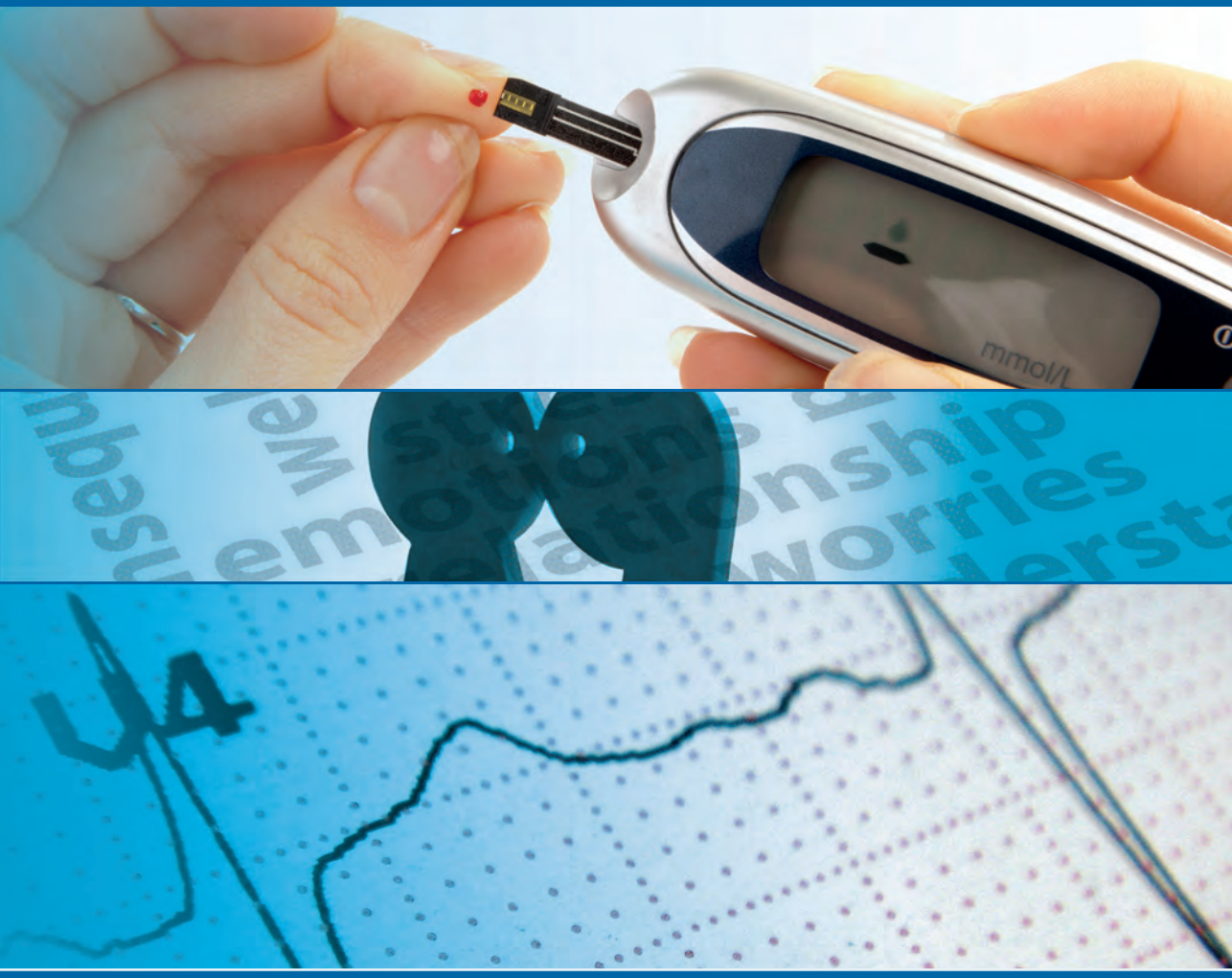
Opportunistic targeted screening for type 2 diabetes in primary care

The Diabscreen study



Erwin P. Klein Woolthuis

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Colophon

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Contents

1

General introduction

Scope of this thesis

This thesis aims to provide insight in a specific approach of screening for type 2 diabetes: opportunistic targeted screening in primary care. This method entails screening in asymptomatic individuals at high risk for undiagnosed type 2 diabetes during regular healthcare consultations. This approach is particularly attractive in general practice, where information is available of individuals' medical and family history, and other personal circumstances to identify risk status. There are strong indications that integrating screening and prevention in regular (primary) healthcare is effective and efficient. In the study reported in this thesis – the Diabscreen study – the information to assess risk for type 2 diabetes was drawn from the general practitioner's (GP) electronic medical record (EMR). Risk information is already available in an EMR, and may be more accurate and complete compared to data obtained from a questionnaire. And with continuity of care in general practice, the GP's EMR might be an attractive, inviting tool for a systematic and repeated identification of high-risk patients in opportunistic screening.

In this chapter, type 2 diabetes and the key issues of screening for type 2 diabetes are introduced. Subsequently, the main screening approaches are described, and the Diabscreen study is briefly explained. Finally, the objectives of this thesis are listed, followed by an outline of the chapters.

Type 2 diabetes

Diabetes mellitus is a metabolic disorder primarily defined by chronic hyperglycemia, giving rise to risk of microvascular complications (diabetic retinopathy, nephropathy and neuropathy). It is also associated with reduced life expectancy, mainly due to an increased risk of macrovascular complications (cardiovascular disease [CVD], for example ischemic heart disease, stroke and peripheral arterial disease), and with diminished quality of life.[1,2]

The classification of diabetes is based on etiological types. In 90% of the cases, patients have type 2 diabetes. This type results from a progressive insulin secretory defect in the pancreas' beta-cells on the background of insulin resistance.[3] Type 2 diabetes is characterized by a long preclinical (asymptomatic) period of up to 12 years,[4] and one third to one half of all people with type 2 diabetes may remain undiagnosed all these years.[5-7] By the time of clinical diagnosis, when patients present with signs or symptoms of hyperglycemia (eg, polyuria and polydipsia), many already have developed complications.[4,8-10] The prevalence of type 2 diabetes is rising globally, mainly due to ageing and an increase of overweight and obese people.

The number of adults with type 2 diabetes is expected to double in the next decades, which will dramatically increase the burden of disease and healthcare costs.[11-13]

Screening for type 2 diabetes

Glycemic control and cardiovascular risk management (mainly treatment of hypertension and hypercholesterolemia) have been proven to decrease microvascular and macrovascular disease and mortality in patients with clinically diagnosed type 2 diabetes.[14-16] And there is some evidence that lifestyle and pharmacotherapeutic interventions can prevent or slow the progression from prediabetes – impaired fasting glucose and impaired glucose tolerance – to diabetes and reduce the risk of CVD.[14,15]

Type 2 diabetes appears to meet the suitability criteria (or principles) for screening, determined by Wilson and Jungner for the World Health Organization in 1968 (Table 1): the disease is an important health problem (item 1); depending on access to healthcare, type 2 diabetes can be easily diagnosed and treated, and treatment seems effective (items 2, 3 and 8); its natural history is well understood, with a long preclinical stage during which it can be detected (items 4 and 7); suitable screening tests exist and the psychological impact on patients of screening appears to be limited (items 5 and 6); health economic models have shown that certain screening strategies can be cost-effective (item 9); and, especially in primary healthcare settings, testing for diabetes can be repeated easily (item 10).[14,17-24]

At present, however, no direct evidence is available from long-term studies, in particular randomized controlled trials (RCTs), to show that treatment of patients with type 2 diabetes detected through screening results in lower vascular event rates when compared with treatment of patients diagnosed by clinical signs or symptoms.[14,15] In addition, it is unclear whether the economic cost of screening can be justified. And there is no consensus on which screening test to use, which diagnostic cut-off points are best, and what the optimal screening interval is.[18,19]

These considerations notwithstanding, screening for diabetes is encouraged nowadays. But without evidence of a direct benefit of routine population-based screening for type 2 diabetes, it is urged to target individuals at high (vascular) risk.[19,20,25] This includes (1) high risk of undiagnosed type 2 diabetes, for example persons with obesity or a family history of diabetes, or people from a high-risk ethnical group; (2) high risk for CVD, for example patients with hypertension or hypercholesterolemia; (3) established CVD, for appropriate disease management. Screening costs will be lower with targeted screening, whereas there is a relatively

Table 1 Principles of early disease detection by Wilson and Jungner (1968)[17]

1.	The condition sought should be an important health problem;
2.	There should be an accepted treatment for patients with recognized disease;
3.	Facilities for diagnosis and treatment should be available;
4.	There should be a latent or early symptomatic stage;
5.	There should be a suitable test or examination;
6.	The test should be acceptable to the population;
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood;
8.	There should be an agreed policy on who to treat as patients;
9.	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
10.	Case finding should be a continuing process and not a 'once and for all' project.

clear potential health benefit. While most clinical guidelines now recommend screening for type 2 diabetes in high-risk groups,[26-29] there is, however, no standardized screening approach.

Screening approaches

There are basically two main approaches to screen for type 2 diabetes: population-based screening or opportunistic screening.[17,18,24,30,31] Both population-based and opportunistic screening can be performed in a subgroup of high-risk persons (targeted or selective screening).[31] Occasionally, individuals may be invited to be screened in a public place, for example in a supermarket, also called haphazard screening, but with a low diabetes prevalence and no support for follow-up, this is both inefficient and inadequate.[30] This also applies to the wide variety of glucose tests that are offered online nowadays.[24]

Population-based screening

Population-based screening was originally directed at an entire population, offering blood glucose testing to every (adult) individual (known as 'universal screening'). Earlier epidemiological studies have used this design to assess diabetes prevalence,[5,32] and so have early clinical screening studies.[33] But due to a low prevalence of diabetes in most populations, universal screening is usually costly and inefficient.

Recent population-based screening programmes have used a stepwise approach to target high-risk individuals. They were identified by means of a questionnaire or simple risk score that was sent to the patient's home, followed by an invitation for blood glucose testing.[34,35] In another study, GPs selected all overweight or obese patients older than 50 years using the EMR, and invited them to screening clinics.[36] Population-based screening has the advantage that it is mathematically precise, readily reproducible, and can operate largely independent of the clinicians' skills.[31] But selecting and inviting participants may also be expensive, time-consuming and have a low yield.[18,37]

Opportunistic (targeted) screening

Opportunistic screening is a form of case finding which involves screening individuals during routine healthcare encounters, usually primary care visits.[18,30,31,38,39] In opportunistic screening it is the patient who makes the appointment, for a reason other than the condition for which screening is offered. This approach is different from screening programmes in which the invitation to come forward and be screened is part of the programme.[30] Opportunistic screening has several advantages. It is not expensive because it requires fewer resources to conduct screening tests and to perform follow-ups, and when performed in a familiar healthcare setting it gives high acceptance rates and repeated opportunities to screen. A primary care setting has also the risk factor information needed for targeted screening. On the other hand, it may have poor coverage since it depends on the patients consulting for some reason, and on the clinical alertness of the doctors or practice nurses. Sometimes it may be inappropriate to offer screening during a consultation. And there is a tendency that some people get too many tests too often, whereas others get too few tests too infrequently.[18,31] Earlier, opportunistic screening in general practice using a screening questionnaire to target high-risk groups was feasible and had a high participation rate.[40] Opportunistic targeted screening using clinical risk factor information from the EMR may be a more efficient and continuous method of detecting undiagnosed type 2 diabetes during usual primary healthcare. This screening approach has been investigated in the Diabscreen study.

The Diabscreen study

The Diabscreen study was an opportunistic targeted screening programme embedded in daily routine care in general practices in the Netherlands, and consisted of a stepwise screening procedure: (1) identification of high-risk and low-risk individuals using the EMR; (2) one and if indicated a second capillary

fasting plasma glucose (FPG) measurement; and (3) if indicated, a venous FPG. Using a computerized cross-sectional analysis of diabetes risk factor information for each patient from the practices' EMR, the patient's risk for undiagnosed diabetes (high or low risk) was marked in the EMR.

During a usual care consultation in the following year, the EMR reminded the GP to verify and, in the case of missing data, complete the patients' risk profile and to invite high-risk patients for an FPG measurement. The study setup and results are described in detail in *Chapters 2, 3* and *4*.

The partner's perspective

Not just the patient but also family members, in particular the partner, play an important role in type 2 diabetes.[41,42] As in other chronic diseases, in type 2 diabetes self-management is essential.[43] Patients need to exercise and follow a diet, have to take medications and sometimes require insulin injections.[26,27,29,44] These self-care behaviours are influenced by both patients' and partners' beliefs – so-called illness perceptions – regarding type 2 diabetes, which are associated with health outcomes.[45,46] In diabetes education and treatment, interventions that target differences in illness perceptions between patients and their partners have been advocated.[47]

Although the psychological impact of a screening-based diagnosis of type 2 diabetes on patients is generally limited,[21] the route to diagnosis of diabetes – by screening in asymptomatic individuals or by clinical signs or symptoms – may affect the illness perceptions of patients and their partners. It may thus be an important factor to consider in diabetes education programmes.

Long-term effectiveness of screening

The effectiveness of screening for type 2 diabetes and early treatment after diagnosis should preferably be estimated by an RCT. Such a trial should contain a control group of individuals who meet the criteria for screening but who do not receive it, thus truly comparing 'screened' with 'not screened' patients. This however appears to be both unethical and unachievable in clinical practice, so at present, no direct supportive evidence for the effectiveness of screening exists.[14,15] Alternatively, an observational study may be used to assess whether treatment of patients with type 2 diabetes detected through screening results in lower vascular event rates when compared with treatment of patients diagnosed by clinical signs or symptoms. Such an approach may be feasible and acceptable in general practice.

Objectives

The first objective of this thesis was to evaluate the feasibility and yield of opportunistic targeted screening in primary care.

Secondly, to address the partner's perspective of screening, this thesis aimed to investigate how the route to diagnosis of type 2 diabetes – through screening or by clinical signs or symptoms – affects illness perceptions in families, particularly in patients and their partners.

The third objective was to assess the effectiveness on long-term vascular outcomes of opportunistic targeted screening for type 2 diabetes, compared with a clinical diagnosis.

Outline of this thesis

Chapters 2, 3, 4 and *5* are about the feasibility and yield of opportunistic targeted screening. In *Chapter 2* the value of the GP's EMR in identifying patients at risk for undiagnosed type 2 diabetes and the feasibility to use this information in usual care to initiate screening are assessed. In *Chapter 3* the stepwise protocol of opportunistic targeted screening is evaluated. In *Chapter 4* the yield of opportunistic targeted screening is assessed and the diagnostic value of various risk factors is investigated. And *Chapter 5* contains a comment on a modelling study which investigated the cost-effectiveness of screening for type 2 diabetes.

Chapter 6 focuses on the partner's perspective of screening. In this chapter data from screen-detected type 2 diabetes patients and their partners are compared with data from patients and their partners after a clinical diagnosis.

Chapters 7 and *8* are about the long-term effectiveness of screening. In *Chapter 7* it is assessed whether opportunistic targeted screening results in lower long-term vascular event rates compared with diagnosis on the basis of clinical signs or symptoms. *Chapter 8* contains the response to a comment on the publication presented in the previous chapter.

And finally, in *Chapter 9*, the main findings of this thesis are summarized and reflected on. The main methodological issues of the studies and the ongoing screening debate are discussed. The chapter ends with clinical implications, recommendations for future research, and five key messages.

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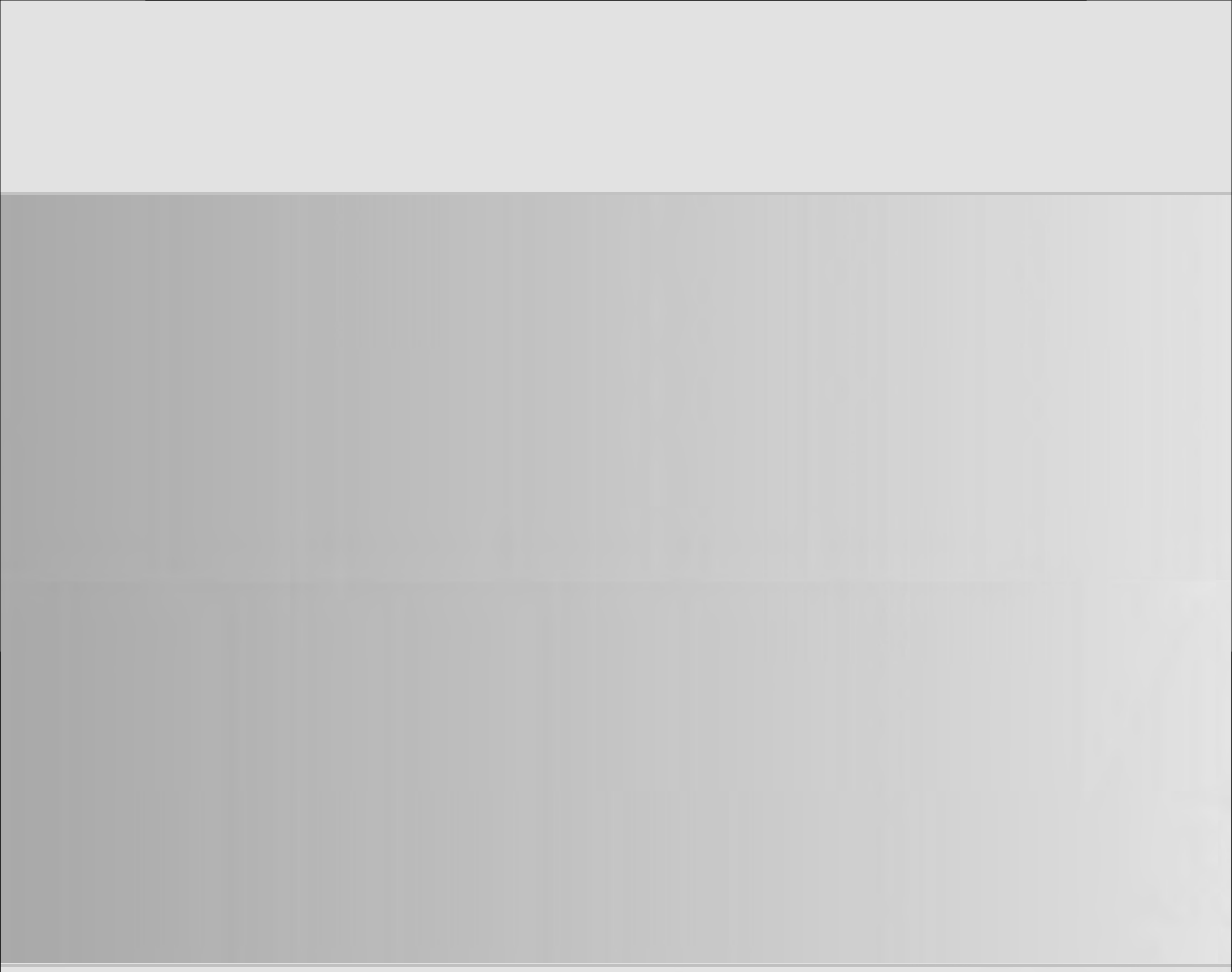
Feasibility and yield



2

Identifying people at risk for undiagnosed type 2 diabetes using the GP's electronic medical record

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Abstract

Background Screening for type 2 diabetes is recommended in at-risk patients. The general practitioner's (GP) electronic medical record (EMR) might be an attractive tool for identifying them.

Objective To assess the value of the GP's EMR in identifying patients at risk for undiagnosed type 2 diabetes and the feasibility to use this information in usual care to initiate screening.

