questionnaire for measuring the quality of life. In diabetes care, International Diabetes Federation clinical guidelines recommend assessing well-being and the psychological status of people with type 2 diabetes by questioning or by using validated measures as part of ongoing care [78].

Literature reviews have reported that foot ulcers affect self-reported quality of life [79, 80]. Qualitative studies show that foot ulceration adversely affects all domains of the quality of life [15]. In quantitative studies, associations between a foot ulcer and mental health are less evident than those between a foot ulcer and physical health. Several studies have associated foot ulceration with reduced scores related to physical health but not mental health [81-83]. Only one recent study in Norway has shown that people with a current diabetic foot ulcer had poorer quality of life than controls with diabetes and the general population sample. In the above study, both mental health scores and physical health scores were reduced, with physical health scores showing the greatest reduction [84]. One prospective study evaluated how a chronic foot ulcer affected the physical and mental functioning of patients and their caregivers at three points in time (baseline and after 20 and 32 weeks) [85]. People with healed ulcers scored better physical and social functioning than those with persisting ulcers. Although the study showed no change in mental functioning among people whose ulcers had healed, the mental health functioning of the caregivers improved significantly. However, mental health scores at baseline were not compared with those of other people without a foot ulcer. Further research in a larger sample was needed to explore psychological well-being among persons with a HFU.

1.3.4 Perceived health

Perceived health reflects an individual's subjective perception of health conditions [86, 87]. Many studies have found that perceived health better predicts morbidity than many objective

measures of health [55, 88-90]. In quality of life research, the SF-36 Health Survey uses perceived health as one of five areas forming the general health domain. Results from the World Health Surveys demonstrated that chronic illness such as diabetes affects perceived health and that people with diabetes generally rate their health as being poorer than people without diabetes [91]. Among people with diabetes, those with current foot ulcers reported poorer perceived health than those with healed ulcers [62], although limited research has been conducted among those who have had foot ulcers.

In conclusion, the literature on the association between a HFU and psychological distress, and between a HFU and perceived health is limited. Comparing the results is difficult, as the above studies used different methods and/or questionnaires, making it unclear whether a HFU is associated with psychological distress. Quality of life research, however, more clearly demonstrates how a HFU affects physical health. The associations between a HFU and anxiety and depression symptoms, psychological well-being and perceived health therefore needed to be investigated in a large population-based study to obtain valuable knowledge concerning psychological distress and perceived health among people with diabetes and a HFU.

1.4 A history of foot ulcer and risk of mortality

Diabetes is the fifth leading cause of death globally [92]. Among those with diabetes most deaths are due to macrovascular and cerebrovascular disease, including ischemia and stroke [93]. Although all main complications of diabetes independently predict excess mortality among people with type 2 diabetes [94], relatively few prospective studies have followed people with diabetic foot ulcers with mortality as the end-point. Samples in these previous studies were drawn from hospitals, foot clinics or outpatient settings, even though a substantial proportion of people with foot ulcers are treated in primary care [12, 95-99]. Most of the studies followed the sample for a short term (1–5 years). Faglia et al. [95] assessed the overall survival of 115 subjects with diabetes hospitalized for foot ulceration at a foot care center from 1990 to 1993 and followed up for 6.5 years. However, these studies in specialized care showed mortality rates of about 50% at 5 years.

Mortality in people with a foot ulcer has often been explained by the presence of comorbid conditions such as cardiocerebrovascular disease and nephropathy [29], because peripheral

arterial disease and microvascular sclerosis associated with diabetic foot ulceration reflect established arterial disease elsewhere in the body [98]. In the study of Ghanasassi et al. [98], only renal impairment was an independent predictor of mortality. Among people with established foot ulcers, increased mortality appears to be independent of factors increasing ulcer risk such as neuropathy and peripheral vascular disease [97]. Mental factors have provided prospective evidence, as Ismail et al. [71] found that depression was associated with mortality among people with their first diabetic foot ulcer. One third of people with their first diabetic foot ulcer had clinically significant depression, and this was associated with a threefold increased risk of death until 18 months later. Young et al. [100] demonstrated that introducing aggressive management of cardiovascular risk may explain improvements in survival rates. People who developed a foot ulcer between 1995 and 1999, and those who were diagnosed between 2001 and 2004 took part in the study of Young et al. Overall 5-year mortality declined from 48.0% in cohort 1 to 26.8% in cohort 2.

A large population-based study among community-dwelling adults and older people was needed to examine the impact of a HFU on mortality. The advantage of HUNT 2 is that participants are well characterized regarding several variables, including cardiovascular disease, microalbuminuria and mental factors including depression. Information on mortality is registered at the Norwegian Cause of Death Registry and would allow for a follow-up study over 10 years.

1.5 Preventive foot care

Norwegian and international guidelines recommend an annual comprehensive foot examination and the provision of foot self-care education to everyone with diabetes and that people with high-risk foot conditions be examined more regularly [18, 101-103]. Recommendations are well established, and several reviews have indicated the importance of preventive strategies [17, 25, 42, 45, 104]. In clinical practice, patients and health care personnel should discuss problems that arise over time to provide adequate monitoring and to emphasize aspects of self-care. Many people cannot perform preventive foot care practices due to poor vision and reduced mobility. Regular contact between patients and providers is therefore important [42].

Despite clinical guidelines and a greater focus on foot complications in diabetes in recent years, studies have shown a gap between recommendations and practices [105-110]. Among people with and without previous lower-extremity complications, 27.2–51.0% had their feet examined by a health professional during the previous year.

A Cochrane review summarized that patient education seemed to be positively influence foot care knowledge and the behaviour of patients in the short term [111, 112]. Gulliford & Mahabir [34] found that adequate foot care knowledge and health behaviour seemed important for seeking health care support. Evidence about the effect of educational interventions in preventing diabetes-related foot ulceration is inconclusive [112-115] and available studies often have poor methodological quality [111].

In Norway, no large epidemiological study had examined preventive foot care practices and the characteristics of those receiving preventive care. Given the challenges associated with diabetes and foot ulcers for the individual and for society as a whole, establishing more data about preventive foot care was important for developing future health care strategies.

2. Aims and objectives of the present study

The overall aim of this study was to obtain more knowledge about people with diabetes who reported a HFU in a large, unselected population in Norway. The study addresses epidemiological issues related to prevention and mortality by examining correlates associated with a HFU, exploring preventive foot care practices, assessing psychological distress and estimating the mortality rate ratios of a HFU.

The more specific aims were as follows.

Paper I:

- To determine the proportion of self-reported foot ulcers that required more than 3 weeks to heal in a population-based sample of people with diabetes and to investigate factors associated with such ulcers.

Paper II:

- To examine preventive foot care practices among people with diabetes in the Nord-Trøndelag Health Study and to identify associated demographic, lifestyle and disease-related factors.

Paper III:

- To compare levels of anxiety and depression symptoms, as well as psychological well-being and perceived health between 1) people with diabetes who reported a HFU, 2) people with diabetes without a HFU, and 3) people without diabetes.
- If differences were found, to examine whether these could be explained by demographic characteristics, lifestyle factors and cardiovascular disease status in addition to diabetes-specific variables.

Paper IV:

- To estimate the mortality risk for those reporting a HFU compared to those without a HFU and the non-diabetic population, after adjustment for other known risk factors for mortality.

3. Material and methods

3.1 Nord-Trøndelag County

Nord-Trøndelag County is one of Norway's 19 counties and is located in central Norway. In 1995, Norway's population was about 4.48 million and Nord-Trøndelag's population was about 127,500. The size of this rural county is 22,463 km² [116]. This area is ethnically homogeneous, with only 3% Sami or other people of non-Caucasian origin, and with migration of 0.3% per year (1996–2000). The average income and the prevalence of higher education and of current smokers are slightly lower than the national average. The county has two hospitals and 24 municipalities but lacks a large urban area. In 1995, the biggest town was Steinkjer, with a population of about 21,000 people. However, Nord-Trøndelag County is fairly representative of Norway as a whole in relation to age distribution, morbidity, mortality, economy, sources of income and the stability of its population, making it suitable for epidemiological purposes.

3.2 The second Nord-Trøndelag Health Study (HUNT 2)

The second Nord-Trøndelag Health Study (HUNT 2) was performed from 1995 to 1997. A personal invitation was sent to all inhabitants 20 years or older ($n=92,434$) [116] inviting them to participate in the study. The invitation included a questionnaire (Q1, Appendix I) and a suggested time and place for a clinical examination. A five-member screening team and a bus with office and laboratory facilities visited the 19 smallest communities, while a stationary team stayed for several months in each of the five largest towns. Specially trained nurses and technicians carried out this fieldwork, which lasted 2 years. At the medical examination performed at the screening stations, a second questionnaire (Q2) and third questionnaire (Q3) were handed out (Appendixes 2 and 3). Four versions of Q2 were used depending on age and sex, and Q3 had three different versions delivered to those with self-reported diabetes, asthma or lung diseases or hypertension in Q1. Those answering yes to diabetes in Q1 were included in the diabetes substudy. Table 1 presents an overview over key elements of HUNT 2 used in the papers in this dissertation.