Methods In 11 Dutch general practices (25 GPs), we performed an EMR-derived risk assessment in all patients aged 45 to 75 years, without known diabetes, identifying those at risk according to the American Diabetes Association recommendations. Patients with an EMR-derived risk or risk after additional risk assessment during regular consultation were invited for capillary fasting plasma glucose (FPG) measurement.

Results Of 13,581 patients, 3,858 (28%) had an EMR-based risk (hypertension, cardiovascular disease, lipid metabolism disorders and/or obesity). Additional risk assessment in those without an EMR-based risk showed that in 51%, greater than one risk factor was present, mainly family history (51.2%) and obesity (59%). Ninety per cent returned for the FPG measurement. In both groups, we found patients with an FPG exceeding the cut point for diabetes (5.9% versus 4.1%).

Conclusions With additional risk assessment during consultation, the GP's EMR was valuable in identifying patients at risk for undiagnosed type 2 diabetes. It was feasible to use this information to initiate screening. At-risk patients were willing to take part in screening. Better registration of family history and obesity will improve the EMR as a tool for identifying at-risk patients in opportunistic screening in general practice.

Introduction

Main reason to urge for screening for type 2 diabetes mellitus is the long preclinical period of diabetes. One-third to half of all people with diabetes remain undiagnosed for many years. In the meantime, complications already begin to develop.[1] Starting treating patients with type 2 diabetes at an earlier stage might prevent or delay the development of complications.[2] However, at this moment, no evidence is available for the effectiveness of screening programmes in reducing diabetes-related morbidity and mortality. There is also little knowledge about the ethical, psychological, and social consequences of both true and false screening results, and there is no consensus on the applied screening test and diagnostic cut off points.[3,4]

Notwithstanding these considerations, nowadays screening for type 2 diabetes is encouraged. It is recommended to perform screening in a subgroup of patients at risk for undiagnosed type 2 diabetes.[5-8] As screening should also be a systematic and continuous process,[3] opportunistic screening of such at-risk patients might be an interesting screening method in general practice. This involves screening of at-risk individuals during usual care, who are seen by health care professionals for reasons not related to the condition for which screening is offered.[9] At-risk patients can be identified using questionnaires or risk scores.[10-12] A pragmatic approach might be assessing risk using risk factors for undiagnosed type 2 diabetes that are already registered in the medical records of the general practitioner (GP).

Relevant medical informations like diagnoses, medication use and referrals are available in the GP's medical record system, nowadays often computerized. If GPs are well trained and software is user-friendly, an electronic medical record (EMR) can be accurate and complete.[13] The GP's EMR might therefore be an attractive, inviting tool for identifying at-risk patients in opportunistic screening.

The aim of this study was to assess the value of the GP's EMR in identifying people at risk for undiagnosed type 2 diabetes and the feasibility to use this information in usual care to initiate screening.

Methods

Patients and setting

Patients were recruited from 11 general practices (25 GPs) in the Netherlands: seven of these practices were participating in the Academic Research Network of the Department of General Practice of the Radboud University Nijmegen Medical Centre, CMR/NMP,[14] two in the Registration Network Family Practices of the University Maastricht (RNH)[15] and two practices were related to the network of the VU University Medical Center Amsterdam.[16] All patients aged ≥45 and ≤75 years

and not known with type 2 diabetes who were listed with these practices were considered for the study. Diabetes – both known and undiagnosed – was defined as having a fasting plasma glucose (FPG) ≥7.0 mmol/l on two different days in asymptomatic patients or a single random plasma glucose >11.0 mmol/l in patients with diabetes related symptoms. Impaired fasting glucose (IFG) was classified as having a single FPG value ≥6.0 mmol/l and <7.0 mmol/l.[17,18]

All practices used the Promedico EMR software (Promedico ICT Inc., Nieuwegein, the Netherlands). Registration of diagnoses was based on the electronic version of the International Classification of Primary Care (ICPC codes).[19] Prescribed medication was coded according to the Anatomical Therapeutic Chemical classification system (ATC codes).[20] This study is part of an opportunistic screening programme for type 2 diabetes in general practice – the Diabscreen study.

Methods

People were considered to be at risk for undiagnosed type 2 diabetes when having one or more of the following diabetes risk factors, derived from the American Diabetes Association's (ADA) recommendations in screening for type 2 diabetes: a family history of diabetes (parent and/or brother and/or sister with diabetes), hypertension, cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, stroke, peripheral vascular disease), lipid metabolism disorders, obesity (body mass index [BMI] >27), and a history of gestational diabetes mellitus (GDM).[6] We translated these risk factors into a set of matching ICPC and ATC codes (Table 1).

Family history of diabetes and a history of GDM were not consistently coded in the EMR by the GPs and could therefore not be used in this list. At the time of study, no medication was registered to treat obesity and therefore an ATC code was not yet available. Almost all patients were Caucasian, so ethnicity was in this study not used as a risk factor. Having children with a birth weight more than 4,000 g was left out as it was not registered. An EMR-derived risk assessment was conducted to identify the patients with ICPC and/or ATC codes mentioned in Table 1. For this purpose, we had developed software that enabled us to extract ICPC and ATC information of each patient from the practices' EMR and to analyse these data anonymously at the university department.

When ATC but no ICPC codes for cardiovascular disease and hypertension were present, the patients' own GPs were asked to check clinical information in the EMR. In case medication matching these codes had been prescribed for other conditions than cardiovascular disease or hypertension, this was considered not a diabetes risk factor.

Table 1 Selection codes matching diabetes risk factors

	Diagnoses (ICPC codes)	Medication (ATC codes)
Hypertension	Elevated blood pressure (K85) Hypertension, complicated (K86) Hypertension, uncomplicated (K87)	Diuretics (C03) Beta blockers (C07) Calcium channel blockers (C08) Angiotensin-converting enzyme inhibitors (C09) Angiotensin II receptor blockers (C09)
Cardiovascular disease	Ischaemic heart disease with angina (K74) Acute myocardial infarction (K75) Ischaemic heart disease without angina (K76) Heart failure (K77) Atrial fibrillation/flutter (K78) Transient cerebral ischaemia (K89) Stroke/cerebrovascular accident (K90) Cerebrovascular disease (K91) Atherosclerosis/peripheral vascular disease (K92)	Anticoagulants (B01) Platelet aggregation inhibitors (B01) Cardiac glycosides (C01) Antiarrhythmics (C01) Nitrates (C01)
Lipid metabolism disorders	Lipid disorder (T93)	Serum lipid reducing agents (C10)
Obesity	Obesity (BMI >30 kg/m^2) (T82) Overweight (BMI 27-30 kg/m^2) (T83)	NA

The EMR-derived risk status (risk/no risk) was then marked in the EMR with an alert to trigger GPs when patients visited the practice for usual care during the following year. GPs were asked to initiate FPG measurement in at-risk patients. For patients without risk factors, the GPs needed to verify the EMR risk profile by checking and in case of missing data completing risk factors coded in the EMR (hypertension, cardiovascular disease, lipid metabolism disorders and obesity) and checking risk factors not coded in the EMR (family history of diabetes and a history of GDM). In case this additional risk assessment revealed risk, the patient was invited by the GP for FPG measurement similar to patients with an EMR-derived risk. FPG measurement was conducted in the patients' own general practice by their own practice assistant. In all participating practices, a Gluco Touch® (LifeScan Beerse [Belgium; LifeScan Benelux]) plasma calibrated capillary blood glucose meter was used. Prior to the start of the study, all meters were checked and adjusted if necessary by its manufacturer.

The practice assistants were trained in using the meters. Patients with a screening FPG >6.0 mmol/l (the cut point for IFG as earlier defined) were followed up for

further diagnostic testing according to the earlier described definition. The two-step screening strategy we used is topic of a separate publication.

Statistical tests

Statistical analysis was performed using the chi-square test for categorical data and the Student's *t*-test or Kruskal-Wallis test for means where appropriate. Data were analysed by means of the SAS 8.0 software package.

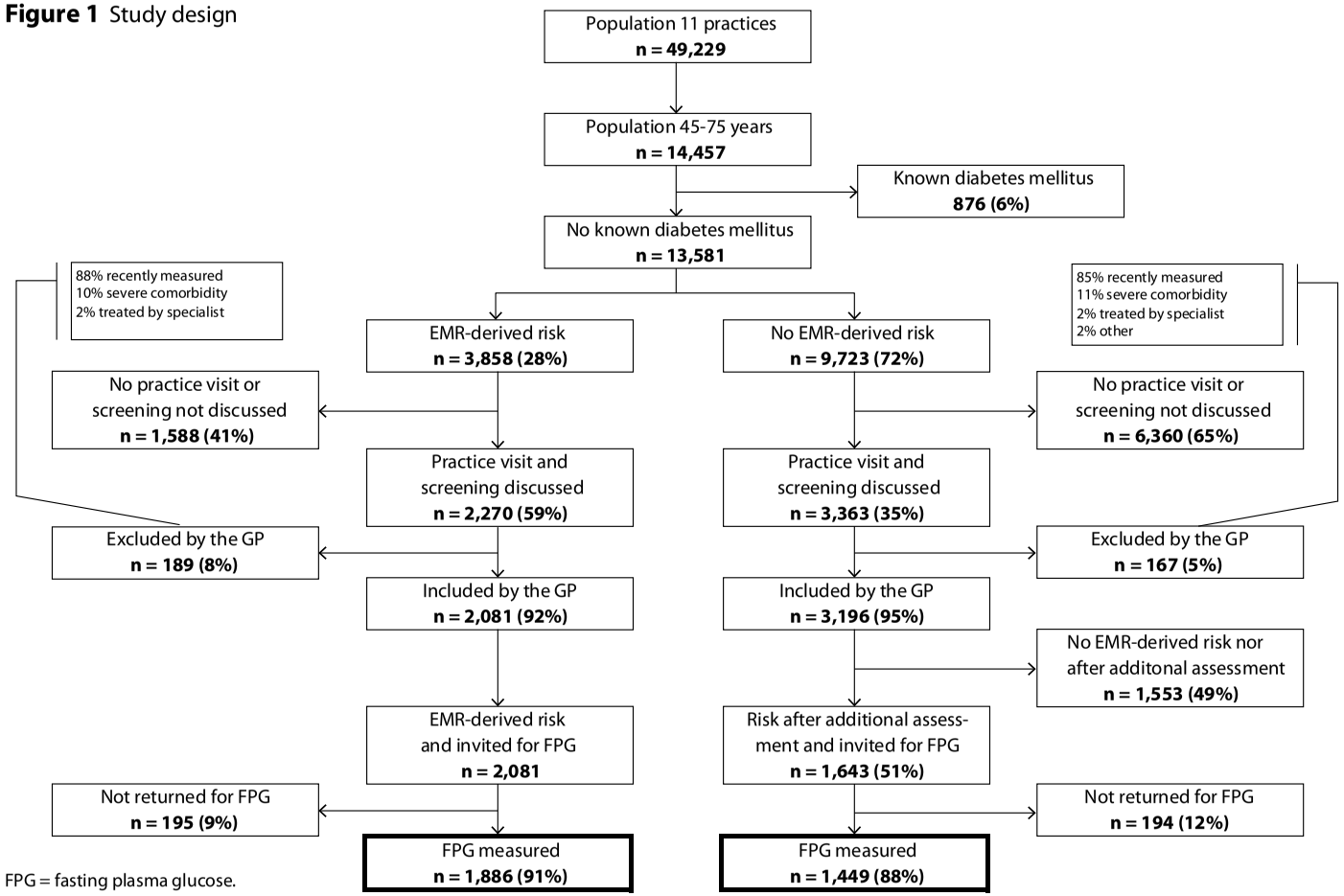
Results

In the 11 participating practices, 49,229 patients were registered, of whom 14,457 were aged ≥45 and ≤75 years. In 876 (6%) patients, diabetes mellitus had already been diagnosed, leaving 13,581 patients for the study (Figure 1). EMR-derived risk assessment identified 3,858 (28%) at-risk patients leaving 9,723 (72%) patients without an EMR-derived risk. Characteristics of patients with and without an EMR-derived risk and patients already diagnosed with diabetes are shown in Table 2. No significant difference in sex was found between the three groups. Patients with known diabetes were older than patients with an EMR-derived risk (mean age 61.4 versus 60.5 years), who in turn were older than those without an EMR-derived risk (mean age 60.5 versus 55.2 years). Younger patients were less likely to be at risk than older patients. We found little interpractice variation. For example, Table 2 shows little interpractice variation concerning mean age.

Table 2 Baseline characteristics of the study subgroups and known diabetes mellitus

	EMR-derived risk *n* = 3,858	**No EMR-derived risk** *n* = 9,723	**Known diabetes mellitus** *n* = 876	*P*
Sex (% male)	48.6	49.3	49.2	NS
Mean age, years (95% CI)	60.5 (60.2-60.8)	55.2 (55.0-55.3)	61.4 (60.9-61.9)	<0.0001
Interpractice variation in mean age (years)	57-63	52-57	57-64	–
45-55 years (%)	17.1	79.7	3.2	<0.0001
55-65 years (%)	31.3	61.0	7.7	
65-75 years (%)	44.0	45.2	10.8	

Figure 1 Study design



FPG = fasting plasma glucose.

EMR-derived risk

In the course of 1 year, the GPs succeeded in bringing up and discussing screening during consultation in 2,270 (59%) of the patients with an EMR-derived risk (Figure 1). Of them, 2,081 (92%) could be included for the study (reasons for exclusion mentioned in Figure 1). We found a risk factor prevalence of 42.4% for hypertension, 25.6% for cardiovascular disease, 16.5% for lipid metabolism disorders and 30.0% for obesity. All 2,081 patients were invited for FPG measurement.

At risk after additional risk assessment

In 3,363 (35%) of the patients without an EMR-derived risk, screening was discussed during consultation (Figure 1). Of them, 3,196 (95%) could be included for the study. Additional risk assessment showed that in 1,643 (51%) at least one risk factor for diabetes was present. In particular, family history of diabetes and obesity were found as a source of missing data: the prevalence after checking was 51.2% (family history), 59.0% (obesity) and 1.0% (history of GDM). All 1,643 patients at risk after additional risk assessment were then invited for an FPG measurement.

FPG measurement

In total, 1,886 patients with an EMR-derived risk (91%) and 1,449 patients at risk after additional risk assessment (88%) returned for an FPG measurement. See Figure 1 and Table 3. Patients of the first group were more often male (44.2% versus 39.9%) and older (mean age 60.3 versus 55.6 years) than patients of the latter group. In both groups, we found patients with an FPG exceeding the cut point for IFG

Table 3 Sex, mean age and mean FPG and percentage of patients with FPG values exceeding IFG or diabetes cut points (bold printed border in Figure 1)

	EMR-derived risk and FPG measured ***n* = 1,886**	**At risk after additional risk assessment and FPG measured** ***n* = 1,449**	***P***
Sex (% male)	44.2	39.9	<0.05
Mean age, years (95% CI)	60.3 (59.9-60.6)	55.6 (55.2-56.0)	<0.0001
Mean FPG, mmol/l (95% CI)	5.6 (5.5-5.6)	5.4 (5.4-5.5)	<0.001
FPG 6.1-7.0 mmol/l (%)	13.5	9.6	–
FPG ≥7.0 mmol/l (%)	5.9	4.1	–

FPG = fasting plasma glucose; IFG = impaired fasting glucose.

(13.5% versus 9.6%) and diabetes (5.9% versus 4.1%). Patients with an EMR-derived risk had a slightly higher mean FPG (5.6 versus 5.4 mmol/l).

Discussion

Summary of main findings

Identifying people at risk for undiagnosed type 2 diabetes mellitus using the medical data stored in the GP's EMR could be achieved during daily routine practice, without any further support, e.g. from trial nurses. Of the population aged ≥45 and ≤75 years and not known with diabetes, 28% had an EMR-derived risk. Of the remaining 72% without an EMR-derived risk, 51% were also found to be at risk after additional risk assessment during usual care. So, in total, about 65% of the study population were at risk.

The diabetes risk factors hypertension, cardiovascular disease and lipid metabolism disorders were well registered in the EMR and could easily be retrieved. Hypertension and cardiovascular disease accounted for 62% of the number at risk. In particular obesity and a family history of diabetes were poorly registered, and were mainly retrieved with additional risk assessment during consultation.
Although patients had to return in a fasting state for the FPG measurement, they were highly willing to do so. Ninety per cent of patients who were invited returned for the measurement.

In both risk groups (EMR-derived and additional risk assessment) we found patients with an FPG value exceeding the cut point of both IFG and diabetes mellitus. Their mean FPG values were about equal. So, EMR-derived and additional risk assessment followed by screening in at-risk patients from both groups seems worthwhile.

Strengths and limitations of the study

As mentioned earlier, screening should be performed systematically and continuously. This important condition can be fulfilled if one uses the GP's EMR combined with an EMR generated alert, as applied in our study. In order to include possible new at-risk patients, identification and labelling of people at risk for undiagnosed type 2 diabetes should be repeated by running the EMR risk extraction software, for example every 3 years.

In 1 year, the GP succeeded in bringing up and discussing screening during consultation in about 60% of patients with an EMR-derived risk, and in 35% of those without an EMR-derived risk. As this screening method could be used continuously, it is estimated that within a period of 3 years, all patients, especially those at risk, would have visited their GP. This equals the 3-year interval recommended by the

ADA in screening for type 2 diabetes. The higher enrolment of patients for screening from the group identified by the EMR might be caused by the fact that, especially in the beginning of the study, GPs were focused on screening within patients with risk factors registered in the EMR. It may also indicate the user-friendliness of such approach. Their risk was clear and discussing screening took less time than additional risk assessment as was done in the second group. Furthermore, the fact that one or more risk factors were recorded in the EMR reflected that co-morbidity was present. Such patients usually visit the GP more often, increasing the possibility to discuss the need for screening.

All participating general practices were related to a university department of general practice, which might have positively influenced adherence to protocol. Nevertheless, they were all standard community practices with a population representative of the Dutch population and a diabetes prevalence equal to that in the Netherlands.[14-16,21] And although we found that some GPs recruited better than others, overall we found little interpractice variation. The fact that the Dutch system of primary care provides for universal access and continuity of patient registration enabled us to use the GP's EMR in a continuous screening programme. In countries with a different health care system, our screening approach might therefore be less feasible.

Cross-checking of medication information by the patients' GPs was necessary to improve validation, but was time consuming. When clinical information (ICPC) in the future is more complete, this would not be necessary anymore, as risk then can be reliably assessed merely on the basis of clinical information.

To screen for type 2 diabetes, we used the FPG test rather than the oral glucose tolerance test (OGTT). The OGTT consists of an FPG and 2-hour plasma glucose value and has been considered as the gold standard test in diagnosing diabetes. The FPG test is nevertheless recommended for screening in clinical settings as it is easier and faster to perform, more convenient and acceptable to patients and less expensive.[6,22]

The portable glucose meters we used are user-friendly and readily available in general practice. A potential set back is their variability,[23] and consequent risk of false-positive and false-negative outcomes. This study was directed at the analysis of identification of at-risk patients and reviewed a single testing. The two-step approach, in which patients with glucose levels above the threshold were measured again, did address the problems of false positives. To take care of false-negative results, the procedure must be repeated – something that is beyond the scope of this paper, but feasible in daily care.

Comparison with existing literature

In literature, several methods for identifying at-risk patients have been described. Smith *et al.*[24] described an opportunistic diabetes screening study performed in general practice using a questionnaire presented to patients while waiting to see their doctor. Participation rate was also high (93%) and 43% had at least two risk factors. If performed continuously or repeated regularly, such a method might help improving quality of the EMR in a continuous screening programme.

Greaves *et al.*[25] showed that identifying patients with type 2 diabetes and IFG using data stored in the GP's databases was feasible. Screening of patients with a BMI ≥27 and aged >50 by fasting glucose identified a substantial prevalence of undetected type 2 diabetes and IFG. But instead of an opportunistic approach, they invited at-risk patients to screening clinics run by trained practice nurses, and other risk factors like family history of diabetes or hypertension were not considered. Nevertheless, the simple screening system they describe – like ours – would promote an efficient use of scarce primary care resources especially when part of a broader cardiovascular disease reducing screening programme.

Other studies concerning screening for type 2 diabetes mainly used questionnaires or risk scores to identify at-risk patients, instead of data already present in the EMR.[10-12]

Implications for clinical practice and future research

Although it was feasible to use the EMR in diabetes screening, it was not valuable without additional risk assessment and updating risk information during consultation. Jordan *et al.*[26] concluded in a recent systematic review concerning morbidity coding in the GP's EMR that a high quality of coding can be achieved, although it is not yet clear which methods can encourage and help GPs to improve quality of coding.

Our study showed that 65% of the population consulting the GP were at risk when applying the current ADA recommendations. About the same figure (70%) was found in the US National Health and Nutrition Examination Survey.[1] Although high percentages, we would not recommend screening all middle-aged people, for example, considering the possible consequences of falsely positive test results, the burden of invasive blood testing and costs of screening tests. Our figures showed that 62% of those at risk have either hypertension or cardiovascular disease. The US Preventive Services Task Force recommendations stress that patients at increased risk for cardiovascular disease may benefit most from screening for type 2 diabetes. Diabetes screening should be part of an integrated approach to reduce cardiovascular risk.[5-8] If FPG measuring would be a structural part of care in all patients with cardiovascular morbidity and hypertension, the number of at-risk patients to be screened would be considerably reduced. This emphasizes the

importance of a systematic registration of overweight/obesity and family history of diabetes in primary care databases.

Conclusion

The GP's EMR is an attractive tool for identifying at-risk patients to initiate screening during usual care. With additional risk assessment during consultation, the GP's EMR was valuable in identifying patients at risk for undiagnosed type 2 diabetes. It was feasible to use this information to initiate opportunistic screening. Patients found to be at risk were highly willing to take part in screening.

Better registration of family history of diabetes and obesity will improve the EMR as a tool for identifying at-risk patients in opportunistic screening in general practice.

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Declaration

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Ethical approval

Ethical approval was obtained from the Helsinki declaration.

Conflicts of interests

None.

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3

Screening for type 2 diabetes in primary care using a stepwise protocol: the Diabscreen study

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Abstract

Aim To evaluate a stepwise protocol in opportunistic screening for type 2 diabetes.

Methods From 2000 to 2001, in 11 Dutch general practices (*n* = 49,229) we invited at-risk patients during usual care for a capillary fasting plasma glucose (cFPG1) measurement. If >6.0 mmol/l, a second sample (cFPG2) was taken on another day, followed by a venous sample (vFPG) if cFPG2 >6.0 mmol/l ánd cFPG1 or 2 ≥7.0 mmol/l.

Results Of 3,724 at-risk patients invited for a cFPG1, 3,335 (90%) returned for the measurement. Ultimately, in 125 (4%) of them a vFPG was measured. In 101 out of 125 patients the vFPG was ≥7.0 mmol/l, giving a positive predictive value of our protocol of 81%.

Conclusion A stepwise screening protocol including two subsequent capillary blood glucose measurements from a portable blood glucose meter is well applicable in screening for type 2 diabetes in primary care.

Introduction

The fasting plasma glucose (FPG) test is an interesting and pragmatic tool for screening for type 2 diabetes in primary care, especially when measured in capillary whole blood using a portable blood glucose meter.[1-5] As the day-to-day variability of FPG is about 15%,[6] in asymptomatic subjects the diagnosis of diabetes should only be made after confirmation by a second test on a subsequent day.[7,8] However, while portable meters are accurate enough for (self-)monitoring of blood glucose,[9-11] its use in screening is only accepted if followed by a venous measurement.[3,5] Therefore a stepwise screening strategy might improve the validation of the portable blood glucose meter.

The aim of this study was to evaluate the applicability (positive predictive value) of a stepwise protocol in opportunistic screening for type 2 diabetes in primary care using a portable blood glucose meter.

Methods

The present study is part of an opportunistic screening programme for type 2 diabetes in primary care – the Diabscreen study. Patients were recruited from 11 general practices (total practice population n = 49,229) in the Netherlands.[12-14] All patients at risk for undiagnosed type 2 diabetes, aged ≥45 and ≤75 years, who were listed with these practices were considered for the study. At-risk was defined as having one or more diabetes risk factors, derived from the American Diabetes Association's recommendations in screening for type 2 diabetes: a family history of diabetes (parent and/or brother and/or sister with diabetes), hypertension, cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, stroke, peripheral vascular disease), lipid metabolism disorders, obesity (BMI >27), and a history of gestational diabetes mellitus (GDM).[3] As described in detail elsewhere, we translated these risk factors into a set of matching ICPC and ATC codes. This enabled us to mark the patients' risk status (risk/no risk) in the electronic medical record.[15] From 2000 to 2001, the GPs verified and in case of missing data completed the patients' risk profile during usual care. At-risk patients were invited for a capillary FPG measurement.

Samples were taken from capillary whole blood using a Gluco Touch® (LifeScan Benelux, Beerse, Belgium) plasma calibrated portable blood glucose meter.

Patients were suspected for having undiagnosed type 2 diabetes when having a capillary FPG >6.0 mmol/l (110 mg/dl; the cut point for impaired fasting glucose (IFG)) on two separate days, with at least one of these values being ≥7.0 mmol/l (126 mg/dl; the cut-off value for diabetes).[7]

For that reason, all patients with an initial value >6.0 mmol/l were invited for a second capillary measurement (cFPG2). This was immediately followed by a venous sample (vFPG) if at least one of the capillary measurements was ≥7.0 mmol/l.

This sample was sent to a central laboratory for further analysis in a Roche/Hitachi analyzer using the glucose oxidase method (the reference method). For the present study, we included those patients (n = 125) who completed the screening protocol (cFPG1, cFPG2 and vFPG).

Data were analyzed with SPSS 14.0.2 for Windows (SPSS Inc., Chicago, IL, USA). To compare the performance of the portable blood glucose meter to the reference method, we calculated the correlation coefficient and the limits of agreement as described by Bland and Altman.[16] As a main outcome, we calculated the positive predictive value of our screening protocol.

Results

In the 11 participating practices, 49,229 patients were registered, of whom 14,457 were aged ≥45 and ≤75 years. In 876 (6%) patients, diabetes mellitus had already been diagnosed, leaving 13,581 patients for the study. During usual care, the participating GPs were able to invite 3,724 at-risk patients for further screening by means of FPG measurement (Figure 1). Of those invited, 3,335 (90%) returned for the cFPG1 measurement and entered the stepwise screening protocol. Their baseline characteristics are shown in Table 1. In 496 (13%) patients a cFPG2 and in 125 (4%) a vFPG was performed according to the stepwise protocol.

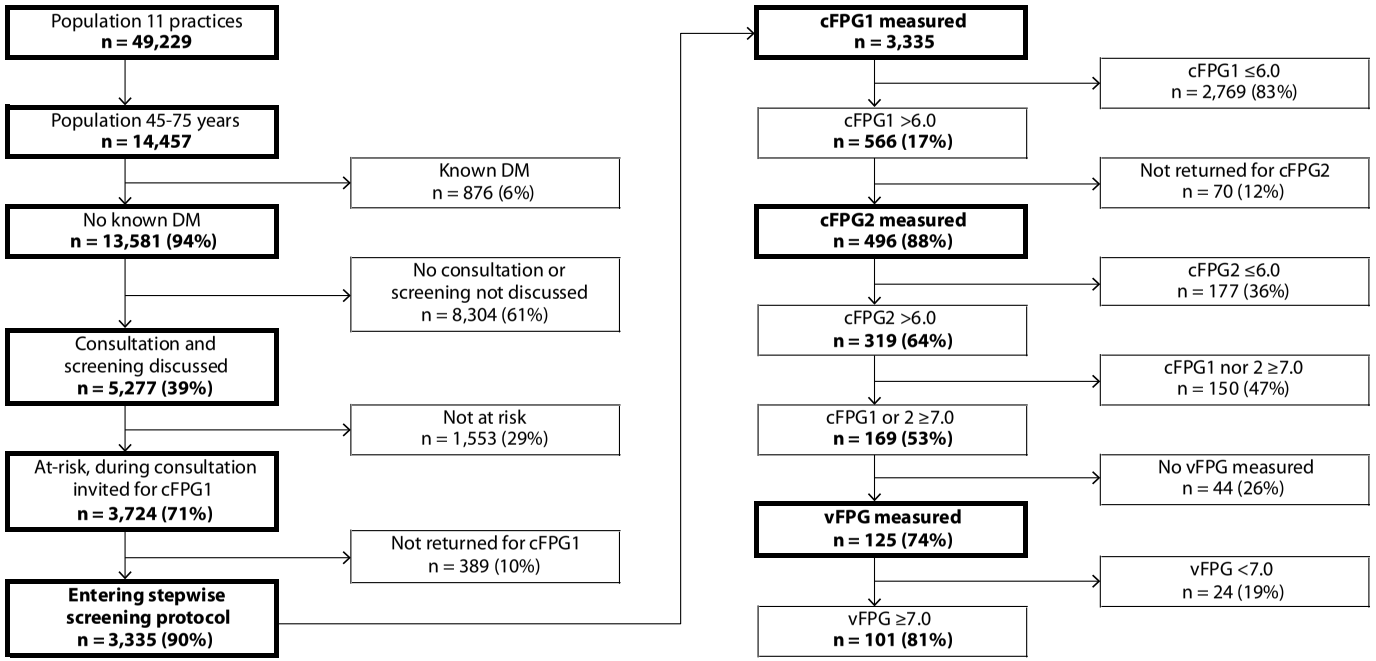
So, as shown in Figure 1, 125 patients completed the stepwise protocol and had three measurements taken (cFPG1, cFPG2 and vFPG). Fifty-seven patients (46%) were male, mean age was 58.8 ± SD 8.5 years. Mean cFPG1, cFPG2 and vFPG were 8.7 ± 3.1, 8.3 ± 2.3 and 8.6 ± 2.3 mmol/l, respectively. Mean BMI was 30.2 ± 4.6.

Fasting capillary and venous glucose values were highly correlated, with the latter being systematically higher. For cFPG2 and vFPG (both not Normally distributed), the Spearman's rank correlation coefficient was 0.77 (p = 0.01).

Despite the high correlation between the two methods, they differed significantly. The mean difference (vFPG minus cFPG2) was 0.35 mmol/l (95% CI 0.17-0.53, p <0.001; limits of agreement (=mean difference ± 1.96 SD) = -1.65 to 2.35 mmol/l). For the diagnostic range of 6.0-8.0 mmol/l (n = 73), the mean difference was 0.31 mmol/l (95% CI 0.16-0.46, p <0.001; limits of agreement -0.96 to 1.59 mmol/l).

In 101 out of 125 patients the vFPG was ≥7.0 mmol/l, giving a positive predictive value (PPV) of our protocol of 81%.

Figure 1 Study population and algorithm of the screening procedure



cFPG1 = first capillary fasting plasma glucose measurement (mmol/l); cFPG2 = second capillary fasting plasma glucose measurement (mmol/l); vFPG = venous fasting plasma glucose measurement (mmol/l).

Table 1 Baseline characteristics of the patients entering the stepwise screening protocol (*n* = 3,335 unless otherwise indicated)

Gender (% male)	42.3
Mean age (years ± SD)	58.2 ± 8.2
Mean cFPG1 (mmol/l ± SD)	5.5 ± 1.2
cFPG1 6.1-7.0 mmol/l (%)	11.8
cFPG1 ≥7.0 mmol/l (%)	5.2
Mean BMI (kg/m^2 ± SD)	28.0 ± 4.5
BMI >27 (%) (*n* = 3,110)	57.4
Hypertension (%)	24.4
Cardiovascular disease (%)	15.0
Lipid metabolism disorders (%) (*n* = 993)	32.1
Family history of diabetes (%)	38.6
History of GDM (%) (*n* = 609)	2.8

BMI = body mass index; cFPG1 = first capillary fasting plasma glucose; GDM = gestational diabetes mellitus.

Discussion

Our stepwise screening protocol performed well using a portable blood glucose meter. The use of two capillary measurements with a combination of two cut-off points (>6.0 and ≥7.0 mmol/l) enabled us to considerably reduce the number of patients in whom we needed to assess a laboratory blood glucose value. The PPV of our protocol was 81%.

One of the strengths of this study was that capillary blood samples were taken during daily routine practice in the patients' local general practice by the practice assistants, without any further support e.g. from trial nurses. Another strength of the study was the practice setting: although related to a university department of general practice, the participating general practices were all standard community practices with a population representative of the Dutch population and a diabetes prevalence equal to that in the Netherlands. A possible limitation was that only patients that visited the GP were invited for screening (referral bias). Also, we did not take three samples (two capillary and one venous) from all study participants and therefore could not calculate sensitivity and specificity. However, the focus was on testing the applicability of our stepwise protocol in identifying patients with undiagnosed type 2 diabetes (positive predictive value).

As we could not consider the whole range of blood glucose values due to our screening protocol, the high correlation we found between capillary and venous blood glucose values was not as high as described in literature.[10] The difference between the two methods has also been described before.[10,17] Because of this difference, the use of portable blood glucose meters in diagnosing diabetes is debated.[18] We found no opportunistic screening studies using a portable blood glucose meter. Nevertheless, studies of fasting capillary glucose screening have reported performances similar to those for fasting venous glucose tests.[9] This has been confirmed by recently performed population-based screening studies using capillary blood glucose samples.[19,20] One of these studies also used a portable blood glucose meter,[20] but in both studies, samples were measured in a controlled laboratory setting.

In conclusion, our study showed that a stepwise screening protocol including two subsequent capillary blood glucose measurements from a portable blood glucose meter is well applicable in screening for type 2 diabetes in primary care. However, further research is needed to estimate the cost-effectiveness of our screening protocol, as well as more detailed testing of the sensitivity and specificity for our stepwise approach.

Acknowledgements

We thank all participating GPs, practice assistants, and patients for their cooperation.

Declaration

Funding

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw), and supported by LifeScan who unconditionally provided the blood glucose meters.

Conflicts of interest

None.

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Yield of opportunistic targeted screening for type 2 diabetes in primary care: the Diabscreen study

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Abstract

Purpose In screening for type 2 diabetes, guidelines recommend targeting high-risk individuals. Our objectives were to assess the yield of opportunistic targeted screening for type 2 diabetes in primary care and to assess the diagnostic value of various risk factors.

Methods In 11 family practices (total practice population = 49,229) in the Netherlands, we conducted a stepwise opportunistic screening program among patients aged 45 to 75 years by (1) identifying high-risk individuals (≥1 diabetes risk factor) and low-risk individuals using the electronic medical record, (2) obtaining a capillary fasting plasma glucose measurement, repeated on a separate day if the value was greater than 6.0 mmol/l (110 mg/dl), and (3) obtaining a venous sample if both capillary fasting plasma glucose values were greater than 6.0 mmol/l and at least 1 sample was 7.0 mmol/l (126 mg/dl) or greater. We calculated the yield (percentage of invited patients with undiagnosed diabetes), number needed to screen (NNS), and diagnostic value of the risk factors (odds ratio and area under the receiver operating characteristic curve).

Results We invited for a first capillary measurement 3,724 high-risk patients seen during usual care and a random sample of 465 low-risk patients contacted by mail. The response rate was 90% and 86%, respectively. Ultimately, 101 high-risk patients (2.7%; 95% confidence interval [CI], 2.2%-3.3%; NNS = 37) and 2 low-risk patients (0.4%; 95% CI, 0.1%-1.6%; NNS = 233) had undiagnosed diabetes (P <0.01). The prevalence of diabetes among patients 45 to 75 years old increased from 6.1% to 6.8% as a result. Among diagnostic models containing various risk factors, a model containing obesity alone was the best predictor of undiagnosed diabetes (odds ratio = 3.2; 95% CI, 2.0-5.2; area under the curve = 0.63).

Conclusions The yield of opportunistic targeted screening was fair; obesity alone was the best predictor of undiagnosed diabetes. Opportunistic screening for type 2 diabetes in primary care could target middle-aged and older adults with obesity.

Introduction

Primary care clinicians are encouraged to be more proactive in detecting and treating both diabetes and pre-diabetes.[1] The recently updated standards of medical care of the American Diabetes Association (ADA) recommend testing adults of any age who are overweight or obese and have additional diabetes risk factors.[2]

The main reason to recommend screening for type 2 diabetes is the disease's long preclinical period of up to 12 years. The condition goes undiagnosed in one-third to one-half of all people with type 2 diabetes during this entire period, and they already have complications by the time of diagnosis.[3]

Starting treatment at an earlier stage might prevent or delay the development of diabetes complications. Studies have shown that in clinically detected (not screening-detected) diabetes, tight glycemic control can reduce progression of microvascular disease, and that treatment of hypertension and hyperlipidemia decreases cardiovascular risk.[4] Screening for and treating prediabetes – impaired fasting glucose (IFG) and impaired glucose tolerance – might prevent or slow the progression to diabetes and reduces the risk of cardiovascular disease.[1,5]

At present, however, randomised controlled trials have failed to show that earlier detection by screening reduces morbidity, mortality, or both among people with undiagnosed type 2 diabetes.[4,6] There is also little knowledge about the ethical, psychological, and social consequences of screening results that are truly or falsely positive or negative, and there is no consensus on which screening tests to use and which diagnostic cut-off points are best. [7-9]

These considerations notwithstanding, screening for diabetes is encouraged nowadays. Targeting high-risk patients is recommended, as there is no evidence of a direct benefit of routine population-based screening for type 2 diabetes.[2,4,10-12] As screening should also be a systematic and continuous process,[7] opportunistic targeted screening might be a valuable screening method in primary care. This method entails screening high-risk individuals during usual care.[6]

The pragmatic nature of opportunistic targeted screening enables initiation of further diagnostic testing and treatment of newly diagnosed with type 2 diabetes. To investigate this approach, we performed a study of a stepwise opportunistic screening program embedded in daily routine care in family practices in the Netherlands, targeting high-risk patients – the Diabscreen study. In the analysis reported here, our objectives were to assess the yield of our screening program and the diagnostic value of the risk factors we used in the study.

Methods

Participants and setting

Participants were recruited from 11 family practices in the Netherlands that were part of academic research networks of university departments of family medicine. The practices had a total practice population of 49,229 patients, cared for by 25 family practitioners, and had not previously performed systematic screening for diabetes. Seven of the practices were from the Radboud University Nijmegen Medical Centre,[13] 2 were from Maastricht University,[14] and 2 from the Amsterdam VU University Medical Centre.[15] We considered for inclusion in the study all patients aged 45 to 75 years inclusive who were listed with these practices and were not known to have diabetes. In the Netherlands, every individual in the population is registered with a family practitioner, usually the same one for many years. Patients need a referral by a family practitioner to consult a specialist.

All practices used an electronic medical record (EMR) with the same software (Promedico ICT Inc, Nieuwegein, the Netherlands) containing relevant medical information, such as medical history, diagnoses, medication use, and referrals. Coding of diagnoses was based on the electronic version of the International Classification of Primary Care (ICPC) codes.[16] Prescribed medication was coded according to Anatomical Therapeutic Chemical (ATC) codes.[17]

In our study, patients were defined as having undiagnosed type 2 diabetes if they had a venous fasting plasma glucose (FPG) value of at least 7.0 mmol/l (126 mg/dl). They were defined as having IFG if they had a venous FPG value of greater than 6.0 mmol/l (110 mg/dl) and less than 7.0 mmol/l.[18,19] We did not study impaired glucose tolerance, because our pragmatic screening protocol involved only FPG testing and no an oral glucose challenge.