Table 1. Key elements used in the different papers

Paper	Questionnaires			Attendance at a clinical examination	Follow-up appointment for those answering yes to diabetes in Q1 at attendance. Reinvited to fasting blood sampling	Urine sampling in those with yes to diabetes in Q1 and in a random sample. Equipment delivered at attendance, returned by mail	10-year follow-up
	Q1	Q2	Q3-diabetes				
I	Mailed invitation, Q1 and time for clinical examination. Q1 returned at attendance	Handed out at attendance Returned by mail	Q3-diabetes Handed out at attendance Returned by mail	Waist (cm) Height (cm) Weight (kg) BMI (kg/m ²)	Fasting blood sample (glucose, C-peptide and GAD antibodies), whole-blood sample (HbA _{1c})	Three morning urine samples (albumin and creatinine used to calculate albumin-creatinine ratio and microalbuminuria)	
II	Self-reported diabetes, age, sex, marital status, education, smoking, physical activity, history of myocardial infarction, angina pectoris, stroke.		HFU, amputation, eye problems due to diabetes, peripheral vascular surgery Diabetes duration, insulin use, ever used antihypertensive medication Preventive foot care questions, HFU, amputation, eye problems, peripheral vascular surgery, diabetes duration, insulin use, membership Norwegian Diabetes Association, attending a course, health care setting	Waist (cm)	Whole-blood sample (HbA _{1c})	Three morning urine samples (microalbuminuria)	
III	Perceived health, psychological well-being (1 item), anxiety and depression (HADS). Self-reported diabetes, age, sex, marital status, smoking, history of myocardial infarction, angina pectoris, stroke	Psychological well-being (3 items)	HFU, amputation, eye problems due to diabetes, peripheral vascular surgery Diabetes duration, insulin use	Waist (cm) BMI (kg/m ²)	Whole-blood sample (HbA _{1c})	Three morning urine samples (microalbuminuria)	
IV	Self-reported diabetes, age, sex, smoking, history of myocardial infarction, angina pectoris, stroke		HFU of foot ulcer, amputation, diabetes duration, insulin use	Waist (cm)	Fasting blood sample (glucose, C-peptide and GAD antibodies), whole-blood sample (HbA _{1c})	Three urine samples (microalbuminuria)	Information on mortality from the Norwegian Cause of Death Registry

The questionnaires: Q1 included questions stating present or previous diabetes, myocardial infarction, angina pectoris, stroke and smoking. In addition, the status of physical activity, education, perceived health, life satisfaction, anxiety and depression (HADS) was solicited. The national personal identification number applied includes the date of birth (used to calculate age at attendance) and sex. Q2 incorporated, among others, questions related to psychological well-being. Q3-diabetes consisted of two pages concerning diagnosis, treatment, disease duration, HFU and amputation, preventive foot strategies and membership in the Norwegian Diabetes Association. The participants were asked to complete Q2 and Q3 and return them by mail using a pre-stamped addressed envelope. As a result of this procedure, data are missing more frequently for Q2 and Q3 than for Q1.

The brief clinical examination included measurements of height, weight and waist circumference. Height was measured without shoes to the nearest centimeter, and weight was measured to the nearest 0.5 kilogram while wearing light clothing without shoes. Waist circumference was measured at the umbilical level in centimeters. Reported blood pressure readings are the mean of the second and third of three systolic and diastolic readings using a Dinamap 845 XT (Critikon) blood pressure device based on oscillometry. Blood sampling was carried out whenever subjects attended (in the non-fasting state). This non-fasting serum sample was analyzed for glucose for all participants in HUNT 2. For those who reported diabetes (Q1), an extra tube of whole blood was drawn to analyze HbA_{1c}. Those confirming diabetes were also reinvited to another blood sampling in the fasting state a few days later for classification of diabetes.

Participants reporting diabetes were included in screening for microalbuminuria. When they attended the clinical examination, they received a unit with three tubes for three repeated first-morning urine samples and one pre-stamped envelope to return the samples by mail to the laboratory. Written instructions were enclosed in the unit. The urine samples were analyzed for albumin and creatinine [116]. According to recommendations for people with diabetes, microalbuminuria was defined as an albumin-creatinine ratio >2.5 mg/mmol [117, 118]. To minimize day-to day variation, microalbuminuria had to be present in at least two of three urine samples.

About 3 weeks after the examination, every participant received a personal letter from the HUNT Research Centre containing the results of the measurements and, if necessary, advice on lifestyle and necessary follow-up. Participants with abnormal clinical or biochemical values were advised to visit their general practitioner.

A follow-up appointment was given to participants reporting known diabetes. A fasting blood sample was drawn and was mailed to the Laboratory of Clinical Chemistry at Levanger Hospital, located in the County. Samples were analyzed for glucose, C-peptide and GAD antibodies (74.8% participation) to differentiate between type 1 and type 2 diabetes [116]. Diabetes was categorized as type 1 diabetes (insulin treatment started within 6 months after diabetes diagnosis and either as: anti-GAD ≥ 0.08 units or anti-GAD < 0.08 and/or C-peptide < 150 pmol/l), or type 2 diabetes (treated with diet only or oral antidiabetic medication or commencement of insulin treatment 12 months or more after the diabetes diagnosis and anti-GAD < 0.08 units). At the new appointment, seven participants reported having had gestational diabetes during a previous pregnancy and did not have diabetes. They were excluded. As recommended by the World Health Organization [119], people with latent autoimmune diabetes of adults (LADA) were combined with those classified as having type 1 diabetes.

3.3 Study samples

This study includes different study samples defined by different questions. Fig. 1 shows the study design of HUNT 2 and how the sample was derived for Papers I–IV (boxes with a thick line). Papers I, II and III were descriptive, cross-sectional studies; Paper IV was a prospective study. Table 2 shows the study samples used in Papers I–IV. Complementary information regarding the proportion of HFU, preventive foot care questions, anxiety and depression (HADS), psychological well-being, perceived health and the follow-up study is given below.

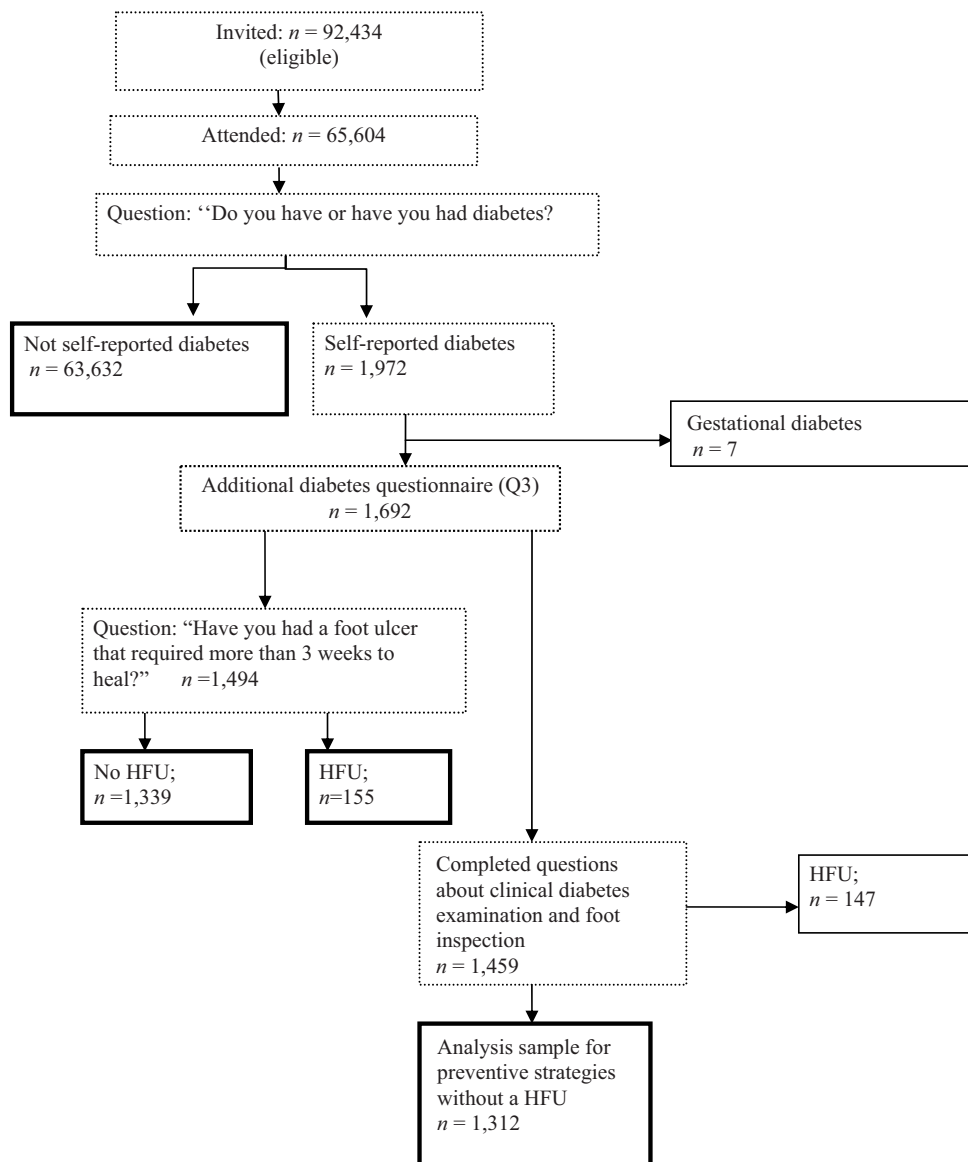


Fig. 1 Sample derivation

The participation rate was 71%. Participants were defined as those who returned Q1 or attended the brief clinical examination.