Ethical approval for the study was obtained by the Radboud University Nijmegen Medical Centre ethics committee.

Screening program

Our opportunistic screening program consisted of a stepwise screening procedure: (1) using the EMR, identification of high-risk and low-risk individuals; (2) a first capillary FPG measurement and, if indicated by the result, a second one; and (3) if indicated by that result, a venous FPG.

Patients were considered to be at high risk for undiagnosed type 2 diabetes in case of one or more of the following diabetes risk factors, derived from the ADA recommendations in screening for type 2 diabetes[2]: a family history of diabetes (defined as diabetes in a parent, brother, or sister, or some combination thereof), hypertension, cardiovascular disease (myocardial infarction, heart failure, atrial fibrillation, stroke, peripheral vascular disease), lipid metabolism disorders, obesity

(body mass index >27 kg/m^2), and a history of gestational diabetes mellitus.[2,11]

We translated these risk factors into a set of matching ICPC and ATC codes.[20] Using a computerized cross-sectional analysis of ICPC and ATC information for each patient from the practices' EMR, we determined the patients' diabetes risk status (high vs low) and entered it in the EMR. During a usual care consultation in the following year, the EMR reminded the family practitioners to verify and, in case of missing data, complete the patients' risk profile and to invite high-risk patients for an FPG measurement. As part of daily practice, an appointment for this test was recorded in the practice schedule. There were no further reminders.

In addition, to assess the yield of opportunistic screening among low-risk patients, from each participating practice, we also invited for FPG measurement a random sample of low-risk patients: patients from the same age-group, but without any of the risk factors listed above. On the basis of an expected prevalence of undiagnosed type 2 diabetes of 0.5%,[21] an intraclass correlation coefficient of 0.03, and a desired precision of 1%, we calculated a required sample size of 380 low-risk patients. These patients were randomly selected from a list of low-risk patients and subsequently invited by mail to visit the practice for screening.

Our stepwise screening protocol was based on cut-off points used for IFG and diabetes.[22] All patients with an initial capillary FPG of greater than 6.0 mmol/l were invited for a second capillary measurement on another day. This second measurement was immediately followed by a venous FPG measurement if both capillary measurements were greater than 6.0 mmol/l and at least 1 was 7.0 mmol/l or greater.

Measurements

Measurements were made in the patients' own family practice by the regular practice assistants. Capillary samples were taken using a Gluco Touch plasma calibrated capillary blood glucose meter (LifeScan Benelux, Beerse, Belgium). Before the start of the study, all participating practices received new meters, which were checked and adjusted, if necessary, by the manufacturer. The practice assistants were trained in using the meters. Venous samples were sent to a central laboratory for further analysis in a Roche/Hitachi chemical analyzer (Roche Nederland BV, Woerden, the Netherlands), using the glucose oxidase method.

Data analysis

We analyzed data with SPSS 16.0 for Windows (SPSS Inc, Chicago, Illinois). Statistical analysis was performed using the χ^2 test for categorical data and the Student *t* test or Kruskal-Wallis test for means where appropriate. We considered a *P* value <.05 to be significant.

We calculated the yield of our screening program (the percentage of invited patients found to have undiagnosed type 2 diabetes); the number of patients who would need to be invited for screening in order to identify 1 patient with undiagnosed type 2 diabetes, or number needed to screen (NNS); and the change in diabetes prevalence among the study population resulting from the program.
We examined possible interactions between the risk factors by calculating the correlation coefficients. Then, we quantified their association with the presence or absence of undiagnosed diabetes using univariate logistic regression analysis. Variables with a *P* value ≤0.15 were included in multivariate binary logistic regression analysis to determine their independent contribution to the risk of undiagnosed type 2 diabetes. Using the backward stepwise (likelihood ratio) method, excluding variables one by one, we were able to produce diagnostic models with an area under the receiver operating curve (AUC).

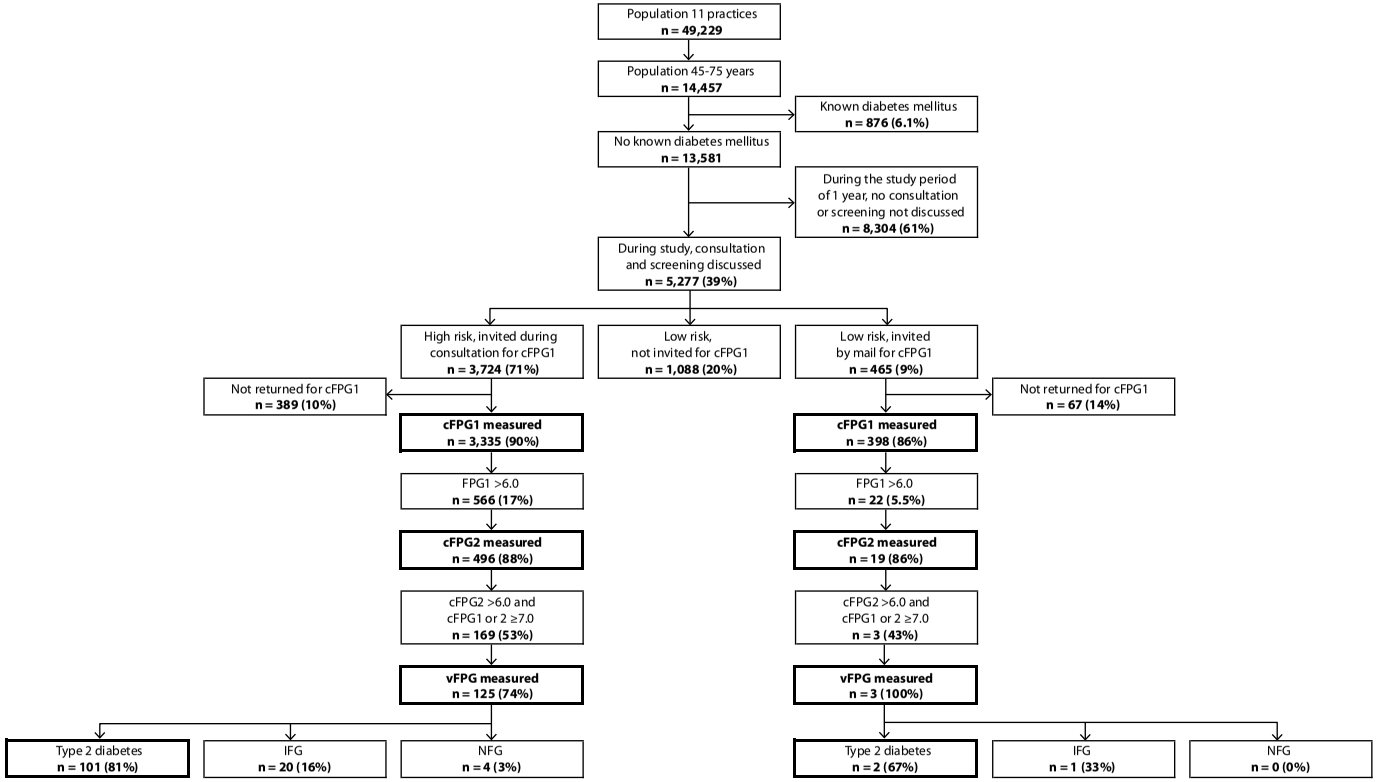
Results

The 11 participating practices had 49,229 registered patients (2,500-9,750 per practice), of whom 14,457 (957-1,831 per practice) were aged 45 to 75 years (Figure 1). The prevalence of known diabetes before our screening program was 6.1%, leaving 13,581 patients for the study. During the 1-year study period, 5,277 (39%) of these patients had an encounter with a family practitioner during which screening was discussed. Risk assessment indicated that 3,724 (71%) were at high risk for diabetes and 1,553 (29%) were at low risk; 90% of the high-risk patients and 86% of the 465 invited low-risk patients returned for a first capillary FPG measurement after invitation. Sex and mean age did not differ significantly between high-risk and low-risk patients, but mean FPG was slightly higher in the former group (Table 1).

High-risk patients

A second capillary FPG was performed in 496 high-risk patients, or 88% of those invited (Figure 1). According to our protocol, 169 (5%) were eligible for venous FPG measurement immediately after the second capillary FPG measurement. A venous sample was collected in 125 (74%) of these patients but not in 44 (26%). In the latter group, the second capillary FPG more often was 6.1 to 7.0 mmol/l, but other characteristics did not differ significantly (Table 2). Of the 125 patients with a venous sample, 81% had undiagnosed type 2 diabetes, 16% had IFG, and 3% had a normal fasting glucose level. These groups differed significantly in terms of mean FPG values and the prevalence of lipid metabolism disorders (Table 3).

Figure 1 Study population and algorithm of the screening procedure



cFPG1, first capillary fasting plasma glucose measurement (mmol/l); cFPG2, second capillary fasting plasma glucose measurement (mmol/l); vFPG, venous fasting plasma glucose measurement (mmol/l); NFG, normal fasting plasma glucose; IFG, impaired fasting glucose.

Table 1 Baseline characteristics of high-risk and low-risk patients in whom a first capillary fasting plasma glucose level was measured

	High-risk patients	Low-risk patients	
Characteristic	***n* = 3,335**	***n* = 398**	***P***
Sex (male), No. (%)	1,411 (42.3)	168 (42.2)	0.97
Age, mean (SD), years	58.2 (8.2)	57.5 (7.2)	0.07
cFPG1			
cFPG1, mean (SD), mmol/l	5.5 (1.2)	5.2 (0.6)	<0.001
cFPG1 6.1-7.0 mmol/l, No. (%)	394 (11.8)	16 (4.0)	<0.001
cFPG1 ≥7.0 mmol/l, No. (%)	172 (5.2)	6 (1.5)	<0.001
BMI[a]			
BMI, mean (SD), kg/m^2	28.0 (4.5)	23.5 (2.2)	<0.001
BMI >27 kg/m^2, No. (%)	1,786 (57.4)	0	–
Risk factors			
Hypertension, No. (%)	814 (24.4)	0	–
Cardiovascular disease, No. (%)	499 (15.0)	0	–
Lipid metabolism disorders,[b] No. (%)	319 (32.1)	0	–
Family history of diabetes, No. (%)	1,288 (38.6)	0	–
History of GDM,[c] No. (%)	17 (2.8)	0	–

BMI = body mass index; cFPG1 = first capillary fasting plasma glucose; GDM = gestational diabetes mellitus.
[a] Missing = 225. [b] Missing = 2,342. [c] Missing = 2,726.

Low-risk patients

In the low-risk group, only 2 patients had undiagnosed type 2 diabetes and 1 patient had IFG (Figure 1). The characteristics within each subgroup are displayed in Table 3. Further analysis was not possible in this group because of to the small number of patients.

Yield of the screening program

We found undiagnosed type 2 diabetes in 101 high-risk patients and 2 low-risk patients. These values corresponded to 2.7% of high-risk patients (95% confidence interval [CI], 2.2%-3.3%; NNS = 37) vs 0.4% of low-risk patients (95% CI, 0.1%-1.6%; NNS = 233) invited for screening (P <0.01). As a result of the screening program, the prevalence of known diabetes among patients aged 45 to 75 years in the study practices increased from 6.1% (876 patients) to 6.8% (979 patients).

Table 2 Characteristics of high-risk patients eligible for venous FPG measurement, comparing patients with and without a venous sample

	Patients with venous sample	Patients without venous sample	
Characteristic	***n* = 125**	***n* = 44**	***P***
Sex (male), No. (%)	57 (45.6)	23 (52.3)	0.45
Age, mean (SD), years	58.8 (8.0)	58.5 (8.1)	0.87
cFPG measurements			
cFPG1, mean (SD), mmol/l	8.7 (3.1)	8.4 (2.8)	0.59
cFPG2, mean (SD), mmol/l	8.3 (2.3)	7.8 (2.1)	0.23
cFPG1 6.1-7.0 and cFPG2 ≥7.0, No. (%)	28 (22.4)	6 (13.6)	0.21
cFPG1 ≥7.0 and cFPG2 6.1-7.0, No. (%)	22 (17.6)	21 (47.8)	<0.001
cFPG1 ≥7.0 and cFPG2 ≥7.0, No. (%)	75 (60.0)	17 (38.6)	0.01
BMI, mean (SD), kg/m^2	30.2 (4.6)	31.0 (6.9)	0.39
Risk factors			
Hypertension, No. (%)	49 (39.2)	15 (34.1)	0.55
Cardiovascular disease, No. (%)	22 (17.6)	5 (11.4)	0.33
Lipid metabolism disorders,[a] No. (%)	12 (33.3)	3 (21.4)	0.41
Family history of diabetes, No. (%)	58 (46.4)	17 (38.6)	0.37
History of GDM,[b] No. (%)	0	0	–

BMI = body mass index; FPG = fasting plasma glucose; cFPG1 = first capillary fasting plasma glucose; cFPG2 = second capillary fasting plasma glucose; GDM = gestational diabetes mellitus. [a] Missing = 94 with venous sample; 30 without venous sample. [b] Missing = 100 with venous sample; 26 without venous sample

Diagnostic value of the risk factors

There were significant but no relevant correlations between the risk factors. For example, the Spearman rank correlation coefficient of obesity with hypertension was 0.08 with P <.01 (data not further shown).

Univariate logistic regression analysis showed that the odds of undiagnosed type 2 diabetes were significantly higher among patients who were obesity (odds ratio [OR] = 3.2; 95% CI, 2.0-5.2) or had hypertension (OR = 2.5; 95% CI, 1.6-3.8) (Table 4). In contrast, a family history of diabetes was not significantly associated with undiagnosed diabetes (OR = 1.4; 95% CI, 0.9-2.1). Because of the large number of missing data, lipid metabolism disorders and history of gestational diabetes mellitus were not included in the analysis.

Table 3 Characteristics of high-risk and low-risk patients in venous FPG subgroups

	High-risk patients			Low-risk patients		
	Diabetes	**IFG**	**NFG**	**Diabetes**	**IFG**	**NFG**
Characteristic	***n* = 101**	***n* = 20**	***n* = 4**	***n* = 2**	***n* = 1**	***n* = 0**
Sex (male), No. (%)	49 (48.5)	6 (30.0)	2 (50.0)	1 (50.0)	0	0
Age, mean (SD), years	59.4 (8.1)	56.0 (7.8)	55.8 (2.6)	67.5 (6.4)	55.0	0
Plasma glucose level						
cFPG1, mean (SD), mmol/l	9.0 (3.3)	7.2 (0.7)	7.0 (0.4)[a]	7.1 (0.1)	7.1	0
cFPG2, mean (SD), mmol/l	8.6 (2.4)	6.9 (0.8)	6.5 (0.4)[b]	7.5 (0.2)	7.2	0
vFPG, mean (SD), mmol/l	9.1 (2.3)	6.7 (0.2)	5.8 (0.3)[c]	7.4 (0.4)	6.1	0
BMI[d]						
BMI, mean (SD), kg/m^2	29.9 (3.9)	32.2 (6.9)	28.2 (4.8)	25.3 (1.5)	25.3	0
BMI >27 kg/m^2, No. (%)	73 (78.5)	17 (89.5)	2 (50.0)	0	0	0
Risk factors						
Hypertension, No. (%)	41 (40.6)	7 (35.0)	1 (25.0)	0	0	0
Cardiovascular disease, No. (%)	17 (16.8)	5 (25.0)	0	0	0	0
Lipid metabolism disorders,[e] No. (%)	6 (23.1)	6 (66.7)	0[a]	0	0	0
Family history of diabetes, No. (%)	43 (42.6)	13 (65.0)	2 (50.0)	0	0	0
History of GDM,[f] No. (%)	0	0	0	0	0	0

BMI = body mass index; cFPG1 = first capillary fasting plasma glucose; cFPG2 = second capillary fasting plasma glucose; FPG = fasting plasma glucose; vFPG=venous fasting plasma glucose; GDM = gestational diabetes mellitus; IFG = impaired fasting glucose; NFG = normal fasting glucose. Analysis of the low-risk group was not possible because of the small numbers.

[a] P <0.01 in high-risk group; [b] P <0.01 in high-risk group; [c] P <0.001 in high-risk group.

[d] Missing in high-risk group = 8 with diabetes; 1 with IFG; 0 with NFG.

[e] Missing in high-risk group = 75 with diabetes; 11 with IFG; 3 with NFG.

[f] Missing in high-risk group = 80 with diabetes; 17 with IFG; 3 with NFG.

Table 4 Univariate analysis of the association between diabetes risk factors and the odds of undiagnosed type 2 diabetes

	Undiagnosed diabetes			
Risk factor	**Yes, No. (%) *n* = 95**	**No, No. (%) *n* = 3,379**	**Odds ratio (95% CI)**	***P***
Sex (male)	46 (48.4)	1,431 (42.3)	1.3 (0.9-1.9)	0.24
Age >60 years	45 (47.4)	1,406 (41.6)	1.3 (0.8-1.9)	0.26
Hypertension	37 (38.9)	691 (20.4)	2.5 (1.6-3.8)	<0.001
Cardiovascular disease	16 (16.8)	429 (12.7)	1.4 (0.8-2.4)	0.23
Obesity (BMI >27 kg/m^2)	73 (76.8)	1,713 (50.7)	3.2 (2.0-5.2)	<0.001
Family history of diabetes	41 (43.2)	1,212 (35.9)	1.4 (0.9-2.1)	0.15

BMI = body mass index; CI = confidence interval. Note: Missing = 259.

Multivariate binary logistic regression analysis showed that obesity was the best predictor of undiagnosed type 2 diabetes: 76.8% of those with the disease were obese (AUC = 0.63; 95% CI, 0.58-0.68) (Table 5). Hypertension and family history of diabetes were poorer predictors.

Table 5 Multivariate analysis of the association between diabetes risk factors and the odds of undiagnosed type 2 diabetes and diagnostic performance

Model	**Odds ratio (95% CI)**	***P***	**Undiagnosed diabetes, No. (%) *n* = 95**	**AUC (95% CI)[a]**
Model 1			12 (12.6)	0.54 (0.48-0.61)
Obesity (BMI >27 kg/m^2)	3.1 (1.9-5.0)	<0.001	–	–
Hypertension	2.3 (1.5-3.5)	<0.001	–	–
Family history of diabetes	1.4 (1.0-2.2)	0.09	–	–
Model 2			30 (31.6)	0.60 (0.54-0.66)
Obesity	3.0 (1.9-4.9)	<0.001	–	–
Hypertension	2.3 (1.5-3.5)	<0.001	–	–
Model 3			73 (76.8)	0.63 (0.58-0.68)
Obesity	3.2 (2.0-5.2)	<0.001	–	–

AUC = area under the receiver operating characteristic curve; BMI = body mass index; CI = confidence interval. Note: Only risk factors with P ≤0.15 in Table 4 were included. [a] An AUC of 0.50 means that the model does not predict the outcome better (more accurately) or worse (less accurately) than random guess; an AUC greater than 0.50 means that the prediction is better than random, and an AUC less than 0.50 means that the prediction is worse than random.

Discussion

The yield of our opportunistic targeted screening program was fair: in 1 year we identified undiagnosed type 2 diabetes in 101 high-risk patients invited for screening (2.7%, NNS = 37). This number represents 30% of cases of known diabetes, considering that 39% of the study population had an encounter with a family practitioner (39% of 876 patients previously known to have diabetes = 342, and 101/342 = 30%). The yield of screening in low-risk patients was, as expected, only 0.4% (NNS = 233). The response rate for the capillary measurements was high, at about 90%. As a result of the screening program, the prevalence of known diabetes among our patients aged 45 to 75 years increased from 6.1% to 6.8%. Of the ADA diabetes risk factors, obesity was the best predictor of undiagnosed type 2 diabetes. The main strength of the study was the setting. High-risk patients were invited for screening during daily routine practice in the patients' local family practice by their own family practitioner. Capillary blood samples were taken by the practice assistants, without any further support (eg, from trial nurses). Although patients had to return in a fasting state for the capillary FPG measurements, they were highly willing to do so. And although all participating family practices were related to a university department of family medicine, they were standard community practices with a population representative of the Dutch population and a diabetes prevalence equal to that in the Netherlands.[13-15,23] Because the Dutch system of primary health care provides for universal access and continuity of patient registration, we were able to use the family practice EMR in a continuous screening program.

Our screening approach calls for the identification of individual risk factors during a regular consultation. To the extent possible, we used available information from the EMR, which is based on the ICPC. A limiting factor is that not all risk factors are included in the ICPC at this time; therefore, we had to ask patients about their risk factors to confirm their status.[20] Our study supports the relevance of routine inclusion of risk factors in the EMR and the importance of extending the ICPC to include this information.

A possible limitation was that we used the FPG test rather than the oral glucose tolerance test. The latter test consists of an FPG measurement plus a 2-hour plasma glucose measurement, and has been considered to be the criterion standard in diagnosing diabetes. The FPG test is, nevertheless, recommended for screening in primary care as it is easier and faster to perform, more convenient and acceptable to patients, and less expensive.[2,24]

Our focus was on testing the applicability of our stepwise protocol during usual care; therefore, we did not collect 3 blood samples (2 capillary and 1 venous) from all study participants. With an 81% concordance between identification for

venous sampling and an undiagnosed type 2 diabetes outcome in high-risk patients (positive predictive value = 81%), our protocol was very useful. Since this protocol was designed to screen for undiagnosed type 2 diabetes, few patients who underwent venous sampling were found to have IFG.

In 26% of our high-risk patients eligible for a venous sample, this measurement was not performed. Considering the high level of compliance with the capillary measurements, the general lack of significant differences between patients with a venous measurement and those without, and the requirement by the protocol that the venous sample be obtained immediately after the second capillary measurement, we believe that the missing venous samples were mainly due to protocol factors (eg, misinterpretation – willingly or not – by the practice assistants) instead of patient factors. The fact that high-risk patients without a venous sample more often had a second capillary FPG of 6.1 to 7.0 mmol/l, supports this assumption. Instead of giving assistents a flowchart with all possible combinations of glucose outcomes (not described) as we did in the study, we now believe it would have been more helpful if we had given them the simple algorithm mentioned in the Methods section. We estimate that if compliance had been 100%, the number of newly diagnosed cases of diabetes among high-risk patients could in fact have been 136, giving an even lower NNS of 28.

The portable glucose meters we used are user-friendly and readily available in primary care. A potential drawback is their variability,[25] and consequent risk of false-positive and false-negative outcomes. Our stepwise approach, in which patients with glucose levels above the threshold underwent measurement again, did address the problems of false-positive results.[22] To address false-negative results, the procedure must be repeated, for example, every 3 years, as recommended by the ADA.[2]

Since we wanted to perform a screening program embedded in daily care without any further support, we did not specifically study disadvantages or harms, or cost-effectiveness of our opportunistic screening program, nor did we specifically investigate acceptability of the screening procedure. As the program was embedded in daily care and the patient attendance rate was 90%, however, we believe we can conclude that it was inexpensive and feasible. Further research is needed, though.

Several diabetes screening studies have been described in the literature. Smith *et al.*[26] undertook an opportunistic diabetes screening study performed in family practice using a questionnaire presented to patients who were waiting to see their doctor. Their participation rate was also high (93%), and 43% of patients had at least 2 risk factors. If performed continuously or repeated regularly, such an approach might provide more complete and up-to-date information on a patient's risk status in the EMR, improving the identification of high-risk patients for screening purposes.

Greaves *et al.*[27] showed that identifying patients with type 2 diabetes and IFG using data stored in family practice databases was feasible (NNS = 21-38 for type 2 diabetes), but instead of using an opportunistic approach, they invited high-risk patients (those aged >50 years and with a body mass index ≥27 kg/m^2) to screening clinics run by trained practice nurses. The response rate was 61%. Nevertheless, the simple screening system they describe – like ours – would promote efficient use of scarce primary health care resources, especially when set up as part of a broader screening program to reduce cardiovascular disease.

In a cross sectional study in a local family practice, Lawrence *et al.*[21] showed that screening of invited patients whose sole risk factor for diabetes is age older than 45 years has a low yield. In this group, they found a diabetes prevalence of just 0.2%. Among individuals with 1 or more other risk factors, the figure increased to 2.8%. Both prevalences are comparable to ours.

Recently, a population-based screening program for type 2 diabetes was performed in the Netherlands.[12] Although the increase in diabetes prevalence achieved with the program (from 6.1% to 7.0% among people aged 50 to 70 years) was comparable to ours, the response to an invitation to glucose testing was 31% and the yield only 1%. The authors concluded that opportunistic screening might be more appropriate.

Primary care practices often have large patient populations, underscoring the need for a targeted approach to screening. In our family practices, more than two-thirds of middle-aged and older study patients eligible for screening were at high risk. But largely because of the stepwise protocol, the yield of our opportunistic targeted screening method was fair.

In a recently updated statement,[28] the US Preventive Services Task Force recommends screening for type 2 diabetes in asymptomatic adults with hypertension. As part of an assessment of cardiovascular disease risk, clinicians should also screen for diabetes to adequately assess patients' risk for this condition as well.[28] With ever greater integration of diabetes screening into cardiovascular risk management, opportunistic screening for type 2 diabetes in primary care could target the middle-aged and older adults with obesity. With this approach, the number of high-risk patients to be screened would be considerably reduced. A similar approach was found to be cost-effective.[29]

With an opportunistic targeted screening program like ours, diabetes screening in primary care can be performed systematically and continuously, with probably few drawbacks for both patients and health care workers, and with efficient use of resources. Further research is needed to estimate its cost-effectiveness and limitations. Also, sensitivity and specificity of our stepwise approach need to be studied.

In conclusion, the yield of opportunistic targeted screening in our study was fair, and obesity alone was the best predictor of undiagnosed diabetes. Our data confirm a low yield when low-risk individuals are screened. As diabetes screening is increasingly integrated into cardiovascular risk management, opportunistic screening for type 2 diabetes in primary care could target the middle-aged and older adults with obesity.

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Declaration

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Conflicts of interests

None.

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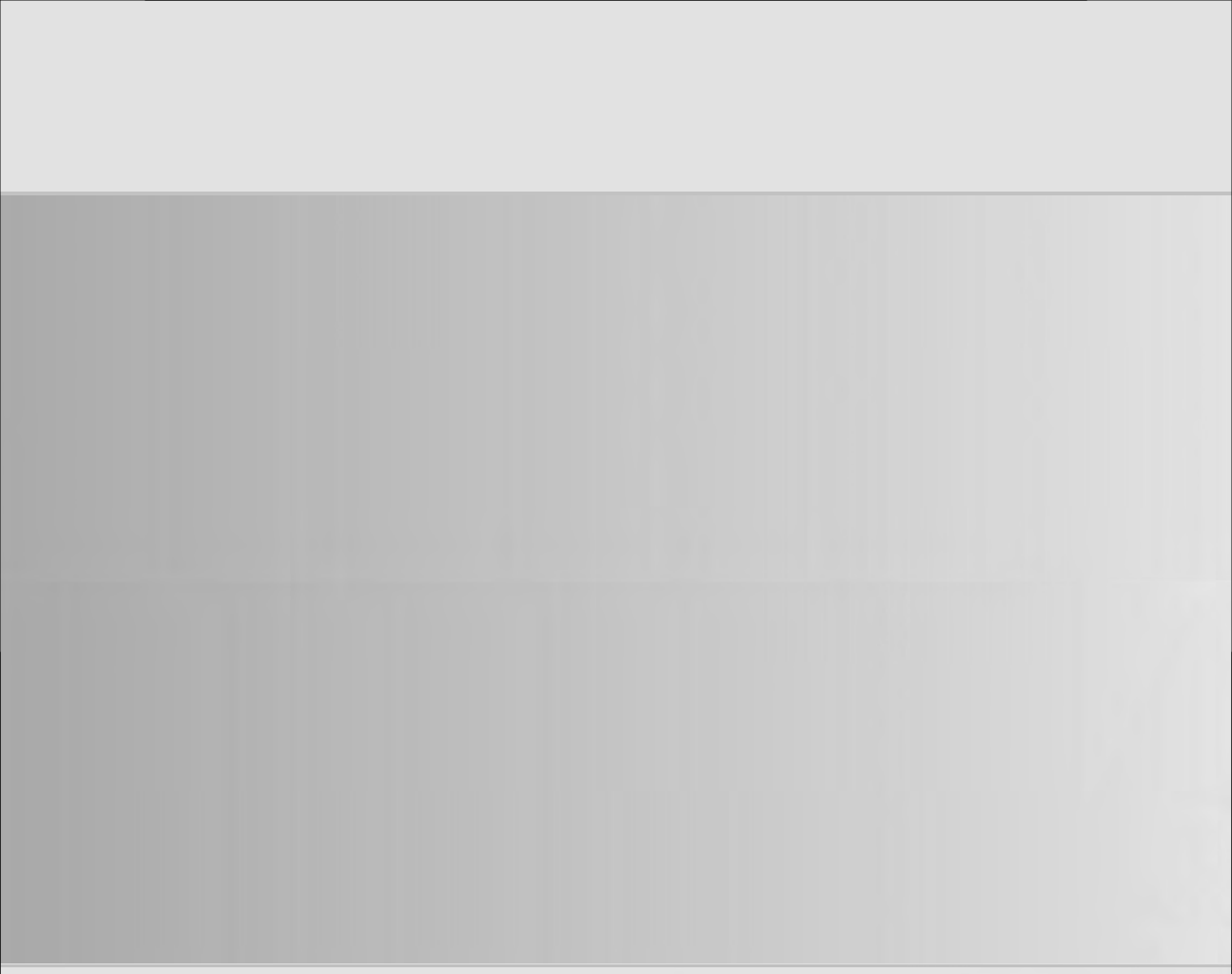

5

Opportunistic screening for type 2 diabetes in primary care

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Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis

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Abstract

Background No clinical trials have assessed the effects or cost-effectiveness of sequential screening strategies to detect new cases of type 2 diabetes. We used a mathematical model to estimate the cost-effectiveness of several screening strategies.

Methods We used person-specific data from a representative sample of the US population to create a simulated population of 325,000 people aged 30 years without diabetes. We used the Archimedes model to compare eight simulated screening strategies for type 2 diabetes with a no-screening control strategy. Strategies differed in terms of age at initiation and frequency of screening. Once diagnosed, diabetes treatment was simulated in a standard manner. We calculated the effects of each strategy on the incidence of type 2 diabetes, myocardial infarction, stroke, and microvascular complications in addition to quality of life, costs, and cost per quality-adjusted life-year (QALY).

Findings Compared with no screening, all simulated screening strategies reduced the incidence of myocardial infarction (3-9 events prevented per 1000 people screened) and diabetes-related microvascular complications (3-9 events prevented per 1000 people), and increased the number of QALYs (93-194 undiscounted QALYs) added over 50 years. Most strategies prevented a significant number of simulated deaths (2-5 events per 1000 people). There was little or no effect of screening on incidence of stroke (0-1 event prevented per 1000 people). Five screening strategies had costs per QALY of about US$10,500 or less, whereas costs were much higher for screening started at 45 years of age and repeated every year ($15,509), screening started at 60 years of age and repeated every 3 years ($25,738), or a maximum screening strategy (screening started at 30 years of age and repeated every 6 months; $40,778). Several strategies differed substantially in the number of QALYs gained. Costs per QALY were sensitive to the disutility assigned to the state of having diabetes diagnosed with or without symptoms.

Interpretation In the US population, screening for type 2 diabetes is cost-effective when started between the ages of 30 years and 45 years, with screening repeated every 3-5 years.

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Richard Kahn and colleagues (April 17, p 1365)[1] used a mathematical model to show that screening for type 2 diabetes is cost-effective when started at the age of 30-45 years and repeated every 3-5 years. They conclude that the cost per quality-adjusted life-year would be improved if screening was done opportunistically and by risk assessment before glucose testing. They state that there are no clinical trials against which to validate their model.

In the Diabscreen study,[2] an opportunistic screening programme for type 2 diabetes in patients aged 45-75 years in primary care in the Netherlands, we used the family practice electronic medical record (EMR) for risk assessment before glucose testing. Risk was marked in the EMR. In 1 year, physicians succeeded in starting stepwise fasting glucose testing during usual care in 39% of the patients. First response rate was 90%. The screening yield was much higher in high-risk than in low-risk patients (number needed to screen 37 versus 233). Obesity was the best predictor of undiagnosed diabetes (odds ratio 3.2). This finding is in line with one of the American Diabetes Association's recommendations to screen all adults aged 45 years and older with a body-mass index of 25 or greater.[3]

Although not a trial, our clinical findings clearly show that opportunistic screening in primary care is feasible. Middle-aged and older adults at high risk, especially those with obesity, can be targeted effectively. An EMR can be most helpful for identification of high-risk patients and also in supporting repeated screening, but this requires universal access and continuity of patient registration.

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The partner's perspective

6

Patients' and partners' illness perceptions in screen-detected versus clinically diagnosed type 2 diabetes: partners matter!

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Abstract

Background In type 2 diabetes, educational interventions that target differences between patients' and partners' illness perceptions have been advocated.

Objective To investigate how the route to diagnosis of type 2 diabetes (through screening versus clinical symptoms) affects illness perceptions of patients and their partners.

Methods In a cross-sectional study, we enrolled patients aged 40-75 years from general practices in the Netherlands with a new diagnosis of type 2 diabetes (≤3 years), detected by either screening (n = 77) or clinical symptoms (n = 32). Patients and their partners each completed a postal Brief Illness Perception Questionnaire (Brief IPQ), and up-to-date clinical data were obtained from their GP. The Brief IPQ scores of the screening and clinical diagnosis groups were compared for both patients and partners, and multiple variable linear regression models with Brief IPQ scores as outcomes were developed.

Results The route to diagnosis did not appear to have a strong influence on patients' illness perceptions, but did influence illness perceptions of their partners. Partners of patients diagnosed through screening perceived greater consequences for their own life, had a stronger feeling that their patient-partners had control over their diabetes, were more concerned about their partners' diabetes, and believed that their patient-partners experienced more diabetes symptoms, compared with partners of patients who were diagnosed through clinical symptoms.

Conclusions The route to diagnosis of type 2 diabetes has a greater impact on the illness perceptions of partners than that of patients. Professionals in diabetes education and treatment should consider these differences in their approach to patient care.

Introduction

Screening for type 2 diabetes is recommended because it may reduce the risk of vascular complications.[1-4] Some questions remain unresolved, however, in particular regarding the psychological consequences of early detection and treatment of type 2 diabetes.[5] Although the psychological impact of a screening-based diagnosis of type 2 diabetes on patients is generally limited,[6] intensive treatment following screen-detected diabetes has been shown to lead to higher levels of anxiety and lower self-efficacy in the first year after diagnosis, without an accompanying improvement in self-care.[7]

Similarly to other chronic diseases, patients with type 2 diabetes must take personal responsibility for the management of their illness.[8] Patients need to exercise and change their diet, take oral medications and may eventually require insulin injections, involving self-monitoring of blood glucose and insulin adjustments.[1,9] Although education provides the required knowledge, self-care behaviours are also influenced by beliefs – so-called illness perceptions – regarding type 2 diabetes.[10]

Illness perceptions include the following cognitive illness representations: consequences (beliefs about effects and impact), timeline (course and duration), personal control (own control over management), treatment control (outcome expectancies of treatment and recommended advice), identity (symptoms and label attributed to illness) and cause (perceived cause of the illness). Emotional representations (concern and emotions) and illness coherence (overall understanding) are also considered to be illness perceptions.[11]

Perceptions of personal control and an understanding of diabetes appear to be particularly important: studies have shown that an increased appreciation of these factors by patients are associated with better adherence to diet, exercise and medications, and with better blood glucose control, lower interference with social and personal functioning, fewer negative feelings and a more positive attitude towards diabetes.[12,13] Evidence exists to support the contention that illness perceptions can be improved through targeted intervention and that these changes may also impact on glycaemic control.[11]

As most type 2 diabetes self-care occurs at home, illness perceptions of family members, in particular the partner, play an important role in adaptation to the disease and in disease outcome.[14] Patients with type 2 diabetes feel greater personal control compared with their partners but show a poorer understanding of their condition.[15] Partners generally perceive diabetes as being more serious and as having a greater impact on daily life, whereas patients are often unaware of this heightened concern and have a more relaxed approach to living with the disease.[16] Gender can also affect illness perceptions of chronic diseases, an example of which is that male patients with coronary heart disease often attribute their condition to

risk behaviours, whereas female patients often identify stress as the cause.[17] The psychological adjustment of female rheumatoid arthritis patients is improved when a husband shares optimistic beliefs regarding personal control, illness coherence and consequences.[18] The considerations above suggest that interventions targeting differences and aiming to improve congruence in the illness perceptions of patients and partners, together with the development of a personalized plan to improve diabetes management, may be important in diabetes education and treatment.[19]

In this exploratory study, we hypothesized that the route to diagnosis of type 2 diabetes – by screening in asymptomatic individuals or by clinical signs or symptoms – may affect the illness perceptions of patients and partners, and thus may be an important factor to consider in diabetes education programmes. We therefore compared data from type 2 diabetes patients and their partners detected by screening with data from type 2 diabetes patients and their partners detected by clinical signs or symptoms in the same study period and setting. In addition, we explored the interaction between gender and screening.

Methods

Participants and setting

We invited individuals aged 40-75 years, who were diagnosed with type 2 diabetes within the last 3 years and were married or living together with a partner, to participate in this cross-sectional questionnaire study.

Couples were recruited via general practitioners in one of two ways: initially, a subset of respondents was recruited using leaflets and posters sent to a random sample of 875 general practices throughout the Netherlands (60 couples responded). To improve response, we recruited additional couples from general practices participating in a practice-based research network (n = 47 couples, response rate 44%)[20,21] and from general practices participating in a diabetes research centre (n = 28 couples, response rate 30%).[6] Patients with type 2 diabetes were treated in line with the Dutch general practice guidelines in all practices.[1] Following completion of their participation form, each couple received both a 'patient' and a 'partner' postal questionnaire.

We excluded 17 couples because either the patient or the partner did not wish to participate or failed to return the questionnaire. We excluded an additional seven couples because of an unclear route to diagnosis and a further two because the partner also had diabetes. In total, 109 heterosexual couples were enrolled in the study.

Questionnaire

The questionnaire included demographic items (e.g. age, sex and educational level), questions regarding the disease (e.g. time since diagnosis, treatment) and questions about the participants' relationship (e.g. duration of marriage).

The patient questionnaire also included a question on the route to diagnosis. Depending on the answer, the couples were divided in two groups: (i) asymptomatic type 2 diabetes detected by (opportunistic) targeted screening (subsequently referred to as 'screening') or (ii) clinically diagnosed type 2 diabetes based on signs or symptoms (subsequently referred to as 'clinical diagnosis').