Table 2. Study samples used in Papers I–IV

	Paper I	Paper II	Paper III	Paper IV
$n = 63,632$			X	X
$n = 1,339$	X		X	X
$n = 155$	X		X	X
$n = 1,312$		X		

3.3.1 Proportion with a history of foot ulcer

A total of 1972 participants answered the question “Do you have or have you had diabetes?”. Those answering affirmatively were invited to take part in the diabetes substudy. The definition of a HFU was based on the question: “Have you had a foot ulcer that required more than 3 weeks to heal?” (Q3). Those answering yes were included in the sample ($n = 155$) and those responding no as having diabetes without a HFU ($n = 1339$). Persons answering affirmatively but reporting that they had had a foot ulcer for less than 3 weeks were excluded from the foot ulcer sample and coded as not having had a foot ulcer for more than 3 weeks ($n = 7$).

3.3.2 Preventive foot care questions

Preventive foot care practices were examined among people with diabetes but without a HFU. This was done to avoid combining examinations for prevention of foot complications with follow-up examinations of the sample.

Two central elements of the prevention of foot complications were combined, as they are essential for quality care [120]. These were defined as including both:

- (a) regular clinical diabetes examination involving physical examination by a physician, nurse or other health care personnel; and
- (b) regular foot inspection, either by health care personnel or by people themselves (Table 3).

Table 3. Questions used to define prevention of foot complication

Elements of the prevention of foot complications	Related questions
<u>Regular</u> clinical diabetes examination involving physical examination by a physician, nurse, or other health care personnel	<i>“Do you see a doctor for regular check-ups for your diabetes?” (yes, no)</i> <i>“If not, do you see a nurse or other health care personnel for check-ups for your diabetes?” (yes, no)</i>
<u>Regular</u> foot inspection, either by health care personnel or self-inspection	<i>“Are your feet examined regularly by any of the following?” (yes, no)</i> - <i>Doctor</i> - <i>Podiatrist</i> - <i>Nurse or home care nurse</i> - <i>Other</i> - <i>Yourself</i>

See Appendix 3 for diabetes questionnaire Q3.

3.3.3 The Hospital Anxiety and Depression Scale

Zigmond & Snaith developed HADS [121] to assess anxiety and depression symptoms. HADS emphasizes the mental signs or consequences of anxiety and depression. HADS consists of 14 items. The seven questions in the anxiety subscale (HADS-A) are related to generalized anxiety but also address fear or panic. The seven questions in the depression subscale (HADS-D) are based on the concept of anhedonia (the absence of positive affect and pleasure from everyday tasks [121]). Five questions refer to reduced pleasure. Anhedonia is central to the concept of depression [122, 123]. Scores range from 0 to 21 for each subscale; higher scores represent more distress. The cut-off points for severity in anxiety and depression are: 0–7, normal; 8–10, mild; 11–14, moderate; and 15–21, severe [123]. Bjelland et al. [58] reported that 8 for both the anxiety and depression subscales represented the optimal cut-off point. This study presents descriptive values continuously; cut-off points of 8 and above and 11 and above are shown. The HADS is well validated [58]. Previous factor analysis of HADS in HUNT has been shown to result in a two-factor solution consistent with the two subscales of anxiety and depression [124]. Regarding internal consistency, Cronbach’s alpha values for the anxiety and depression subscales in HUNT were 0.80 and 0.76 respectively [124].

3.3.4 Psychological well-being and perceived health

The concept of psychological well-being is used to assess whether people with a HFU report poorer psychological well-being (mood) than comparisons groups. The psychological well-

being index used in the study was constructed using a sum score of four items, covering life satisfaction, vigor, calmness and cheerfulness (Table 4); a higher score indicates a higher level of well-being. These questions have been used as single questions [125] and as a scale [75, 126]. We preferred to use a scale as opposed to single questions, because this reduces random error. One question was located in Q1 and the other three in Q2. Regarding reliability, Cronbach's alpha and inter-item correlation were measured for the psychological well-being index.

Cronbach's alpha for the psychological well-being index was 0.81, and inter-item correlations ranged from 0.47 to 0.60. Principal component analysis of the four items was performed and yields a clear unidimensional solution, which is an assumption for combining questions into one single scale.

Table 4. Psychological well-being scale.

Item
"Considering how you feel these days, are you generally satisfied with your life, or are you generally dissatisfied?"
"At present, do you mostly feel strong and fit or tired and worn out?"
"Do you by and large feel calm and good about yourself?"
"Would you say you are usually cheerful or dejected?"

See Appendixes 1 (Q1) and 2 (Q2)

Perceived health was measured using the following item: "How is your health these days?" (measured on a scale from 1 = poor to 4 = very good). We cannot measure the reliability of one single item, but several studies have used this single item measure of perceived health and highly similar versions, which have been shown to have acceptable psychometric properties [88]. The question concerning perceived health was placed in Q1.

3.3.5 Follow-up

In the follow-up study, we estimated mortality rates for people with diabetes with and without a HFU and for the people without diabetes. All participants were followed for 10 years- with mortality as the end point. Information on main causes of death was obtained by linking individual data to the Norwegian Cause of Death Registry using the unique 11-digit –personal identification number assigned to each resident of Norway.

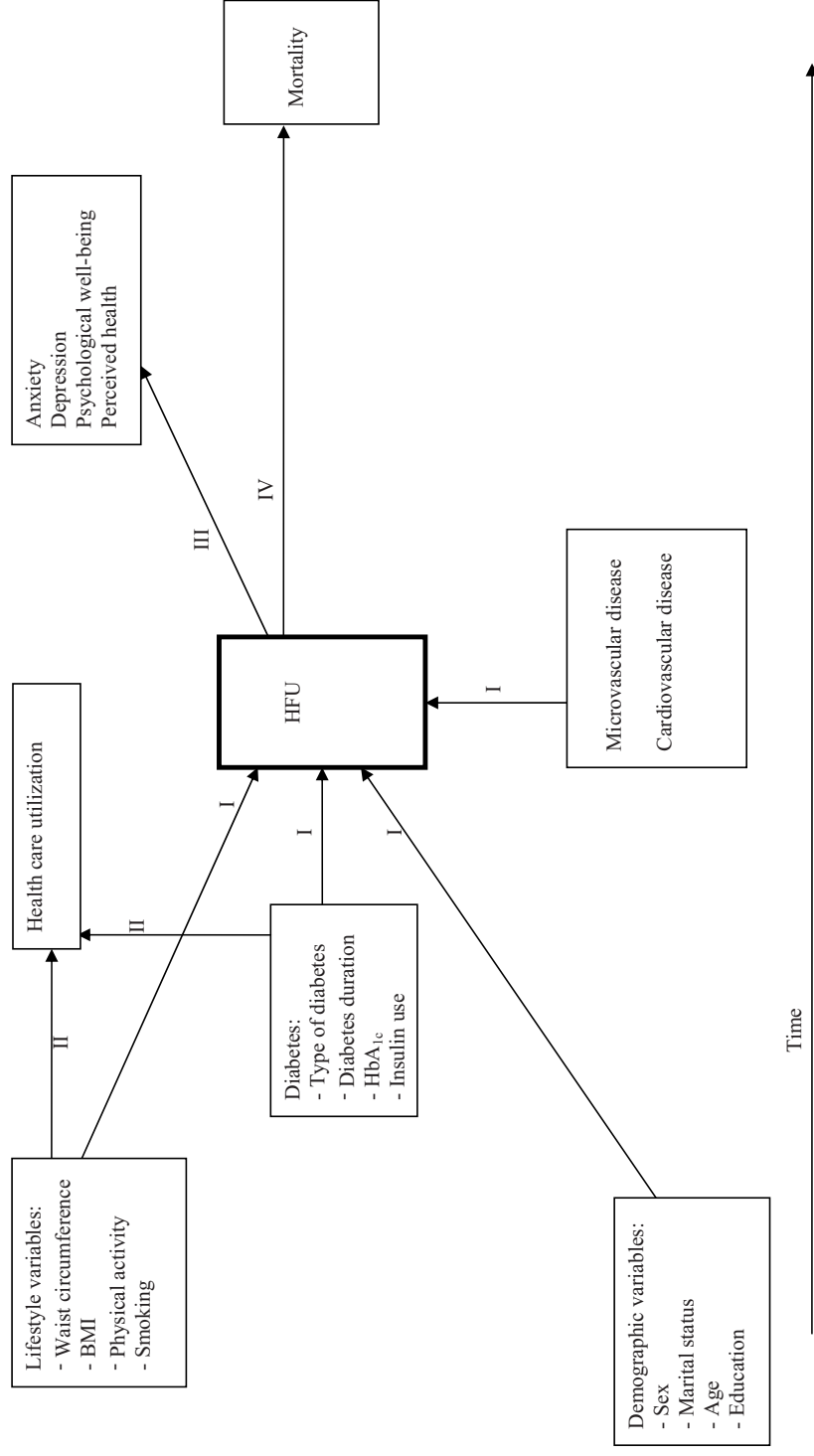
Mortality data with mortality diagnosis were obtained from the Norwegian Cause of Death Registry. Mortality diagnoses are coded according to the International Classification of Diseases (10th revision) and were categorized into diseases as follows: diabetes mellitus

(E10–E14), ischemic heart disease (I20–I25), cerebrovascular disease (I60–I69), other circulatory diseases (I00–I15, I26–I28, I30–I52, I70–I79, I80–I99), renal disease (N00–N39), cancer (C) and other diseases: certain infectious and parasitic diseases, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system, congenital malformations; deformations and chromosomal abnormalities; other endocrine, nutritional and metabolic diseases; ill-defined causes of violent deaths; and sudden death of unknown cause (A, B, D, E00–E07, E15–E90, F–H, J–M, N40–N99, O–Y).