Illness perceptions were measured in patients and partners using questions from the Brief Illness Perception Questionnaire (Brief IPQ), a shorter version of the popular Revised Illness Perception Questionnaire (IPQ-R).[11] The Brief IPQ is a validated questionnaire for rapid assessment of illness perceptions and was developed for use with ill or elderly people.[22] It has nine single items without a total score (Box 1): items 1-8 are individually rated using a 0-to-10 visual response scale, with higher scores reflecting a stronger belief in or perception of the item, and item 9 probes the causes of diabetes by an open-ended question, asking the respondent to list up to three factors in rank order which he or she believes to have caused their diabetes. For partners, the questions were reformulated to address their specific perspectives. The partner questionnaire's Cronbach's alpha, a measure of internal reliability, was an acceptable 0.65.

Clinical data

To compare baseline characteristics, we obtained recent clinical data from the patients' own general practitioner (GP). These data were extracted from the electronic medical records by the GPs and included information derived from physical examination (body mass index and blood pressure), laboratory testing (hemoglobin A_{1c} and cholesterol), and glucose-lowering treatment (diet, oral agents, insulin).

Statistical analysis

Differences between the screening and clinical diagnosis groups were analysed in both patients and partners. Demographic and clinical characteristics were compared using the chi-square test for categorical data and the *t*-test for means. Descriptive statistics were used to calculate the mean Brief IPQ scores for patients and partners in both the screening and the clinical diagnosis groups. Responses to the causal item were grouped into categories, followed by a kappa measure of agreement within couples (generally ranging from 0 to 1.0, where larger numbers mean better agreement) and categorical analysis using chi-square tests.

Box 1 The Brief IPQ items with matching questions, adjusted for diabetes and partners (0-10 response scale, except item 9)[a]

1. Consequences	How much does your (partner's) diabetes affect your life? *(0=no affect at all, 10=severely affects my life)*
2. Timeline	How long do you think your (partner's) diabetes will continue? *(0=a very short time, 10=forever)*
3. Personal control	How much control do you feel you have (your partner has) over your (his/her) diabetes? *(0=absolutely no control, 10=extreme amount of control)*
4. Treatment control	How much do you think the treatment can help your (partner's) diabetes? *(0=not at all, 10=extremely helpful)*
5. Identity	How much do you (does your partner) experience symptoms from diabetes? *(0=no symptoms at all, 10=many severe symptoms)*
6. Concern	How concerned are you about your (partner's) diabetes? *(0=not at all concerned, 10=extremely concerned)*
7. Understanding	How well do you feel you understand your (partner's) diabetes? *(0=don't understand at all, 10=understand very clearly)*
8. Emotional response	How much does diabetes affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?) *(0=not at all affected emotionally, 10=extremely affected emotionally)*
9. Causal representation	Please list in rank-order the three most important factors that you believe caused your (partner's) diabetes. The most important causes for me are: 1. _____ 2. _____ 3. _____

[a] Cognitive illness representations: items 1, 2, 3, 4 and 5; emotional representations: items 6 and 8; illness comprehensibility: item 7; causal representation: item 9.

To calculate the effect of a screening-based diagnosis versus clinical diagnosis on illness perceptions, we developed multiple variable linear regression models. In each model, we applied one of the Brief IPQ items (except item 9) as the dependent variable and the method of diagnosis as the independent variable. The unstandardized regression coefficient (ß), with matching 95% confidence interval (CI) and *P* value, was considered to be the absolute effect on the mean Brief IPQ score. Analyses were controlled for the additional independent variables such as age, sex, educational level, duration of diabetes, duration of marriage and insulin use. All analyses were carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL), all were two sided and we considered a *P* value less than 0.05 to be significant.

Results

Our study included 109 patients with a new diagnosis of type 2 diabetes, of whom 77 were detected by screening and 32 diagnosed by clinical signs or symptoms (Table 1). Although the two patient groups did not differ significantly in age or gender, clinically diagnosed patients were more often male. Partners in the screening group were more likely to be male, and partners in the clinical diagnosis group were significantly younger.

Statistically significant differences in educational level and duration of marriage between the screening and clinical diagnosis patient groups included a mainly secondary educational level in the screening group, and more equally distributed educational level and a shorter duration of marriage in the clinical diagnosis group. Body mass index and use of glucose-lowering tablets and insulin were higher in the clinical diagnosis group but the differences were not statistically significant. All other characteristics were similar between groups.

With the exception of educational level, which was more often at primary or tertiary level in clinically diagnosed males than in females, no significant differences were found between male and female patients (data not shown).

Brief IPQ mean scores and the results of linear regression models (with the adjusted absolute effect (β) of screening compared with clinical diagnosis on scores) are shown in Table 2. Brief IPQ mean scores within patients were comparable between the two groups, and no statistically significant effect of screening was found for any of the scores. Patients in both groups tended to recognize few effects on their own life and to believe that they were in control of their diabetes, reporting perceptions of symptoms, concern and emotional impact as low.

As for partners, however, significantly higher scores were found on four items in the screening group compared with the clinical diagnosis group: on the one hand, partners of screen-detected patients perceived greater consequences for their own life and had a stronger sense that their patient-partner was in control of his or her diabetes, but on the other hand, they were more concerned about their patient-partner's diabetes and believed that their patient-partner experienced more symptoms of diabetes (Table 2). Significant differences appeared to be mainly caused by younger age (<60 years; Appendix 1) and by a longer duration of diabetes (>6 months since diagnosis; Appendix 2).

Respondents' answers to the open-ended question (causes of diabetes) could be categorized into three main, but not mutually exclusive, causes: lifestyle, hereditary factors, and older age. Couples showed some agreement regarding these causes (kappa 0.35, 0.42 and 0.31, respectively; data not shown). Comparing the study groups, the screening group was less likely to identify lifestyle as the cause of diabetes (70.6% versus 87.9%, respectively, $P = 0.01$) and more likely to believe

Table 1 Characteristics of patients with newly diagnosed type 2 diabetes and their partners, for screening and clinical diagnosis groups

	n (%), unless otherwise specified					
	Patients			Partners		
	Screening *n* = 77	Clinical diagnosis *n* = 32	*P*	Screening *n* = 77	Clinical diagnosis *n* = 32	*P*
Demographic factors, individual						
Age, mean (SD) years	61.4 (8.7)	59.3 (8.7)	0.26	61.6 (9.2)	56.9 (7.7)	0.01
Sex, male	42 (54.5)	22 (68.8)	0.17	35 (45.5)	10 (31.2)	0.17
Educational level						
Primary	8 (10.7)	10 (31.2)	0.002	9 (12.0)	5 (16.1)	0.85
Secondary	59 (78.6)	14 (43.8)		53 (70.7)	21 (67.8)	
Tertiary	8 (10.7)	8 (25.0)		13 (17.3)	5 (16.1)	
Employment status[a]						
Employed	24 (31.2)	9 (28.1)	0.92	26 (33.8)	8 (25.0)	0.29
Homemaker	13 (16.9)	6 (18.8)		22 (28.6)	12 (37.5)	
Unemployed	9 (11.7)	5 (15.6)		3 (3.9)	4 (12.5)	
Retired	30 (39.0)	11 (34.4)		25 (32.5)	7 (21.9)	
Demographic factors, couple						
Duration of marriage, mean (SD) years[b]	36.4 (10.7)	31.7 (11.2)	0.04			
Children <18 years old	6 (7.8)	2 (6.2)	0.78			

Clinical characteristics			
Diagnosis ≤6 months ago	16 (21.3)	7 (21.9)	0.95
Glucose-lowering treatment[a]			
Diet only	26 (33.8)	6 (20.0)	0.16
Oral agents	44 (57.1)	22 (73.3)	0.12
Insulin	3 (3.9)	4 (13.3)	0.10
BMI, mean (SD) kg/m^2	28.6 (4.4)	30.7 (6.4)	0.05
SBP, mean (SD) mm Hg	139 (18)	139 (15)	0.96
HbA_{1c}, mean (SD) %	7.1 (1.7)	7.3 (1.4)	0.61
HbA_{1c}, mean (SD) mmol/mol	54 (18)	56 (15)	0.61
Total cholesterol, mean (SD) mmol/l	4.9 (1.1)	5.0 (1.7)	0.65

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; SBP = systolic blood pressure. [a] Figures do not add up to 100% due to missings or combinations of treatment. [b] Including duration of cohabitation if not (yet) married.

Table 2 Brief IPQ mean (SD) scores[a] and the effect (β) of screening on these scores compared with clinical diagnosis

	Patients				Partners			
Brief IPQ item	**Screening *n* = 77**	**Clinical diagnosis *n* = 32**	**β (95% CI)[b]**	***P***	**Screening *n* = 77**	**Clinical diagnosis *n* = 32**	**β (95% CI)[b]**	***P***
1. Consequences for own life	4.0 (2.8)	4.3 (2.8)	-0.56 (-1.98 to 0.86)	0.43	**6.4 (3.0)**	**5.1 (2.6)**	**1.53 (0.07 to 2.98)[c]**	**0.04**
2. Length of time diabetes will last	7.8 (3.5)	7.8 (3.6)	0.60 (-0.71 to 1.90)	0.36	8.8 (2.3)	9.5 (1.2)	-1.00 (-2.08 to 0.08)	0.07
3. Patient's ability to control his/her diabetes	6.7 (2.3)	6.1 (3.0)	0.62 (-0.71 to 1.95)	0.36	**8.0 (2.1)**	**6.6 (2.8)**	**1.49 (0.43 to 2.55)[c]**	**0.01**
4. Belief in effect of treatment	7.6 (1.9)	7.4 (2.6)	0.63 (-0.42 to 1.68)	0.24	7.3 (2.2)	7.7 (1.8)	-0.21 (-1.26 to 0.84)	0.69
5. Symptoms experienced by the patient	3.4 (3.1)	3.7 (2.8)	-0.94 (-2.35 to 0.47)	0.19	**6.3 (3.0)**	**5.0 (2.7)**	**1.86 (0.56 to 3.17)[c]**	**0.01**
6. Concern about patient's diabetes	4.1 (2.8)	4.3 (3.0)	-0.66 (-2.14 to 0.83)	0.38	**4.8 (3.0)**	**3.5 (2.4)**	**1.49 (0.11 to 2.87)[c]**	**0.04**
7. Understanding of patient's diabetes	7.2 (2.6)	7.2 (1.8)	0.27 (-0.89 to 1.43)	0.64	7.6 (2.3)	7.5 (1.8)	0.61 (-0.32 to 1.55)	0.19
8. Emotional impact, e.g. anger, fear, depression	3.5 (3.1)	3.3 (3.2)	-0.29 (-1.79 to 1.22)	0.71	7.1 (2.8)	5.8 (3.1)	1.13 (-0.34 to 2.60)	0.13

[a] Items are rated using a 0-to-10 response scale, with higher scores reflecting a stronger belief in or perception of the item. [b] Adjusted for age, sex, educational level, duration of diabetes, duration of marriage and insulin use. [c] Significant (P <0.05) relative to reference category (=clinical diagnosis group).

that hereditary factors also played a causal role (47.8% versus 31.0% in the clinical diagnosis group, $P = 0.03$). Older age as a cause of the disease was identified equally (24.3% of the screening group and 25.9% of the clinical diagnosis group, $P = 0.81$). The results of linear regression models by gender are presented in Table 3. Female patients detected by screening had a significantly greater belief in the effect of treatment compared with those in the clinical diagnosis group, whereas Brief IPQ scores within male patients were not significantly affected by the route to diagnosis. Female partners in the screening group were more concerned by their patient-partner's diabetes and believed that their patient-partner experienced more diabetes symptoms following diagnosis, but they were optimistic about the duration of their partner's diabetes. Male partners' illness perceptions were comparable with male patients and showed no significant effect due to screening, although they appeared to perceive greater consequences for their own life and experience a higher emotional impact.

Table 3 Effect of screening on Brief IPQ scores, compared with clinical diagnosis, by gender

	Patients		Partners	
Brief IPQ item	**Male patients β (95% CI)[a]**	**Female patients β (95% CI)[a]**	**Female partners β (95% CI)[a]**	**Male partners β (95% CI)[a]**
1. Consequences for own life	-0.96 (-2.77 to 0.86)	0.53 (-2.39 to 3.46)	1.29 (-0.55 to 3.13)	2.07 (-1.13 to 5.26)
2. Length of time diabetes will last	-0.05 (-1.79 to 1.68)	1.80 (-0.70 to 4.29)	**-1.44 (-2.77 to -0.10)[b]**	-0.03 (-2.20 to 2.15)
3. Patient's ability to control his/her diabetes	-0.15 (-1.87 to 1.58)	2.06 (-0.59 to 4.71)	1.32 (-0.04 to 2.67)	0.87 (-1.35 to 3.09)
4. Belief in effect of treatment	-0.38 (-1.73 to 0.97)	**2.17 (0.30 to 4.04)[b]**	-0.22 (-1.60 to 1.15)	-0.80 (-2.96 to 1.36)
5. Symptoms experienced by the patient	-0.88 (-2.57 to 0.80)	-0.89 (-4.17 to 2.39)	**2.31 (0.73 to 3.88)[b]**	0.14 (-2.70 to 2.98)
6. Concern about patient's diabetes	-0.34 (-2.25 to 1.56)	-1.74 (-4.83 to 1.35)	**1.82 (0.14 to 3.49)[b]**	0.40 (-2.66 to 3.45)
7. Understanding of patient's diabetes	0.98 (-1.42 to 1.62)	0.59 (-1.66 to 2.83)	0.63 (-0.56 to 1.82)	-0.13 (-1.56 to 1.31)
8. Emotional impact, e.g. anger, fear, depression	0.21 (-1.70 to 2.12)	-1.55 (-4.68 to 1.58)	0.71 (-1.05 to 2.47)	2.47 (-0.53 to 5.47)

[a] Adjusted for age, educational level, duration of diabetes, duration of marriage and insulin use.
[b] Significant ($P < 0.05$) relative to reference category (=clinical diagnosis group).

Discussion

Summary of main findings

Patients diagnosed with type 2 diabetes shared similar illness perceptions, which appeared to be little affected by the route to diagnosis.

In contrast, the partners of patients who were detected by screening perceived greater effects on their own life compared with partners of patients identified by clinical diagnosis. However, partners in the screening group also showed a stronger belief in the ability of their patient-partner to control his or her diabetes and tended to overestimate ability to success-fully perform self-care. Female partners in the screening group were especially concerned about their partner's diabetes and perceived more symptoms in their patient-partner.

Couples showed some agreement when identifying the causes of diabetes, the screening group primarily focusing on hereditary factors and the clinical diagnosis group on lifestyle factors.

Strengths and limitations

The major strength of this study is that our findings are based on patient and partner data from regular general practices, rather than from a trial setting. Patients were diagnosed with type 2 diabetes in general practice and participants were recruited by their own GP. It therefore seems likely that the patterns found in this study are generally representative for primary care patients with type 2 diabetes. Additional strengths derive from the use of a validated questionnaire and an acceptable internal reliability of the questionnaire when adapted for partners. Furthermore, as our analyses were controlled for age, sex, educational level, duration of marriage, duration of diabetes and insulin use, findings cannot be attributed to any of these variables.

A limitation of the study may be the relatively small number of participants, resulting in a statistical power that may not have been sufficient to detect very small differences in illness perception scores among patient groups. Nevertheless, we were able to detect significant differences among partners, and the distribution of participants (screening group 71%, clinical diagnosis group 29%) was comparable with an earlier and larger study (n = 565; screening 64% versus clinical diagnosis 36%).[23]

Although many of our participants were recruited from general practices with an interest in diabetes and research, these practices are normal community practices with a population and diabetes prevalence rates representative of the general Dutch population. A selection bias due to a selective allocation to one study group is unlikely because patients were not randomized to a group but selected by the route to diagnosis. Patients in both study groups were all treated

according to the same practice guidelines during usual care.[1] Volunteer or self-selection bias cannot be entirely ruled out, however, because response rates were low and some baseline characteristics differed between the study groups. We adjusted our data analyses for these differences so as to account for any possible bias.

Another possible limitation is that three quarters of the patients participating in our study had a diagnosis older than 6 months, by which time many had already received education and treatment. However, time of diagnosis was comparable between the screen-detected and clinically diagnosed patient groups and similar low mean hemoglobin A_{1c} values reflected good glycaemic control in both groups. Nevertheless, and as stated in the section "Introduction", dissimilarities in illness perceptions should still be targeted in order to improve self-care.

Comparison with existing literature

This study is the first to explore the effects of the route to diagnosis of type 2 diabetes (through screening versus clinical diagnosis) on both patients' and partners' illness perceptions.

The patients' Brief IPQ scores in our study were comparable with those reported in literature.[22] Furthermore, our findings that patients with a recent screening-based diagnosis of type 2 diabetes tend to report low emotional distress, low threat perceptions and a strong belief in personal control also agrees with previous studies.[6,7] In addition, we found that illness perceptions were similar following a recent clinical diagnosis.

Our data confirm that compared with patients, partners generally perceive diabetes as a more serious disease and as having a greater impact on daily life[16] but indicate that these beliefs are especially prevalent following a screening-based diagnosis.

In an earlier study of illness perceptions that used the IPQ-R, patients with type 2 diabetes reported a greater sense of control over their diabetes than was the case with their partners.[15] This contrasts with our findings, which showed that partners in the screening group had a stronger sense that their patient-partners were in control of their diabetes than that felt by the patients themselves. However, although the Brief IPQ and the IPQ-R are broadly comparable, the Brief IPQ personal control item was significantly associated with diabetes self-efficacy, in contrast to the IPQ-R personal control item, suggesting that the Brief IPQ may have an advantage in the area of control.[22]

Finally, prospective research has shown that patients' illness perceptions develop in the early stages of disease and that unless directly challenged by treatment or change in clinical state, they are likely to remain constant.[24] In our study, significant differences in the Brief IPQ-scores of partners appeared to be

related to a longer diabetes duration in their patient-partners, perhaps indicating that partners' illness perceptions may be less stable.

Implications for practice and research

We have shown that the screening route to the diagnosis of type 2 diabetes mainly impacts on the illness perceptions of patients' partners. Partners of patients diagnosed through screening not only have greater negative beliefs regarding diabetes but also perceive enhanced personal control in their patient-partners. After 3 years, partners of screen-detected patients still appear to be more overwhelmed by the diagnosis than partners of clinically diagnosed patients and tend to believe, inaccurately, that their patient-partners have a high level of control over their diabetes.

Our study yielded new and unexpected findings and stresses the importance of the partner's role in diabetes education and treatment in daily primary care, especially following a screening-based diagnosis of type 2 diabetes. However, the exploratory, cross-sectional study design and the small sample size did not provide enough evidence for a well-defined explanation of our findings. For example, it remains unclear why a diagnosis resulting from screening appears to be more distressing for partners than that for patients. Additional qualitative research may provide further insights.

In patients with poorly controlled type 2 diabetes, a psychological family-based intervention targeting negative or inaccurate illness perceptions recently reported improvements both in glucose control and in beliefs regarding diabetes, well being, diet, exercise and family support.[25] A similar approach may be useful in the treatment of patients with diabetes detected by screening and further study is needed on the effects of interventions that target illness perceptions in patients and their partners following a screening-based diagnosis. Future studies should be larger, prospective in design and show a greater focus on changes in illness perceptions in the first years after diagnosis.

In conclusion, the illness perceptions of partners are the most influenced by the route to diagnosis of type 2 diabetes. Professionals involved in diabetes education and treatment should focus on and target the illness perceptions of partners, especially where screening is concerned. The Brief IPQ is a simple and effective tool with which to investigate these illness perceptions in daily practice.

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Ethical approval

The study did not require approval by an ethics committee.

Conflicts of interest

None.

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Appendix 1 Effect of screening on Brief IPQ scores, compared with clinical diagnosis, by age group

	Patients		Partners	
Brief IPQ item	**<60 years β (95% CI)[a]**	**≥60 years β (95% CI)[a]**	**<60 years β (95% CI)[a]**	**≥60 years β (95% CI)[a]**
1. Consequences for own life	**-2.01 (-4.00 to -0.02)[b]**	0.64 (-1.49 to 2.77)	**2.13 (0.20 to 4.05)[b]**	0.70 (-1.71 to 3.10)
2. Length of time diabetes will last	-0.27 (-1.63 to 1.10)	1.18 (-1.05 to 3.40)	**-1.67 (-3.28 to -0.05)[b]**	-0.46 (-1.92 to 0.99)
3. Patient's ability to control his/her diabetes	0.82 (-1.24 to 2.89)	0.23 (-1.74 to 2.20)	**2.09 (0.51 to 3.68)[b]**	1.14 (-0.42 to 2.70)
4. Belief in effect of treatment	0.23 (-0.98 to 1.45)	1.40 (-0.40 to 3.20)	-0.48 (-1.96 to 1.01)	-0.10 (-1.59 to 1.78)
5. Symptoms experienced by the patient	-1.79 (-3.89 to 0.32)	-0.25 (-2.38 to 1.88)	**3.05 (1.41 to 4.70)[b]**	0.60 (-1.40 to 2.59)
6. Concern about patient's diabetes	-1.61 (-3.75 to 0.53)	0.65 (-1.49 to 2.79)	1.32 (-0.37 to 3.02)	2.32 (-0.14 to 4.78)
7. Understanding of patient's diabetes	-0.03 (-1.60 to 1.54)	0.22 (-1.64 to 2.09)	0.04 (-1.44 to 1.53)	1.19 (-0.03 to 2.42)
8. Emotional impact, e.g. anger, fear, depression	-1.37 (-3.61 to 0.86)	0.95 (-1.25 to 3.15)	**1.85 (0.12 to 3.57)[b]**	0.58 (-2.05 to 3.20)

[a] Adjusted for sex, educational level, duration of diabetes, duration of marriage and insulin use.
[b] Significant (P <0.05) relative to reference category (=clinical diagnosis group).

Appendix 2 Effect of screening on Brief IPQ scores, compared with clinical diagnosis, by time since diagnosis

	Patients		Partners	
Brief IPQ item	**≤6 months β (95% CI)[a]**	**>6 months β (95% CI)[a]**	**≤6 months β (95% CI)[a]**	**>6 months β (95% CI)[a]**
1. Consequences for own life	-0.45 (-3.00 to 2.10)	-0.75 (-2.50 to 0.99)	1.53 (-1.54 to 4.61)	1.59 (-0.22 to 3.41)
2. Length of time diabetes will last	0.99 (-2.98 to 4.96)	-0.08 (-0.66 to 2.25)	-0.44 (-2.88 to 2.00)	**-1.46 (-2.70 to -0.22)[b]**
3. Patient's ability to control his/her diabetes	-0.86 (-4.42 to 2.70)	0.80 (-1.74 to 2.20)	0.53 (-0.95 to 2.00)	**1.73 (0.34 to 3.12)[b]**
4. Belief in effect of treatment	1.59 (-0.79 to 3.96)	0.09 (-1.13 to 1.31)	-1.41 (-3.85 to 1.03)	0.15 (-1.06 to 1.35)
5. Symptoms experienced by the patient	-0.42 (-3.62 to 2.78)	-1.38 (-3.08 to 0.32)	3.01 (-0.18 to 6.20)	**1.83 (0.30 to 3.36)[b]**
6. Concern about patient's diabetes	0.51 (-2.79 to 3.82)	-1.10 (-2.86 to 0.66)	0.15 (-3.39 to 3.69)	**2.00 (0.38 to 3.62)[b]**
7. Understanding of patient's diabetes	-0.08 (-2.45 to 2.30)	0.28 (-1.10 to 1.67)	1.14 (-0.24 to 2.51)	0.43 (-0.76 to 1.62)
8. Emotional impact, e.g. anger, fear, depression	0.06 (-3.27 to 3.39)	-0.45 (-2.20 to 1.31)	-0.52 (-4.15 to 3.10)	1.58 (-0.13 to 3.29)

[a] Adjusted for age, sex, educational level, duration of marriage and insulin use.
[b] Significant (P <0.05) relative to reference category (=clinical diagnosis group).

Long-term effectiveness

7

Vascular outcomes in patients with screen-detected or clinically diagnosed type 2 diabetes: Diabscreen study follow-up

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Abstract

Purpose Screening guidelines for type 2 diabetes recommend targeting high-risk individuals. Our objective was to assess whether diagnosis of type 2 diabetes based on opportunistic targeted screening results in lower vascular event rates when compared with diagnosis on the basis of clinical signs or symptoms.

Methods In a prospective, nonrandomized, observational study, we enrolled patients aged 45 to 75 years from 10 family practices in the Netherlands with a new diagnosis of type 2 diabetes, detected either by (1) opportunistic targeted screening (n = 359) or (2) clinical signs or symptoms (n = 206). Patients in both groups received the same guideline-concordant diabetes care. The main group outcome measure was a composite of death from cardiovascular disease (CVD), nonfatal myocardial infarction, and nonfatal stroke.

Results Baseline vascular disease was more prevalent in the opportunistic targeted screening group, mainly ischemic heart disease (12.3% vs 3.9%, P = 0.001) and nephropathy (16.9% vs 7.1%, P = 0.002). After a mean follow-up of 7.7 years (SD = 2.4 years) and 7.1 years (SD = 2.7 years) years for the opportunistic targeted screening and clinical diagnosis groups, respectively, composite primary event rates did not differ significantly between the 2 groups (9.5% vs 10.2%, P = 0.78; adjusted hazard ratio 0.67, 95% confidence interval, 0.36-1.25; P = 0.21). There were also no significant differences in the separate event rates of deaths from CVD, nonfatal myocardial infarction, and nonfatal strokes.

Conclusions Opportunistic targeted screening for type 2 diabetes detected patients with higher CVD morbidity at baseline when compared with clinical diagnosis but showed similar CVD mortality and major CVD morbidity after 7.7 years. Opportunistic targeted screening and guided care appears to improve vascular outcomes in type 2 diabetes in primary care.

Introduction

Targeting screening for type 2 diabetes to high-risk individuals is recommended for the prevention of vascular complications.[1] The justification for the promotion of screening is that patients with type 2 diabetes are already at risk for developing microvascular complications before clinical diagnosis[2] and have a twofold higher risk of cardiovascular disease and mortality.[3] The worldwide prevalence of type 2 diabetes is expected to keep rising in the next decade, dramatically increasing the burden of disease and health care costs.[4,5]

Glycemic control and cardiovascular risk management (mainly treatment of hypertension and hypercholesterolemia) decrease vascular disease and mortality in patients with type 2 diabetes.[6,7] It is currently uncertain, however, whether treatment of patients with type 2 diabetes detected through screening results in lower vascular event rates when compared with treatment of patients diagnosed by clinical signs or symptoms.[6]

To address this issue, we undertook a study that builds on a type 2 diabetes-screening program performed by the Diabscreen study, in which diabetes screening was conducted during regular primary care in the Netherlands. The Diabscreen study reported a fair yield of opportunistic screening, targeting patients at high risk for undiagnosed type 2 diabetes who visited their family physician.[8] After evaluation, the program was implemented in daily practice. Because of the continuous nature of the primary care setting of the program, we are now able to report a follow-up of up to 10 years after screening.

We compared outcomes in patients with type 2 diabetes that had been diagnosed by opportunistic targeted screening with outcomes of patients given a diagnosis after displaying diabetes signs or symptoms during the same period and in the same family practices. All patients had received the same guideline-concordant diabetes care after diagnosis, ie, the same glycemic control and cardiovascular risk management.[9]

Our main aim was to assess whether opportunistic targeted screening, compared with clinical diagnosis, would beneficially affect the risk of death from cardiovascular disease, myocardial infarction and stroke.

Methods

Participants and setting

For the current Diabscreen study follow-up, data were available from 10 family practices in the Netherlands, all taking part in the Nijmegen Monitoring Project (NMP).[10,11] The NMP is a practice-based research network of the Radboud University

Nijmegen Medical Centre, with an audit-enhanced monitoring system for chronic diseases such as type 2 diabetes. Despite this academic alliance, all participants are standard community family practices.

Every individual in the Netherlands is registered with a family physician, and this registration is usually maintained over many years. Type 2 diabetes is commonly treated in primary care, and patients may consult a specialist only upon referral by the family physician.

We included data from all patients, aged 45 to 75 years, with newly diagnosed type 2 diabetes who were enrolled in the monitoring system by their family physician between 1998 and 2005. For the purposes of this study, patients were not randomized into a subgroup but were selected by the detection method of their diabetes, as recorded in the NMP database: (1) type 2 diabetes detected by opportunistic targeted screening; or (2) clinically diagnosed type 2 diabetes based on signs or symptoms. These 2 groups are described in detail.

Type 2 diabetes by opportunistic targeted screening

The opportunistic targeted screening procedure was based on the Diabscreen study, and some of the current data were derived from that study.[8] In brief, we considered patients to be at high risk for undiagnosed type 2 diabetes if they had 1 or more of the following diabetes risk factors, derived from the American Diabetes Association (ADA) recommendations for screening for type 2 diabetes[1]: a family history of diabetes (defined as diabetes in a parent, brother, sister, or a combination thereof); a history of cardiovascular disease (heart failure, ischemic heart disease, myocardial infarction, transient cerebral ischemia, stroke, or peripheral arterial disease); obesity (body mass index [BMI] >27 kg/m^2); hypertension (blood pressure ≥140/90 mm Hg or taking antihypertensive agents); hypercholesterolemia (total cholesterol >5.0 mmol/L [>193 mg/dL] or taking a lipid-lowering agent); or a history of gestational diabetes mellitus.[1,9]

High-risk patients were labeled as such in the electronic medical record. When visiting their family practice for a regular care consultation, high-risk patients were invited for screening using fasting plasma glucose testing. Screening was accepted in 90% of cases.[12] Diagnosis of type 2 diabetes was based on international criteria, requiring two fasting plasma glucose measurements on 2 separate days, both with a value ≥7.0 mmol/L (≥126 mg/dl).[13]

Type 2 diabetes by clinical diagnosis

Patients with clinically diagnosed type 2 diabetes had signs or symptoms of diabetes during a practice consultation. If they had classic symptoms of hyperglycemia (polyuria and polydipsia), a single, random, plasma glucose measurement of ≥11.1 mmol/L (≥200 mg/dL) was sufficient for diagnosis. When they had milder symptoms

(eg, fatigue, frequent infections, blurred vision), 2 fasting plasma glucose samples, on separate days and both ≥7.0 mmol/L (≥126 mg/dl), were required.[13]

Diabetes treatment

Patients in both study groups received the same standard of diabetes care and were treated during routine care consultations by their own family physician and practice nurses. Diabetes care was in line with the Dutch family practice guidelines for type 2 diabetes:[9] recorded on intake and then yearly are family history, smoking status, and comorbidities; a physical examination; an ophthalmologic examination (fundoscopy or fundus photography); laboratory testing for fasting blood glucose, hemoglobin A_{1c}, lipids, plasma creatinine, and albuminuria; and education and lifestyle advice.

Three times a year patients have weight and blood pressure measured, fasting blood glucose and hemoglobin A_{1c} tested if on insulin; and education and lifestyle advice. Glycemic control is undertaken to reduce hemoglobin A_{1c} to less than 53 mmol/mol (<7.0%), using a stepwise approach with metformin as a first-choice agent when diet is insufficient; a sulphonylurea derivative or insulin is added, if necessary.

For cardiovascular risk, the target systolic blood pressure is less than 140 mm Hg. A statin is recommended unless untreated low-density lipoprotein cholesterol is less than 2.5 mmol/L (<160 mg/dL) or the absolute 10-year mortality risk is less than 5%. An angiotensin-converting enzyme inhibitor is recommended for microalbuminuria even with normal blood pressure, and a platelet aggregation inhibitor is indicated for secondary prevention only.

Definition of outcomes

All data were collected from the NMP electronic database. We used all clinical information available up to the end of 2009. The primary group outcome during follow-up was the composite of death from cardiovascular disease (CVD), nonfatal myocardial infarction, and nonfatal stroke. Secondary outcomes included microvascular complications (diabetic retinopathy, neuropathy, and nephropathy), any first CVD event (nonfatal myocardial infarction, nonfatal stroke, heart failure, ischemic heart disease, transient cerebral ischemia, or peripheral arterial disease), all-cause death, and non-CVD death. Retinopathy was diagnosed with funduscopy or fundus photography by an ophthalmologist who reported the result to the family physician. Neuropathy was diagnosed by the family physician by physical examination in cases showing loss of monofilament sensation in the toes. Nephropathy was defined as a glomerular filtration rate <60 mL/min/1.73 m^2, estimated by the Modification of Diet in Renal Disease Study equation.[14]

Statistical analysis

We analyzed participant characteristics at baseline and at last follow-up visit using the Pearson χ^2 or Fisher exact test for categorical data and the Student *t* test for means where appropriate. The main process and outcome variables of care during follow-up were similarly analyzed.

To compare the primary and secondary outcomes between the 2 study groups, we calculated the incidences of the events and applied the Pearson χ^2 or Fisher exact test for statistical analysis.

In Cox regression models, hazard ratios for the outcomes with their 95% confidence intervals and *P* values were calculated. Time to event was defined as the time between date of diagnosis and date of cardiovascular event or death. For microvascular outcomes, the date of event was the date of diagnosis during follow-up. Patients were followed until death, loss to follow-up, or end of study (December 31, 2009). Hazard ratios were unadjusted and adjusted for 6 baseline variables: age, sex, CVD, fasting plasma glucose, systolic blood pressure, and plasma creatinine.

We conducted all analyses in SPSS 16.0 for Windows (SPSS Inc). All analyses were 2-sided, and we considered a *P* value <0.05 to be significant.

Results

Opportunistic targeted screening detected type 2 diabetes in 359 patients. A clinical diagnosis of type 2 diabetes based on signs or symptoms was found in 206 patients (Table 1). Patients with clinically diagnosed type 2 diabetes were more likely to be men and were generally younger than patients with diabetes detected by screening.

At baseline, the prevalence of macrovascular disease was significantly higher in the opportunistic targeted screening group, which could be primarily explained by ischemic heart disease. Prevalence of diabetic retinopathy and neuropathy were similar, but nephropathy was more commonly found with opportunistic targeted screening. Mean systolic blood pressure and plasma creatinine were also significantly higher in the screening group. As expected, fasting plasma glucose and hemoglobin A_{1c} levels were significantly elevated in patients with clinically diagnosed diabetes. Other characteristics were similar at baseline.

Follow-up

Mean systolic blood pressure and plasma creatinine no longer differed between the opportunistic targeted screening and clinical diagnosis groups after a mean follow-up of 7.7 years (SD [standard deviation] = 2.4 years) and 7.1 years (SD = 2.7 years), respectively (Table 1). Glucose and cholesterol values had improved and smoking had decreased in both groups.

Table 1 Characteristics of patients with newly diagnosed type 2 diabetes for opportunistic targeted screening (n = 359) and clinical diagnosis (n = 206) groups at baseline and after follow-up

Characteristic	Baseline			Follow-up		
	Opportunistic targeted screening	Clinical diagnosis	*P*	Opportunistic targeted screening	Clinical diagnosis	*P*
Age, mean (SD), years	61.8 (7.8)	59.0 (8.1)	<0.001			
Sex (male), No. (%)	175 (48.7)	118 (57.3)	0.05			
Follow-up, mean (SD), years				7.7 (2.4)	7.1 (2.7)	0.01
Previous vascular disease						
History of macrovascular disease,[a] No. (%)	88 (24.5)	24 (11.7)	<0.001			
Ischemic heart disease, No. (%)	44 (12.3)	8 (3.9)	0.001			
Myocardial infarction, No. (%)	26 (7.2)	11 (5.3)	0.38			
Stroke, No. (%)	12 (3.3)	3 (1.5)	0.18			
Other, No. (%)	24 (6.7)	11 (5.3)	0.52			
History of microvascular disease,[a] No. (%)	63 (17.5)	24 (11.7)	0.06			
Retinopathy, No. (%)	1 (0.3)	3 (1.7)	0.12			
Neuropathy, No. (%)	6 (1.7)	8 (3.9)	0.10			
Nephropathy, No. (%)	57 (16.9)	13 (7.1)	0.002			
Blood-glucose control						
FPG, mean (SD), mmol/l	8.8 (2.9)	12.9 (5.0)	<0.001	7.9 (1.7)	8.2 (2.2)	0.06
HbA_{1c}, mean (SD),[b] mmol/mol	55 (17)	74 (28)	<0.001	51 (10)	54 (12)	0.001
HbA_{1c}, mean (SD),[b] %	7.2 (1.6)	8.9 (2.5)	<0.001	6.8 (0.9)	7.1 (1.1)	0.001

Table 1 Continued

Characteristic	Baseline			Follow-up		
	Opportunistic targeted screening	Clinical diagnosis	*P*	Opportunistic targeted screening	Clinical diagnosis	*P*
CVD risk factors						
Current smoking, No. (%)	66 (19.3)	41 (21.9)	0.47	45 (13.5)	29 (15.8)	0.48
Systolic blood pressure, mean (SD), mm Hg	153 (20)	147 (21)	0.004	145 (18)	144 (17)	0.59
Diastolic blood pressure, mean (SD), mm Hg	86 (10)	85 (11)	0.33	80 (10)	81 (9)	0.16
BMI, mean (SD), kg/m^2	30.5 (4.7)	29.7 (5.0)	0.07	29.9 (4.7)	29.6 (4.6)	0.51
Total cholesterol, mean (SD), mmol/l	6.0 (1.2)	6.0 (1.4)	0.38	4.7 (1.1)	4.7 (1.1)	0.58
LDL cholesterol, mean (SD), mmol/l	3.7 (1.1)	3.8 (1.2)	0.72	2.6 (1.0)	2.7 (0.9)	0.86
Plasma creatinine, mean (SD), mmol/l	88.7 (18.1)	84.1 (17.3)	0.004	89.4 (24.5)	87.4 (19.9)	0.32

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein.

[a] Some patients had multiple events.

[b] Missing at baseline = 201 in opportunistic targeted screening group; 126 in clinical diagnosis group.

Process and outcome variables of care

Processes of care were comparable between both study groups after follow-up (Table 2). With regard to outcome variables, we found significantly better glycemic control among patients from the opportunistic targeted screening group and less frequent insulin treatment, but a higher use of antihypertensive medications. Other outcomes of care did not differ significantly from those of the clinical diagnosis group.

Primary outcomes

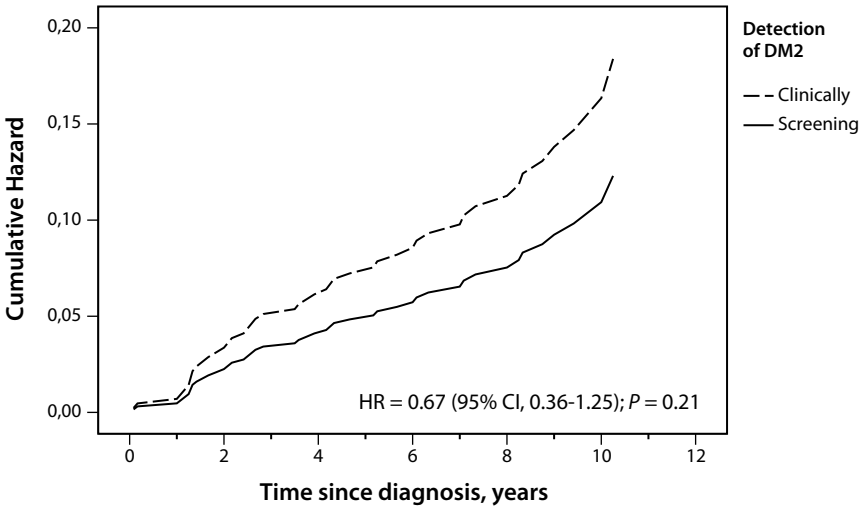
The composite primary event rates during follow-up did not differ significantly between the opportunistic targeted screening and clinical diagnosis groups (9.5% vs 10.2%, *P* = 0.78; adjusted hazard ratio [HR] = 0.67, 95% CI, 0.36-1.25; *P* = 0.21; Table 3). The hazard curves, however, show a more steeply increasing risk for a major macrovascular event in patients with clinically diagnosed diabetes (Figure 1).