3.4 Model of the variables investigated

The model in Fig. 3 provides an overview of associations between variables investigated and HFU. The associations investigated that are presented in Papers I–IV are indicated by the numbers I, II, III and IV, respectively, in an effort to operationalize the objectives of this study.

Fig. 3. Model showing investigated associations between variables and foot ulcers.



The associations investigated in Papers I–IV are indicated by numbers I, II, III and IV, respectively.

4. Data analysis and statistical methods

4.1 Data analysis and covariates

The covariates included in the final analyses of Papers I–IV were selected due to either rationale in the literature, preliminary analysis or statistical limitations. The section below gives an overview of the covariates used.

Sociodemographic factors

Age was defined as the age of the participants on the day of attendance in HUNT 2. In the logistic regression models, age was represented with dummy variables (indicator variables), as age and outcome (HFU or preventive foot care) were not linearly related. In Paper I, age was dichotomized as less than 75 years versus 75 years or more. In Paper II, age was categorized as less than 65 years, 65–74 years and 75 years or more. In Papers III and IV, age was used continuously.

Education: The questionnaire provided five categories for education. Education was categorized as education less than 10 years versus 10 years or more (Papers III and IV) [69]. Paper IV included a separate category for missing cases.

Marital status was dichotomized as single or alone (unmarried, widowed, divorced or separated) versus not single or alone (married or cohabiting) (Paper II).

Height was dichotomized at the median for each sex (men >175 cm, women >161 cm) (Paper I).

Lifestyle factors

Waist circumference was dichotomized as men ≥ 102 cm and women ≥ 88 cm (Papers I, II and IV) [127].

Body mass index (BMI) was calculated as kilograms per m^2 (Paper III).

Current smoking (yes/no) was dichotomized (Papers I–IV).

In relation to *diabetes self-education* the question was: “Are you a member of the Norwegian Diabetes Association?” (yes/no) was used (Paper II).

Clinical factors

Duration of diabetes was dichotomized as less than 10 years versus 10 years or more [101].

HbA_{1c} was categorized as $HbA_{1c} < 7.5\%$; $7.5\text{--}9.0\%$; $> 9.0\%$ in Paper II [128]; and used continuously in Papers III and IV.

Insulin use (used/did not use). Those who did not answer but reported that they used tablets to regulate their diabetes were coded as “did not use” (Papers I–IV).

Hypertension was defined as blood pressure of 140/90 mmHg or more or as current use of antihypertensive drugs (Paper IV) [129].

Complications were defined as *microvascular complications* (microalbuminuria, self-reported eye problems due to diabetes) or *macrovascular complications* (history of stroke, myocardial infarction, angina pectoris and peripheral vascular surgery) (Papers I and II).

Cardiovascular disease was defined as being present in those who responded positively to one or more of the following items: a history of angina pectoris, myocardial infarction and stroke (Papers III and IV).

Mental health

Hospital Anxiety and Depression Scale depression scores (HADS-D ≥ 8) were used as a covariate (Paper IV).

4.2 Statistical methods

Statistical analysis was conducted using SPSS version 13.0, 14.0 and 15 (SPSS Inc., Chicago, IL, USA). Statistical significance was assessed with two-sided $P < 0.05$. Several types of statistical analysis were used depending on the research questions and the variables.

Descriptive analysis

Descriptive statistics (mean, standard deviation and percentages) were calculated for subgroups of diabetes, demographic, lifestyle and disease-related variables and variables related to health care settings, diabetes examination, foot inspection and psychological assessment (Papers I, II and III). Cronbach’s Alpha was used to determine the internal consistency reliability of the psychological well-being scale and HADS (Paper III).

Simple comparisons

T-tests were used to compare mean values, chi-square tests for proportions and Mann-Whitney tests for median values between people with diabetes with and without a HFU and people without diabetes (Papers I, III and IV). In bivariate analysis chi-square tests were used to compare variables by subgroups defined by type of examination, (a) regular foot inspection by health care personnel, (b) regular foot self-inspection or (c) regular monitoring (regular clinical diabetes examination combined with regular foot inspection by a health care provider or regular foot self-inspection) (Paper II). Chi-square tests were used to determine whether the outcome measures of the regular inspection by health care personnel of respondents' feet and regular self-inspection were related (Paper II).

Multivariate analyses

Logistic regression analysis: Logistic regression was used to generate odds ratios for independent correlates that were associated with the binary outcomes, a HFU (Paper I) and preventive foot care (Paper II). Increasingly complex models were developed by adding one set of variables at a time. For bivariate and multivariate models, odds ratios (OR) and 95% CI are reported (Paper II).

Univariate multiple linear regression analysis: In Paper III, the four continuous variables symptom levels of anxiety (HADS-A) and depression (HADS-D), psychological well-being and perceived health were transformed to *z*-scores (variables with a mean of zero and a standard deviation of 1), to facilitate comparisons of effects (mean differences) between subgroups across outcomes.

The three participant subgroups were used as an independent categorical variable, entered in the univariate multiple regression analysis as two dummy variables with the subgroup without diabetes as reference. In separate univariate multiple regression analyses of the two diabetes subgroups, those without a HFU were used as the reference group.

Cox proportional hazards regression analysis: In Paper IV, Cox proportional hazards regression analysis was used to estimate mortality rate ratios (hazard ratios) and 95% CI from the date of inclusion in the study (1995–1997) to December 31, 2005. We created dummy variables for the people with diabetes without a HFU and those with a HFU such

that the hazard ratio for each category represents the comparison of that category to the non-diabetic population.

Preliminary, simple Cox regression analysis was performed to examine the association between all baseline covariates and all-cause mortality. For covariates with more than 2% missing data in the foot ulcer group, we included missing cases for education ($n = 16$), waist circumference ($n = 5$), microalbuminuria ($n = 10$) and depression ($n = 11$); separate “unknown” categories were used.

Multiple Cox proportional hazard regression analyses were then performed to estimate mortality rate ratios (hazard ratios) and 95% CI. Analysis was performed with adjustment for other known risk factors for mortality. Covariates were organized thematically in blocks, and increasingly complex models were developed by adding one set of variables at a time using forced entry. Variable selection in multivariable modelling was carried out a priori based on previous knowledge and assessment of the variable in relation to time, cause and effect.

We performed some separate additional analyses to explore whether this would alter results: 1) we excluded those with a history of amputation; and 2) we included diabetes classification and diabetes duration in Cox regression analysis (Paper IV).

Survival curves

Kaplan-Meier survival curves were calculated to describe the all-cause mortality in the subgroups (Paper IV).

Power calculations

In Paper IV, power calculations were performed before study start. Analysis showed a statistical power of 78% to detect an increased risk of 33% among the foot ulcer group compared with the population with diabetes without a HFU and assuming a mortality of 30% during follow-up in this group.

Collinearity

Collinearity for the final models (Papers I and II) was assessed using the condition index [130].

Statistical interaction

In separate models, the presence of statistical interaction (effect modification) was tested by adding multiplicative terms involving the sample subgroups variable to the full regression model while retaining each of the other independent variables. Interaction terms were tested for one pair of variables at a time (Paper III). Also, in Paper IV, separate Cox regression analyses were performed to test for possible interactions between the main exposure (non-diabetic subjects and diabetic subjects with and without a HFU) and the other covariates in the model among people with diabetes.

Table 5. Statistical tests used in Papers I–IV

Statistical methods used	Paper I	Paper II	Paper III	Paper IV
Descriptive statistics	x	x	x	x
<i>T</i> -tests	x	x	x	x
Chi-square tests	x	x	x	x
Mann-Whitney tests	x	x	x	x
Logistic regression analysis	x	x		
Univariate multiple regression analysis			x	
Cox proportional hazards regression analysis				x
Power calculations				x
Survival curves				x
Condition index	x	x		
Tests for possible effect modification			x	x

5. Ethical and legal issues

The Norwegian Data Inspectorate and the Regional Committee for Medical Research Ethics approved the HUNT 2 study. All information in HUNT is treated according to the guidelines of the Data Inspectorate [116].

Participation in this study was voluntary, and each participant signed a form giving informed consent to participate in the screening, brief examination and follow-up, and allowing the use of data and blood samples for research purposes. Participants also consented to linking their data to other registries. After data were collected, the HUNT Research Centre removed all names and personal identification numbers before further research was conducted [116]. This study therefore complies with the Declaration of Helsinki. The HUNT Research Centre was responsible for ensuring that all the ethical formalities associated with the study were in order. Thus, we used existing data and did not have contact with the participants.

In substudy IV, we applied for approval from the Central Norway Regional Committee for Medical Research Ethics, and the HUNT Research Centre to 1) merge the data from the foot ulcer study related to HUNT 2 with information about death in the years 1997–2007 (Cause of Death Registry) and 2) analyze mortality in a 10-year follow-up of people reporting a diabetic foot ulcer in HUNT 2 (1995–1997) and those who did not. We also requested information on death during 1997–2007 from the Norwegian Cause of Death Registry. Information on main causes of death and date of death was obtained by linking individual data to the Cause of Death Registry using the unique 11-digit personal identification number assigned to each resident of Norway. The HUNT Research Centre did this.

6. Summary of results

6.1 Paper I

History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trøndelag Health Study

Marjolein M. Iversen, Kristian Midthjell, Truls Østbye, Grethe S. Tell, Elizabeth Clipp, Richard Sloane, Monica W. Nortvedt, Sverre Uhlving & Berit R. Hanestad

Scandinavian Journal of Public Health, 2008; 36: 62–68.

The aim was to describe the proportion of people with diabetes with a HFU and to examine factors associated with a HFU. The overall proportion with a HFU was 10.4% [95% CI: 8.8%–11.9%]. Table 6 shows the sample with diabetes and a HFU stratified by age and sex.

Table 6. The sample with diabetes and a HFU stratified by age and sex

Age (years)	Men		Women		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<50	11	12.5	11	16.4	22	14.2
50–64	19	21.6	10	14.9	29	18.7
65–74	25	28.4	17	25.4	42	27.1
75–84	32	36.4	23	34.3	55	35.5
85 +	1	1.1	6	9.0	7	4.5
	88	100.0	67	100.0	155	100.0

Those reporting a HFU were asked about how many weeks the ulcers took to heal (reported in weeks; if several times, the time that lasted the longest). The response rate was 71.6% among those with a HFU. Thirty percent of the foot ulcers required more than 16 weeks to heal. The median healing time was 8 weeks (range 4–220).

In bivariate analyses among those with diabetes, height, waist circumference, less than 1 hour of physical activity per week, HbA_{1c}, insulin treatment, duration of diabetes, self-reported stroke, peripheral vascular surgery, any lower limb amputation, microalbuminuria and eye problems related to diabetes were associated with a HFU. Finally, in multivariate analysis, significant correlates of a HFU were male gender [OR 1.5, 95% CI: 1.03–2.2], age older than 75 years [OR 1.8, 95% CI: 1.2–2.8], height above the median (men >175 cm,

women >161cm) [OR 1.9, 95% CI: 1.3–2.8], using insulin [OR 1.6, 95% CI: 1.1–2.4], and presence of macrovascular complications [OR 1.8, 95% CI: 1.2–2.6].

The relationships between age, height, waist circumference, duration and a HFU were not linear. Nevertheless we repeated the last model including age, height, waist circumference and duration as continuous variables. For height, waist circumference (measured in cm) and duration (measured in years), we received rather similar results to the main results presented in the paper, with OR of 1.047, 1.016 and 1.015 respectively. This corresponds to an OR of 1.58 for a difference of 10 cm of height and an OR of 1.17 for a difference of 10 cm in waist circumference and an OR of 1.16 for a difference of 10 years of duration. However, for age the effect disappeared, reflecting the nonlinear relationship. There was a threshold, effect with marked increased risk for people older than 75 years but no relationship between the outcome and age for the group of people younger than 75 years. We decided to keep the model with the dichotomized variables since these odds ratios might be easier to interpret in clinical practice.

6.2 Paper II

Regularity of preventive foot care in persons with diabetes: results From the Nord-Trøndelag Health Study

Marjolein M. Iversen, Truls Østbye, Elizabeth Clipp, Kristian Midthjell, Sverre Uhlving, Marit Graue, Berit R. Hanestad

Research in Nursing and Health, 2008; 31: 226–237.

Since regular foot inspection by health care providers and by people themselves is a primary aspect of prevention, we wanted to explore the regularity of preventive foot care practices and to assess the characteristics of those getting preventive foot care and those not. To separate examinations for prevention of foot complications from follow-up examinations of those who already might have foot ulcers, we included only those with known diabetes but without a HFU (n=1312).

Among these 1312 persons, 58.8% reported regular preventive foot care. Almost 85% reported receiving regular clinical diabetes examinations, but only 31.7% reported regular foot inspection by health care personnel and 66.3% reported foot self-inspection. In addition,

participants' reports of health care provider inspections was strongly related with their own inspections ($P < 0.001$).

Independent variables associated with getting preventive foot care were: female gender, long diabetes duration (>10 years), using insulin and being a member of the Norwegian Diabetes Association. Those who reported macrovascular complications were less likely to receive regular preventive diabetes foot care.

6.3 Paper III

The association between history of diabetic foot ulcer, perceived health and psychological distress: the Nord-Trøndelag Health Study.

Marjolein M. Iversen, Kristian Midthjell, Grethe S. Tell, Torbjørn Moum, Truls Østbye, Monica W. Nortvedt, Sverre Uhlving, Berit R. Hanestad.

BMC Endocr Disord, 2009, 9:18.

The purpose of this study was to obtain more knowledge regarding psychological distress and perceived health associated with a HFU. The mean depression score was significantly higher among people with a HFU than among people without diabetes (4.7 versus 3.5). The proportions scoring 8 and above were 18.8% for those with a HFU and 10.8% for those without diabetes ($P = 0.002$). The percentages scoring 11 or more were 7.6% for those with a HFU and 3.2% for those without diabetes ($P = 0.002$). However, in multivariate analyses we found that anxiety and depression symptoms did not differ for those with a HFU compared with whether those without diabetes or those with diabetes but without a HFU.

Perceived health and psychological well-being were significantly poorer among those with a HFU than among those without diabetes. Within the diabetes groups we found that perceived health was significantly worse among those reporting a HFU, but psychological well-being did not differ.

6.4 Paper IV

A history of foot ulcer increases mortality among persons with diabetes: 10-year follow-up of the Nord-Trøndelag Health Study, Norway.

Marjolein M. Iversen, Grethe S. Tell, Trond Riise, Berit R. Hanestad, Truls Østbye, Marit Graue, Kristian Midthjell.

Diabetes Care, 32:2193–2199, 2009.

We intended to examine the relationship between a HFU and subsequent 10-year registry-assessed mortality. The main findings were that the subjects who reported a HFU experienced increased mortality compared with both the subjects who did not report diabetes [hazard ratio 2.29, 95% CI: 1.82–2.88] and the subjects who reported diabetes but not a HFU [hazard ratio 1.41, 95% CI: 1.09–1.82].

The excess risk persisted after adjusting for comorbidity and depression scores. Table 7 provides characteristics at entry (baseline) for the subgroups by whether they died during the follow-up period. Table 8 shows the distribution of main causes of death by subgroups (“diabetes with a HFU”, “diabetes without a HFU” and “non-diabetes”).

In separate analyses including people with HFU only, the estimated effects of HbA_{1c}, insulin use, microalbuminuria and depression scores increased. The estimated effect of HbA_{1c} was slightly stronger, although it was not significant due to the low number [hazard ratio 1.11; 95% CI: 0.97–1.28]. The estimated effects of insulin use [hazard ratio 2.13; 95% CI: 1.16–3.90], microalbuminuria (hazard ratio 2.77; 95% CI: 1.54–4.98) and depression scores [hazard ratio 1.93; 95% CI: 1.03–3.64] were significant associated with mortality. However, the estimated effects of older age, sex (male), current smoking and cardiovascular disease decreased and were not significantly associated with mortality.

Table 7. Characteristics at entry stratified by mortality status during the follow-up period^a

Characteristics	Diabetic subjects with a HFU <i>n</i> = 155 ^b		Diabetic subjects without a HFU <i>n</i> = 1,339 ^b		Subjects without diabetes <i>n</i> = 63,632 ^b	
	Died <i>n</i> = 76	Survived <i>n</i> = 79	Died <i>n</i> = 471	Survived <i>n</i> = 868	Died <i>n</i> = 6,664	Survived <i>n</i> = 56,958
Sociodemographic characteristics						
Age (years)	74.7 (SD 9.5)	60.0 (SD 13.8)^c	74.4 (SD 7.4)	60.8 (SD 13.8)^c	73.0 (SD 12.0)	46.9 (SD 15.6)^c
Age 65–74 years (versus ≥75 years)	20 (47.6%)	22 (52.4%)^d	172 (38.0%)	281 (62.0%)^c	1,868 (21.9%)	6,676 (78.1%)^c
Sex male (%)	41 (46.6%)	47 (53.4%)	235 (35.3%)	431 (64.7%)	3,590 (12.1%)	26,143 (87.9%)^c
Marital status (single or alone) (%)	39 (54.9%)	32 (45.1%)	213 (41.8%)^c	297 (58.2%)^c	3,147 (12.4%)^c	22,331 (87.6%)^c
Education (<10 years) (%)	48 (52.2%)	44 (47.8%)	292 (39.6%)^c	446 (60.4%)^c	3,634 (16.8%)^c	17,963 (83.2%)^c
Lifestyle characteristics						
BMI (kg/m ²)	28.8 (SD 4.8)	29.7 (SD 5.7)	28.6 (SD 4.6)	29.1 (SD 4.9)^d	26.6 (SD 4.3)	26.2 (SD 4.0)^c
Waist (cm)	98.2 (SD 12.5)	98.1 (SD 12.3)	95.4 (SD 11.7)	94.7 (SD 12.1)	91.0 (SD 11.8)	85.7 (SD 11.5)^c
Current smokers (%)	8 (47.1%)	9 (52.9%)	85 (37.9%)	139 (62.1%)	1,638 (9.0%)^c	16,625 (91.0%)^c
Clinical characteristics						
HbA _{1c} (% units)	8.8 (SD 2.0)	8.3 (SD 1.9)	8.4 (SD 1.79)^c	8.0 (SD 1.72)^c	-	-
Insulin use (%)	36 (53.7%)	31 (46.3%)	144 (34.0%)	279 (66.0%)	-	-
Microalbuminuria ^e (%)	39 (67.2%)	19 (32.8%)^c	181 (52.6%)	163 (47.4%)^c	-	-
Eye problems due to diabetes (%)	24 (66.7%)	12 (33.3%)^d	64 (42.4%)	87 (57.6%)^d	-	-
Self-reported stroke (%)	9 (50.0%)	9 (50.0%)	32 (49.2%)	33 (50.8%)^d	533 (47.2%)	597 (52.8%)^c
Self-reported myocardial infarction (%)	17 (73.9%)	6 (26.1%)^d	101 (60.8%)	65 (39.2%)^c	823 (43.5%)	1,070 (56.5%)^c
Self-reported angina pectoris (%)	22 (66.7%)	11 (33.3%)^d	134 (55.1%)	109 (44.9%)^c	1,107 (37.9%)	1,816 (62.1%)^c
Any lower-limb amputations (%)	7 (87.5%)	1 (12.5%)^d	3 (33.3%)	6 (66.7%)	-	-
Perceived health and psychological distress						
Perceived health	2.16 (SD 0.60)	2.35 (SD 0.62)	2.24 (SD 0.64)	2.53 (SD 0.62)^c	2.43 (SD 0.67)	2.92 (SD 0.66)^c
HADS depression score (0–21)	5.8 (SD 3.4)	3.8 (SD 3.5)^d	4.8 (SD 3.5)	4.1 (SD 3.3)^d	4.7 (SD 3.6)	3.3 (SD 3.0)^c
HADS depression (score ≥8) (%)	17 (63.0%)	10 (37.0%)^d	89 (42.2%)^d	122 (57.8%)^d	1,173 (17.8%)	5,413 (82.2%)^c
HADS depression (score ≥11) (%)	8 (72.7%)	3 (27.3%)	26 (41.9%)	36 (58.1%)	399 (20.7%)	1,530 (79.3%)^c

^aNumbers represent *n* (percentages) or means (standard deviations). ^bTotal population *n* varies slightly depending on the actual number completing the various tests and questionnaires. ^c*P*-value < 0.001 for comparing the groups: died versus survived (bold). ^d*P*-value < 0.05. ^eMicroalbuminuria is defined as an albumin–creatinine ratio ≥2.5 mg/mmol in at least two of three urine samples.

Table 8. Main causes of death by subgroups: diabetes with a HFU, diabetes without a HFU, diabetes without a HFU and non-diabetics

ICD-10 code	Main causes of death	Diabetes with a HFU		Diabetes without a HFU		Non-diabetes	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total		76/155 (49.0)	471/1,339 (35.2)	6,664/63,632 (10.5)			
C	Cancer (neoplasms)	11 (14.5)	89 (18.6)	1,835 (27.5)			
E10-E14	Endocrine diseases related to diabetes mellitus	18 (23.7)	55 (11.7)	36 (0.5)			
E11.9,E14.9	Without complications	3 (3.9)	16 (3.4)	18 (0.27)			
E11.2,E14.2	Renal complications	4 (5.2)	1 (0.2)	2 (<0.001)			
E10.6,E11.6, E14.6	Neurological complications	3 (3.9)	29 (6.2)	10 (0.15)			
E14.5	Peripheral circulatory complications	1 (1.3)	5 (1.1)	3 (<0.001)			
E10.7,E11.7, E14.7, E14.3	Multiple complications	5 (6.5)	2 (0.4)	1 (<0.001)			
E10.0,E14.0	Ophthalmic complications	1 (1.3)	-	-			
E10.8	Diabetes with coma	1 (1.3)	1 (0.2)	2 (<0.00)			
	Unspecified complications	-	1 (0.2)	-			
I	Cardiovascular disease	37 (48.7)	236 (50.1)	2,993 (44.9)			
I20-I25	Ischemic heart disease						
I60-169	Stroke (cerebrovascular disease)	21 (27.6)	127 (27.0)	1,327 (19.9)			
I00-I15, I26-I52, I70-199	Other circulatory diseases (hypertensive diseases; rheumatic or cardiac valve illnesses, other forms)	6 (7.9)	51 (10.8)	774 (11.6)			
		10 (13.2)	58 (12.3)	892 (13.4)			
N00-N39	Renal diseases	-	13 (2.6)	92 (1.3)			
A, B, D, E00-E07, E15-E90, F-H, J-M, N40-N99, O-Y	Other diseases ^a	10 (13.1)	78 (16.0)	1,708 (25.6)			

^aOther diseases: certain infectious and parasitic diseases, diseases of the musculoskeletal system and connective tissue, diseases of the genitourinary system, congenital malformations, deformations and chromosomal abnormalities, other endocrine, nutritional and metabolic diseases, ill-defined causes of violent deaths, sudden death of unknown cause, ICD coding error (n = 22) in the non-diabetes group.

7. Discussion

The aim of this study was to gain more knowledge about people with diabetes reporting a HFU in a large, unselected population in Norway. This study, which is a substudy of HUNT 2, is the largest population-based study ever conducted on foot ulcers among people with diabetes. Our study is also the first investigating a HFU and the associated risk of mortality among community-dwelling persons. This section considers the methodological strengths and limitations and the extent to which bias and confounding may have influenced the results of the study. There is also a discussion of the main findings.

7.1 Methodological considerations

7.1.1 Study design

Our study designs reported in Papers I–III were cross-sectional: measuring the associations between various factors and either a HFU (Paper I) or receiving preventive foot care (Paper II) and the association between a HFU, perceived health and psychological distress (Paper III). In these cross-sectional designs, measurements of the various factors were determined approximately at the same point in time. The study reported in Paper IV used a prospective design with baseline factors as predictors of mortality over a 10-year period in the three study groups: people with diabetes with and without a HFU and people without diabetes.

The cross-sectional design is especially appropriate for describing associations between variables at a fixed point in time [131]. The most important limitation of a cross-sectional study is that conclusions regarding causality cannot be drawn. In the prospective design, we started out with a presumed cause and followed the cohort forward in time to observe the effect, allowing inferences, although cautiously, regarding cause and effect.

7.1.2 Selection bias and representativeness

Selection bias is systematic error resulting from the procedures used to select subjects and from factors that influence study participation [132] and is present when factors related to

the outcome (such as a HFU) differ between the participants and nonparticipants. Selection bias can never be corrected by statistical analyses.

Among those eligible, about 70% participated in HUNT 2. The nonparticipants were compared with HUNT 2 participants in a separate study, which revealed that a larger proportion of nonparticipants older than 70 years had health problems than participants of the same age [116], which suggests some selection bias.

In the current study, we had to deal with missing answers on selected questions or questionnaires. Among the 1972 persons reporting diabetes in HUNT 2, 1692 returned Q3 and 280 did not. Among those who returned Q3, 198 did not answer the question: “Have you had a foot ulcer that required more than 3 weeks to heal?” (Fig. 1). We compared characteristics between participants and nonparticipants in the missing groups. A larger proportion of nonparticipants had unfavorable lifestyle characteristics, had suffered a stroke and had depressive symptoms. Hence, our study population probably had better physical and mental health than the nonrespondents. Selection bias may have resulted in an underestimation of the number of people with a HFU, as discussed in Paper I. In the sample reporting preventive foot care (Paper II), those with a HFU were excluded. Selection bias would thus only occur in this sample if factors associated with preventive strategies differed between participants and nonparticipants.

An underrepresentation of individuals with more severe illness may have resulted in weaker observed effects, such as the association between depressive symptoms and a HFU. Although a higher proportion of people with a HFU may have declined to participate compared to people without a HFU, this should not have affected the validity of the results presented in Papers II, III and IV.

Generalizability means the degree to which the results of a study may apply to, be relevant for, or be generalized to populations or population groups outside the study [133]. The population sample in this study is not fully comparable to the general population in Norway, as Nord-Trøndelag lacks a large urban area, and the average income, the prevalence of higher education and the prevalence of current smokers are slightly lower than the national average. Nevertheless, we have no reason to believe that the proportion having a HFU differs much among Caucasians in Norway, even though factors such as insulin use,

microalbuminuria, HbA_{1c} and depression scores influence the excess mortality associated with a HFU.

The prevalence of foot ulcer may differ between various ethnic groups [46, 47]. Thus, because our study sample is ethnically homogeneous, our results may not be applicable to other ethnic groups.

The data from HUNT 2 were collected 10 years ago, and this may reduce the relevance of the study (Papers I–III). However, the proportion of people reporting regular preventive foot care and the proportion reporting a HFU are still relevant in current practice, as national guidelines regarding foot care practices have not changed during the past 10 years [103, 128, 134]. Concordant with our findings, preliminary results from community-based cross-sectional studies carried out in Norway in 1995 [108, 135], 2000, and 2006 [135] have also shown that foot care practices have not improved over these years.

7.1.3 Information bias

Information bias results from errors concerning information received from or about subjects in a study, leading to incorrect measurements of exposure or outcome [132]. Incorrect information or incorrectly measured variables may lead to misclassification; this bias may result in systematic error in the estimation of effect.

Self-report bias

Health care personnel did not verify people's HFU, and people may have incorrectly reported HFU status, which might have contributed to misclassification. Although asking people with diabetes to self-report a HFU has inherent limitations, clinically validating the diagnosis by clinical data or by interview in this large epidemiological study was not feasible. A group of clinical experts discussed the diagnostic cut-off time for an ulcer. The 3-week timeline was considered a natural cut-off, because when ulcers need more than 3 weeks to heal, they are more likely to be directly related to the underlying diabetic condition. Even though some participants may erroneously have reported other types of ulcers, such as venous leg ulcers, the term foot ulcer (*fotsår*) is probably less ambiguous in Norwegian than it is in English.

HUNT 2 included validated questionnaires where possible. Section 3.3.3 discusses the reliability and validity of HADS, the psychological well-being scale and perceived health.

Information on demographics, lifestyle and prevalent disease was collected using questionnaires. Almost all questions had some missing values. Missing values were recoded as 'no' for the questions on diabetes, stroke, myocardial infarction, angina pectoris and problem with eyes due to diabetes (Q1) and for amputated legs/toes (Q3). The rationale for this was that we assumed that people do not forget such significant events in their lives. Due to sampling procedures, data were missing more frequently for variables located in Q2 than Q1 (three of four questions in the psychological well-being scale were located in Q2) (Paper III). We performed missing substitution for individuals not answering one or two questions in HADS-A or HADS-D according to standard procedures for the HADS questionnaire [121, 136]. We did not alter missing values on other questions. One consequence of this was that information on physical activity, with 22,5% missing values, could not be included in the multivariate analyses. In Paper IV, for covariates with more than 2% missing data in the foot ulcer group, separate "unknown" categories were used. This involved education ($n = 16$), waist circumference ($n = 5$), microalbuminuria ($n = 10$), and depression ($n = 11$).

Self-reported diabetes was validated by blood tests. Midthjell et al. [137] reported that using this self-administered questionnaire to determine diabetes diagnosis provided reasonably accurate information about diabetes mellitus, as a substudy revealed that diabetes was verified in 163 out of 169. Nevertheless, some subjects with diabetes were probably misclassified as not having diabetes. Including an unknown number of subjects with diabetes in the non-diabetes group at baseline may have influenced the results. Among the people without known diabetes, 62,757 delivered a non-fasting venous blood sample for glucose measurement. Of these, 217 had a non-fasting glucose concentration exceeding 11 mmol/l but were included in the non-diabetes group. Including these cases in the non-diabetic group did not influence the mortality risk estimate. However, the self-reported question about diabetes probably underestimated the number of subjects with diabetes, and if these 217 persons were diagnosed as having diabetes they would have constituted a considerable part of the diabetes group.

Approximately 25% of the participants with diabetes were not classified with regard to type of diabetes because they failed to attend the follow-up appointment in a fasting state. For

some, the invitation for a follow-up appointment was sent during the summer holidays, and thus missed some participants. The proportions of type 1 and type 2 diabetes should, therefore, be viewed with caution. Because of missing information regarding the classification of type 1 and type 2 diabetes, this variable was not included in the multivariate analyses.

Urine samples

Microalbuminuria was measured in those who delivered three urine samples (individuals with diabetes and hypertension). The attendance rate was high (almost 90%), minimizing selection bias [138]. In previous studies, the threshold for microalbuminuria has varied from 2.5 to 3.5 mg/mmol for men and women [118]. In this study, we used a cut-off of ≥ 2.5 mg/mmol for both sexes based on previous studies [117, 118, 138]. However, since women have less muscle mass and excrete less creatinine in urine than men, a higher cut-off value for women has also been recommended [117]. This study might therefore overestimate the proportion of women with microalbuminuria and the results should be considered with caution.

Follow-up

As the incidence of type 2 diabetes is increasing dramatically and type 1 diabetes moderately, new cases of diabetes most likely occurred in the non-diabetes group during the follow-up period. However, the only information we have for subjects without diabetes during the follow-up period is that 0.5% of deaths in this group were diabetes-related.

7.1.4 Confounding

Confounding means that the estimated effect of the exposure is mixed together with the effect of another factor [132]. There are three criteria for a confounding factor: it must be a risk factor for the disease; it must be associated with the exposure being studied in the source population; and it should not be an intermediate step in the causal pathway between the exposure and the disease. Further, the confounder should not be an effect of the exposure or the outcome.

Observational studies use stratification or various multivariate statistical techniques such as multivariate regression models to reduce the effect of confounding. The challenge is to identify whether a factor is actually a confounder or not. Age and sex are well-known

confounders in the association between exposure and outcome, and are therefore often adjusted for in multivariate analyses. Separate analyses revealed that age was a confounder in the association between a foot ulcer and mortality. Factors related to lifestyle, such as current smoking, waist circumference or BMI, are often associated with exposures under investigation and various diseases or health problems. In this study, we therefore adjusted for these variables in multivariate analyses. However, if a factor is an intermediate step in the causal pathway between the exposure and the disease it is considered as mediating the effect of the exposure. Hence, because amputation is most likely an effect of a HFU, we did not adjust for this variable. On the other hand, comorbidity such as microalbuminuria or having had a myocardial infarction, stroke or angina can be potential mediators and may act as intermediate variables as well as confounders. The covariates in Paper IV, however, did not markedly change the estimates of the association between a HFU and mortality.

Higher HbA_{1c}, insulin use and longer duration of diabetes are related to the severity of diabetes, and are considered risk factors for a HFU. In regression analyses among those with diabetes, with and without a HFU, we considered these variables as covariates. In Paper I, we only included duration and insulin use in the multivariate model due to limited degrees of freedom and information in the literature [36, 41, 107]. In Paper IV, we included HbA_{1c} and insulin use based on information in the literature [71, 100, 139].

In Paper IV, we included the HADS-scores as covariates in multiple Cox proportional hazards regression analyses with mortality as the outcome. In Paper III, however, we considered a HFU, lifestyle factors, clinical factors and comorbidity as covariates (confounders) and adjusted for them in the regression analyses, as psychological distress (HADS-A, HADS-D, psychological well-being and perceived health) might be a consequence of a HFU, rather than the cause.

7.2 Main discussion

7.2.1 Diabetes and a history of foot ulcer

In this study, 10.4% of those with diabetes reported a HFU. Other studies have reported that between 2.1% and 12% of those with diabetes have current or previous foot ulceration. Two

previous studies conducted in primary health care settings, one from the Trinidad and Tobago [34] and the other from the United States [35], reported quite similar proportions. However, the results of the latter study, the Behavioral Risk Factor Surveillance System [35], should be considered with caution due to methodological weaknesses. This was a random-digit-dialing telephone survey conducted in 50 states, but the response rate was only 48.9%, the number of people participating was not reported and people without telephones were not included [35]. Compared with the Trinidad and Tobago study [34], we would expect to find a higher proportion of HFU in our study as other reports have emphasized the role of ethnicity in the onset of foot ulcers [46]. It has previously been suggested that height may serve as a proxy for ethnicity but also for childhood socioeconomic status [140]. In our study, height was positively associated with a HFU. The previous proposed explanation of the link between height and neuropathy (neuropathy is often present in the foot at risk) is that height is also associated with the length of axons, and longer axons are more prone to metabolic disturbances [41, 141]. As Norwegians are relatively tall and may have a higher risk of neuropathy, this may contribute to a higher prevalence of foot ulcers. However, the very fact that Norway has a comprehensive health care system, with closer medical follow-up of diabetes patients, may account for a lower proportion of HFU among Norwegians with diabetes. In any case, we found that a HFU is a relatively common problem among community-dwelling people with diabetes, as 1 out of 10 with diabetes reported having had a foot ulcer. Due to potential selection bias, our estimates of the proportion of people with diabetes who currently have or have had a HFU are probably conservative.

7.2.2 Psychological distress and perceived health

The results presented in Paper III do not support an association between a HFU and depression in this population-based sample of people with diabetes. Psychological distress such as depression seems to be more pronounced when people have a current foot ulcer [71]. Nevertheless, depressive symptoms are reported to be associated with impaired healing and recurrence of ulcers in older people with type 2 diabetes [72]. However, our results presented in Paper IV support an increased risk of mortality among people with a HFU who also have depressive symptoms, in accordance with Ismail et al. [71]. Systematic monitoring and treatment of depression among those with a HFU and those at risk of developing a diabetes-related foot ulcer, should therefore be considered [139].

Studies estimate the prevalence of anxiety disorders in general population samples as ranging from 13% to 17% [142, 143]. The prevalence of anxiety measured by HADS (subscore ≥ 8) in HUNT 2 was about 15% [124, 144]. Results from various studies are difficult to compare as different study designs, samples and/or different questionnaires have been used. Methodological differences create difficulty in comparing these study results [145]. In our study, however, the prevalence of anxiety symptoms in the diabetes groups with and without a HFU did not differ from that of the general population, and more specific ways to measure diabetes-related anxiety, such as fear of hypoglycemia, may be needed.

A HFU had an independent impact on perceived health in addition to the underlying diabetes illness itself, indicating more severe diabetes (Paper III). The fact that a foot ulcer is likely to indicate more severe disease has become clearer during recent years [40, 100, 146], and our results showed that simply having had a foot ulcer influences perceived health, suggesting that advanced diabetes influences perceived health in everyday life. Hence, a HFU was associated with poorer perceived health, no association was found between a HFU and more psychological distress. This may indicate that a HFU is more the result of biological factors rather than mental ones. The clinical picture of people who have had diabetes for a long time is complex, with several complications appearing at the same time, perhaps affecting their ability to self-manage their diabetes. Focusing on perceived health may help to identify vulnerable people with diabetes and to offer them more intensive, individual support and an appropriate foot care program.

7.2.3 Importance of preventing of foot ulcers

This large population-based cohort study examined the relationship between a HFU and subsequent 10-year risk of mortality. The increased mortality risk was about 40% at 10 years among those with a HFU compared to those without a HFU. Previous studies from specialized care show an increased mortality rate of about 50% at 5 years for people with foot ulceration compared to those with diabetes without foot ulceration [12, 95-98]. The present results reinforce previous evidence of a link between foot ulceration in diabetes and risk of death and extend knowledge concerning excess mortality to a community-wide population sample in Norway.

In HUNT 2, the diabetes groups did not differ statistically in mortality rates due to cardiovascular disease, although people with a HFU had a higher prevalence of cardiovascular disease and more cardiovascular risk factors at baseline than those without a HFU. A possible explanation for this may be that only the main cause of death was included and that cardiovascular disease and the cardiovascular risk factors may have contributed to death, but not been the main cause for some cases in the HFU group.

The risk of foot ulceration among community-dwelling people with diabetes has been investigated less than foot ulceration in hospital diabetes clinics and dedicated foot clinics [45]. As we included the general diabetes population in our study, we also included those with previous foot ulcers that have healed without encountering the health care system. As a group, the persons with diabetes who reported a HFU are expected to have less severe diabetes than hospital-based samples. In our study, the median healing time for previous ulcers was 8 weeks (range 4–220). The median time for healing foot ulcers in a recent cohort study among people with diabetes treated in a multidisciplinary foot center in Sweden was 18 weeks (range 1–235) [40]. These findings lend support to the assumption that diabetes is more severe among people attending hospital and foot care clinics, as opposed to among community-based samples.

Although people with diabetes-related foot ulcers in this sample seemed to have less severe diabetes than those in hospital settings, early identification of foot ulcers and intensified treatment at an early stage seem to be important. Systematic implementation of evidence-based guidelines seems particularly important for those with a HFU, who are susceptible to adverse outcomes. One out of 10 diabetic participants in our study had a foot ulcer, and this subgroup had excess mortality. During 2003–2004, a large multicenter study in Europe collected data on foot ulcers, characteristics, health care organization and clinical outcomes in 14 foot ulcer centers. Twenty-seven percent of the people with foot ulcers had been treated for more than 3 months before being referred to a foot clinic [30, 147]. Prompers et al. [30] reported that the severity of diabetes-related foot ulcers at presentation was greater than previously reported; the treatment that many people received was not in accordance with current guidelines, and countries and centers differed widely. These results complement the results of our study and underscore the fact that promoting the prevention of foot ulcers in diabetes care needs greater emphasis.

Compared to women, a higher proportion of men reported a HFU [14, 40, 148]; and men were also less likely to get regular preventive foot care [149]. Among all persons with diabetes, men had higher mortality rates than women, however this was not seen in the HFU subgroup. Different explanations have been proposed for the observed higher risk in men, including genetic differences, hormonal factors protecting women from vascular comorbidity, and differences in life expectancy [40]. Further, sex differences in mean body height have been proposed as an explanation, as longer nerve fibers are thought to be more prone to metabolic disturbances and to influence the development of peripheral neuropathy [41, 150].

Aggressive treatment has shown to have favourable effects on mortality among people with a diabetes-related foot ulcer [100]. However, with regard to sex differences, reports from European registries show that women with diabetes are treated less frequently with aggressive medical treatment such as aspirin, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and revascularization therapy than men [151-153].

The results of our study indicate that men are more likely to report a HFU than women, and men were less likely to report regular preventive diabetes foot care. Within diabetes foot care, the focus on biological explanations has been greater than on behavioral explanations. Concerning behavioral aspects, however, it has been reported that men express fear of the future, show a passive attitude and mobilize their social networks to obtain additional care, whereas women are more prone to use preventive measures and are more active in self-care than men [149]. This complements and is in accordance with our results and suggests that health care workers need to use different approaches in educating men in foot self-care than in educating women.

The results from a recent posttrial report from the United Kingdom Prospective Diabetes Study found that better glycemic control at the beginning of the trial was associated with reduced risk of myocardial infarction and death from any cause after a 10-year follow-up [154]. Further, Young et al. [100] showed that implementing a systematic and aggressive strategy for managing cardiovascular risk improved survival among those with diabetes-related foot ulcers. In our study, a 1 percentage point increase in HbA_{1c} was associated with a 7% increase in the risk for all-cause mortality after 10 years. More than half of our study

participants with type 2 diabetes had HbA_{1c} values exceeding 8.0%, indicating the clinical relevance of this finding.

People with diabetes and chronic foot ulcers often have cardiovascular disease [155, 156]. Also, those reporting macrovascular complications were less likely to report regular preventive diabetes foot care. The 2009 Norwegian recommendations [134] and the current American Diabetes Association recommendations [8] indicate that peripheral vascular disease is a risk factor, but do not list cardiovascular disease as a characteristic of people at risk of a HFU. Physicians, diabetes nurses and nurses in coronary care units need therefore to be aware that people with diabetes and heart disease may be particularly vulnerable to foot ulcers and that early implementation of preventive foot care strategies is of utmost importance.

The results from a foot clinic study in Scotland [100] indicated that implementing a more systematic and aggressive strategy for managing cardiovascular risk improved survival among those with diabetes-related foot ulcers. Further, a study of primary care patients in Norway showed substantial improvements in the quality of care among those with type 2 diabetes, and this improvement was related to better outcomes, including improved HbA_{1c}, systolic blood pressure, cholesterol, and 10-year risk of coronary heart disease [157]. Follow-up studies from HUNT 1 and HUNT 2 have also shown a general reduction in mortality rates from cardiovascular disease [129]. Although those with diabetes benefited from the overall decline in mortality, the more than twofold higher mortality rate from cardiovascular disease associated with diabetes persisted over time. Thus, systematically implementing of evidence-based guidelines in diabetes care and foot care is very important for those with a HFU who are particularly susceptible to adverse outcomes.

7.3 Implications for clinical practice

The following implications may be drawn from this study.

- Foot ulcers appear to be a marker of more severe illness, not only among people with diabetes in specialist care but also for those in primary care. A greater focus on foot care among people with diabetes in primary health care is therefore needed. Close

follow-up in primary health care also appears to be important for those with a minor foot ulcer that seems to be healing well.

- Health care personnel in primary health care (home care, nursing homes and general practitioners' offices) need to promote the prevention of foot ulcers among people with diabetes. Those who are at risk of foot ulcers or have foot ulcers need to be followed-up closely.
- Men were more likely to report a HFU than women. However, men were less likely to report regular preventive diabetes foot care. Health care workers may need to employ different approaches in the education of men in foot self-care than those used for women.
- Cardiovascular disease is often prevalent among people with diabetes and chronic foot ulcers. Health care personnel in diabetes care and coronary care need to be aware that people with diabetes and heart disease are more vulnerable to developing foot ulcers.
- The clinical picture of people with HFU and long diabetes duration is often complex, with several complications affecting their ability to self-manage. Systematic screening of perceived health and depression among people with a HFU should be considered.
- The increasing prevalence of diabetes is also likely to increase long-term diabetes-related complications. Diabetes foot care in Norway may need to be organized more efficiently.
- Greater emphasis needs to be placed on applying national guidelines in diabetes foot care in Norway.

7.4 Implications for future studies

The results of this study encourage further research in different areas.

Determining whether primary preventive foot care strategies can make a difference. Future studies should follow up the samples described in Paper II and examine whether those reporting regular preventive care and those who did not in HUNT 2 (Paper II) differ in the onset of a foot ulcer in HUNT 3 (conducted in 2006-2008). Such a prospective study can determine whether primary preventive foot care strategies can make a difference. Statistical probability needs to be explored a priori to determine whether a 10-year follow-up with this sample size will have enough power to detect differences.

Estimating the prevalence and incidence of HFU. Health care personnel did not verify a HFU in our study. Norway is in the early stages of establishing a population-based registry of people with diabetes (adults). Having reliable data on foot ulcers enables both the prevalence and the incidence of this diabetes-related complication to be estimated accurately in Norway and will minimise misclassification of a HFU. Further, the longitudinal data above will enable the illness trajectory of those with diabetes to be mapped during their lifetime and the foot ulceration process to be monitored, including both current and healed foot ulcers.

Monitoring and reporting on the standard of quality of foot care in Norway. A nationwide follow-up of registry data in primary health care is needed in order to monitor the identification of foot ulcers and their treatment at an early stage. Several examples in Norway, and elsewhere show that equal conditions are treated unequally [158]. Studies using data from the national registry of people with diabetes in Norway that is being developed might contribute to improving Norway's standard of quality of foot care for people with diabetes.

Improving the quality of foot care in community health care. An intervention study might contribute to enhancing the prevention of foot ulcers in diabetes care. Updated knowledge and intersectoral collaboration are necessary so that health care personnel can detect susceptibility to diabetes-related foot ulcers among community-dwelling people with

diabetes. An intervention study that combines intersectoral collaboration between all levels of care with updated knowledge concerning diabetes may facilitate the delivery of high-quality health care [78, 120].

8. Conclusions

The issues investigated in this study cover a broad range, which hopefully will contribute to the knowledge base concerning people with diabetes in the general population. Major findings from our study include:

- Overall, 1 out of 10 community-dwelling people with diabetes reported a HFU.
- The characteristics associated with a HFU were male gender, older than 75 years, height above the median (gender specific), insulin use and the presence of macrovascular complications.
- Reported regular preventive foot care strategies are associated with female gender, insulin use and diabetes duration of more than 10 years. Further, those reporting macrovascular complications were less likely to report regular preventive diabetes foot care.
- Reporting a HFU among people with diabetes is associated with poorer perceived health in everyday life. However, a HFU among people with diabetes was not associated with more anxiety or depression symptoms or poorer psychological well-being.
- Among people with diabetes those reporting a HFU had an excess mortality risk of about 40 % which was explained only partly by older age, sex (male), a higher HbA_{1c}, current smoking, insulin use, microalbuminuria, cardiovascular disease and depression.
- Our findings indicate the importance of identifying and closely following up of people with foot ulcers at an early stage and suggest that systematically implementing evidence-based guidelines in diabetes care and foot care may be very important for those with a HFU who are particularly susceptible to new ulcers and other adverse outcomes.

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