Table 2 Main process and outcome variables of care, at last follow-up for opportunistic targeted screening (*n* = 359) and clinical diagnosis (*n* = 206) groups

Variable	Opportunistic targeted screening No. (%)	Clinical diagnosis No. (%)	*P*
Process of care			
HbA_{1c} recorded	345 (96.1)	196 (95.1)	0.59
Systolic blood pressure recorded	349 (97.2)	197 (95.6)	0.32
LDL Cholesterol recorded	332 (92.5)	182 (88.3)	0.10
Eye examination recorded	344 (95.8)	189 (91.7)	0.04
Foot examination recorded	348 (96.9)	192 (93.2)	0.04
Outcome of care			
HbA_{1c} <53 mmol/mol (7.0%)	220 (63.8)	99 (50.5)	0.003
Systolic blood pressure <140 mm Hg	126 (36.1)	69 (35.0)	0.80
LDL cholesterol <2.5 mmol/l	159 (47.9)	81 (44.5)	0.46
Glucose-lowering treatment			
Diet only	96 (26.7)	34 (16.5)	0.01
Oral agent(s)	231 (64.3)	147 (71.4)	0.09
Insulin	19 (5.3)	26 (12.6)	0.002
Anti-hypertensive agent(s)	228 (71.2)	90 (52.3)	<0.001
Lipid-lowering agent(s)	216 (67.7)	109 (63.7)	0.38

HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein.

Figure 1 Cumulative hazard of primary outcome following diagnosis of type 2 diabetes by opportunistic targeted screening, compared with clinical diagnosis



CVD = cardiovascular disease; HR = hazard ratio.
Notes: Cumulative hazard of death from CVD, nonfatal myocardial infarction, or nonfatal stroke, adjusted for age, sex, and the following baseline characteristics: CVD, systolic blood pressure, fasting plasma glucose, and plasma creatinine.

Lower incidences and risk for nonfatal myocardial infarction and for nonfatal stroke were observed in the opportunistic targeted screening group, whereas risk for CVD death was higher. Because of the small numbers and a large confidence interval, the differences for CVD death were not statistically significant.

Secondary outcomes

Microvascular event rates were also not significantly different between the study groups (Table 3), although incidence and risk for diabetic retinopathy were lower after opportunistic targeted screening (1.5% vs 3.9%; $P = 0.08$; adjusted HR = 0.75, 95% CI, 0.19-3.08; $P = 0.69$).

Risk for any first CVD event did not differ significantly between the groups (Table 3). Lower incidences and risk were observed in the opportunistic targeted screening group for ischemic heart disease, whereas they were higher for heart failure, transient cerebral ischemia, and peripheral arterial disease, but these differences were not statistically significant or the 95% confidence intervals were large (data not shown).

Table 3 Events after diagnosis of type 2 diabetes for opportunistic targeted screening (n = 359) and clinical diagnosis (n = 206) groups

Events	Incidence, No. (%)			Unadjusted HR (95% CI)[a]		Adjusted HR (95% CI)[a]	
	Opportunistic targeted screening	Clinical diagnosis	*P*		*P*		*P*
Primary Outcomes							
Major macrovascular event[b]	34 (9.5)	21 (10.2)	0.78	0.84 (0.49 to 1.44)	0.52	0.67 (0.36 to 1.25)	0.21
CVD death	16 (4.5)	4 (1.9)	0.16	2.10 (0.70 to 6.28)	0.19	1.88 (0.41 to 8.57)	0.42
Nonfatal MI	11 (3.1)	11 (5.3)	0.18	0.54 (0.23 to 1.25)	0.15	0.43 (0.18 to 1.02)	0.06
Nonfatal stroke	10 (2.8)	9 (4.4)	0.32	0.57 (0.23 to 1.40)	0.22	0.68 (0.23 to 2.02)	0.49
Secondary Outcomes							
Microvascular event[b]	54 (17.1)	24 (15.2)	0.59	1.04 (0.64 to 1.68)	0.88	0.94 (0.55 to 1.60)	0.81
Retinopathy	5 (1.5)	7 (3.9)	0.08	0.32 (0.10 to 1.01)	0.05	0.75 (0.19 to 3.08)	0.69
Neuropathy	40 (11.5)	16 (8.3)	0.25	1.33 (0.74 to 2.37)	0.34	1.23 (0.63 to 2.39)	0.54
Nephropathy	18 (5.5)	10 (5.9)	0.87	0.86 (0.39 to 1.85)	0.69	0.93 (0.38 to 2.24)	0.87
Any first CVD[c]	68 (18.9)	28 (13.6)	0.10	1.33 (0.86 to 2.07)	0.21	1.03 (0.63 to 1.67)	0.92
All-cause death	31 (8.6)	22 (10.7)	0.42	0.73 (0.42 to 1.26)	0.26	0.60 (0.31 to 1.13)	0.12
Non-CVD death	15 (4.2)	18 (8.7)	0.03	0.43 (0.22 to 0.85)	0.02	0.33 (0.15 to 0.71)	0.01

CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction.

[a] Hazard ratios with matching P values compare hazards in type 2 diabetes detected by opportunistic targeted screening with those in clinically diagnosed type 2 diabetes, unadjusted, and adjusted for age, sex, and the following baseline characteristics: CVD, systolic blood pressure, fasting plasma glucose, and plasma creatinine.

[b] Some patients had multiple events.

[c] Nonfatal MI, nonfatal stroke, heart failure, ischemic heart disease, transient cerebral ischemia, or peripheral arterial disease.

All-cause death rates did not differ significantly (8.6% vs 10.7%; *P* = 0.42; adjusted HR = 0.60, 95% CI, 0.31-1.13; *P* = .12), in contrast to non-CVD death (4.2% vs 8.7%; *P* = 0.03; adjusted HR = 0.33, 95% CI, 0.15-0.71; *P* = 0.01; Table 3). We observed more deaths caused by infections or pulmonary disease (2.2% vs 1.5%) in the opportunistic targeted screening group but fewer deaths that were due to cancer (1.9% vs 7.3%). No specific type of cancer could explain the higher prevalence in the clinical diagnosis group (data not shown).

Discussion

This study is the first to compare patients from the same population with type 2 diabetes detected by either opportunistic targeted screening or by clinical signs or symptoms and observed for long-term vascular outcomes.

For patients with type 2 diabetes detected by opportunistic targeted screening who had higher CVD morbidity at baseline, in particular ischemic heart disease and hypertension-related nephropathy, after up to 10 years follow-up, major macrovascular event rates did not significantly differ between the 2 groups. Secondary vascular event rates were also not significantly different between groups, although the opportunistic targeted screening group did show a lower risk for diabetic retinopathy than the clinical diagnosis group.

Differences at diagnosis between patients with type 2 diabetes detected by screening and clinically were described earlier in the Hoorn Screening Study,[15] a targeted diabetes screening study in the Netherlands. Our data confirmed the findings of the Hoorn Screening Study and showed that glucose levels were higher among patients with signs or symptoms at diagnosis, whereas retinopathy and neuropathy were equally prevalent in the 2 groups. Additionally, these authors already noted strikingly prevalent macrovascular complications in patients with diabetes detected by screening.[16]

The major strength of our study was its particular setting. Although all NMP practices are affiliated academically with the Radboud University Nijmegen Medical Centre, they are normal community practices with a population representative of the general Dutch population and a diabetes prevalence equal to that anywhere in the Netherlands.[10,17] That the Dutch system of primary health care provides for universal access and continuity of patient registration enabled us to collect and present follow-up data from daily practice.

The effectiveness of screening for type 2 diabetes should preferably be investigated in a randomized controlled trial.[18] In the current absence of such trials and with limited evidence found in recent case-control, cross-sectional, and modeling studies,[6] we believe that an observational study can provide important

new data. Because we could show that patients in both study groups received the same level of diabetes care,[9] we were able to investigate outcomes related to time of diagnosis and early treatment.

Overall, we found lower vascular event rates than expected in both the opportunistic targeted screening group and the clinical diagnosis group. This finding might reflect the impact of the guideline-concordant diabetes care in the practices, which includes cardiovascular risk management. Diabetes treatment had been successful in reducing blood pressure, smoking, and blood glucose and lipid levels in both groups.

We showed that the hazard curve of the primary outcome was higher for clinically diagnosed diabetes than for opportunistic targeted screening, which might be explained by lead-time bias: the longer interval between diagnosis and development of complications in patients detected by opportunistic targeted screening might be due to earlier detection in the natural history of the disease, instead of earlier treatment.[19] The lower glucose levels at diagnosis and lower risk for retinopathy for patients with diabetes detected by screening suggests that screening detects patients at an earlier stage of disease.[2] Patients with diabetes detected by screening also tend to show milder disease and slower progression, with better clinical outcomes after follow-up (length-time bias).[19] Although we screened patients in a high-risk population who had a higher initial prevalence of ischemic heart disease, nephropathy and hypertension than patients in the clinical diagnosis group, vascular outcomes were similar between the groups upon follow-up. Even adjusted hazard ratios were not significantly different between groups. The opportunistic targeted screening group may have developed diabetes complications caused by longer exposure to hyperglycemia as a result of a slower progression.

A final possibility is that patients who volunteer for screening programs are more health conscious and therefore more likely to have a better disease outcome even without screening (selection bias).[19] The initiation of screening during routine care, the targeting of patients with diabetes risk factors, and the high response rate of 90%,[8] all suggest that selection bias did not play a major role in our study. As previously stated, however, patients with clinically diagnosed diabetes were more often men and were generally younger than patients with diabetes detected by opportunistic targeted screening. This difference may have been because only patients visiting the family practice were invited for screening, and younger men might be more likely to postpone a primary care consultation. We adjusted data analyses for age and sex to account for this possible bias.

A selection bias that is due to a selective allocation to a group or treatment by the patient's family physician is also unlikely, because patients were not randomized into a group, and although detection method was not blinded, it was recorded in the database for analysis purposes only. Patients from both study

groups received the same guided treatment during normal care from their own family physician, independent of the detection method.

A possible limitation may have been the diagnosis of patients with type 2 diabetes by the fasting plasma glucose test rather than the oral glucose tolerance test. The oral glucose tolerance test consists of a fasting plasma glucose test and 2-hour plasma glucose value and is considered to be the reference standard test in the diagnosis of diabetes. The fasting plasma glucose test is more user-friendly, however, faster to perform, more convenient and acceptable to patients, and less expensive. The recent American Diabetes Association recommendation to use hemoglobin A_{1c} for screening was still under debate at the time of our study.[1,20] Although later rectified, there was a large amount of data missing for hemoglobin A_{1c} at baseline, because hemoglobin A_{1c} was not yet registered in the database at the beginning of the study in 1998. The missing hemoglobin A_{1c} values were comparable between groups, reflecting similar care, and the outcome was in line with the mean fasting plasma glucose values at baseline.

With the exception of smoking, we were not able to investigate potential differences in lifestyle between groups, such as exercise or diet, because these data were not collected in the NMP database. Lifestyle advice is, however, an important part of the guided care in the practices.[9]

We have shown that within the first decade after diagnosis, in contrast to our expectations, opportunistic targeted screening for type 2 diabetes resulted in similarly low macrovascular event rates compared with diabetes diagnosed on the basis of signs or symptoms. This central finding of our study might be taken as an argument against screening. Even so, our finding that higher CVD morbidity at baseline did not significantly increase vascular event rates after screening argues in favor of opportunistic targeted screening. We also showed that opportunistic targeted screening identified patients in an earlier stage of diabetes and that these patients had a lower risk for retinopathy during follow-up. Furthermore, we found a trend toward a higher risk for a major macrovascular event in clinically diagnosed type 2 diabetes, and significant differences may yet become apparent over time.[21]

We have no explanation for the higher risk for non-CVD death (mainly caused by various types of cancer) in the group with clinically diagnosed diabetes. Although type 2 diabetes has been associated with an increased cancer risk, hyperglycemia could not be causally linked to this risk.[22]

Even though the overall statistical power of the study may not have been sufficient to detect small differences between groups, our observational study based on daily care did show some interesting results and trends. Further research is needed to investigate our findings in a larger setting and with a longer follow-up.

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Declaration

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None.

Conflicts of interests

None.

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8

Authors' response to "Comment on: Vascular outcomes in patients with screen-detected or clinically diagnosed type 2 diabetes: Diabscreen study follow-up"

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Comment on: Vascular outcomes in patients with screen-detected or clinically diagnosed type 2 diabetes: Diabscreen study follow-up

Rebecca K. Simmons, Simon J. Griffin

Annals of Family Medicine 2013; eLetter February 4

We congratulate the authors on an interesting study, which adds to the limited literature on screening and early treatment for diabetes. As the authors note, screening for type 2 diabetes identifies individuals at high cardiovascular risk[1] who might benefit from early intervention. However, while it is tempting to speculate that finding and treating individuals earlier in the disease trajectory will lead to improved vascular outcomes for people with type 2 diabetes in primary care, we do not share the authors' confidence that this can be concluded from the data that they report. The study design does not allow for this research question to be answered without recruiting a group of individuals who meet the criteria for opportunistic screening but who do not receive it and are subsequently followed up for vascular outcomes. As the authors note, their observational data are subject to both lead and length time bias, which make the results challenging to interpret.

Examination of Table 1 shows that there were baseline differences in nephropathy and BMI, which were not adjusted for in Cox regression models. Further, it may have been useful to adjust for HbA1c, rather than fasting blood glucose, which better predicts long-term CVD outcomes. Data from Table 2 suggest that screen-detected and clinically diagnosed diabetes patients did not receive the same level of treatment. Larger proportions of the screen-detected individuals received diet and anti-hypertensive treatment, while higher numbers of clinically diagnosed patients received oral agents and insulin. Again, these differences make it challenging to directly compare the vascular experience of the two groups. It would be interesting to know how information on vascular outcomes was collected in this study, and how these were assessed or adjudicated. Some attempt to quantify or discuss the potential harms of screening would also have strengthened the author's assertion about the net benefits of screening.[2]

The only way to avoid lead and length time bias and to assess the net benefit of screening and early treatment is to conduct an RCT. Intensive treatment in the lead time between early detection and clinical diagnosis was associated with a non-significant 17% relative risk reduction in a cardiovascular composite

outcome among screen-detected individuals in the ADDITION-Europe trial after five years of follow-up.[3] Furthermore, examination of the impact of invitation to screening on mortality at the population level showed that there was no significant difference in all-cause, cardiovascular, or diabetes-related mortality between screening and control groups after ten years of follow-up.[4] Thus, while early detection and treatment might improve outcomes for the minority with detectable disease, these results constitute the strongest evidence to date that the benefits of population screening for diabetes might have been overestimated.

Given the current uncertainties concerning the cost effectiveness of screening and early treatment for diabetes, we agree with Klein Woolthuis and colleagues that it is probably most efficient to restrict opportunistic screening to those known to be at highest risk based on readily available information.

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eLetter

We thank Simmons and Griffin for congratulating us on our recent observational study which showed that a diabetes diagnosis via opportunistic targeted screening or via clinical signs and symptoms gave similar rates of illness and death from cardiovascular disease over a 7-year period,[1] and we appreciate their comments.

We agree that the effectiveness of diabetes screening should preferably be estimated by an RCT, so therefore we highly respect their recent work.[2,3] Strictly speaking, as Simmons and Griffin rightly state, an RCT should contain a control group of individuals who meet the criteria for screening but who do not receive it. While guidelines nowadays recommend targeted screening in high-risk individuals,[4] and with people at risk being more aware than ever of the need of glucose testing, we do not think it would be possible to rule out any kind of (opportunistic) screening in control groups. Unfortunately, it appears that Simmons and colleagues did not have access to this information in their no-screening control group.[3]

Our observational study was suitable for daily care and could therefore be implemented in other practices without much effort. Since patients in both study groups received the same guided treatment during normal care from their own family physician, we were able to investigate outcomes related to time of diagnosis and early treatment.

Indeed, lead- and length-time bias could not be ruled out, but were not likely to play a major role in our study. The lower glucose levels and prevalence of retinopathy at diagnosis showed that screening detected diabetes at an earlier stage of disease, and recently it has been shown that screening may bring forward the diagnosis of diabetes by only 3 years.[5] Also, our study outcomes were not significantly different between the study groups, making our findings comparable with those from the recent trial by Simmons and colleagues.

Simmons and Griffin formulated some specific critiques. Regarding Table 1, we already adjusted for plasma creatinine, and BMI was not significantly different between the two groups. We agree that it might have been useful to adjust for HbA_{1c}, but unfortunately the amount of missing values at baseline was high as this test was fairly new at the time. The level of treatment between groups was similar with respect to process of care. Medication differences reflected earlier treatment in the screening group, and showed that it was easier to control hyperglycemia in this group with much less effort, which may be an argument in favor of screening. Vascular outcomes were retrieved from the family physicians' electronic medical record (EMR), in which all diagnoses of disease and death are reliably ICPC coded, as part of our academic registration network.[6,7] And recently we have reported that the route to diagnosis of type 2 diabetes has a greater impact on the illness perceptions of partners than of patients.[8]

Together with a high response rate of 90% and a fair yield,[9] we showed that with an opportunistic targeted screening program like ours, using the EMR for risk assessment prior to glucose testing, diabetes screening in primary care can be performed systematically and continuously, as part of cardiovascular risk management.

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9

General discussion and conclusions

In retrospect

Clinical guidelines recommend screening for type 2 diabetes in high-risk groups, assuming that this will prevent vascular complications.[1-4] However, no direct supportive evidence exists, nor is there a standardized screening approach.

This thesis addressed several aspects of opportunistic targeted screening for type 2 diabetes in primary care, which entails screening individuals at high risk for undiagnosed type 2 diabetes during regular care consultations.

The studies described in this thesis were part of or used data from the Diabscreen study, an opportunistic targeted screening programme for type 2 diabetes in patients aged 45 to 75 years in general practices in the Netherlands, using the general practitioner's (GP) electronic medical record (EMR) for risk assessment before glucose testing. The GP's EMR might be an attractive, inviting tool for a systematic and repeated identification of high-risk patients in opportunistic screening.

The feasibility and yield of opportunistic targeted screening in primary care were evaluated. Moreover, it was investigated how the route to diagnosis of type 2 diabetes – through screening or by clinical signs or symptoms – affects illness perceptions in patients and their partners. And finally, the effectiveness on long-term vascular outcomes of screening, compared with clinical diagnosis, was assessed.

This final chapter summarizes and reflects on the main findings of this thesis. The main methodological issues of the studies and the ongoing screening debate will be discussed. The chapter ends with clinical implications, recommendations for future research, and five key messages.

Main findings

Feasibility and yield

The Diabscreen study has shown that the medical data stored in the GP's EMR were helpful but in themselves incomplete in identifying individuals at high risk for undiagnosed type 2 diabetes (*Chapter 2*). In particular, obesity and a family history of diabetes, both risk factors that may change over time, were poorly registered. This made additional risk assessment during consultation required to come to a reliable valuing of individuals' risk status. After updating the EMR for missing data, though, it was feasible to use the acquired risk status to opportunistically initiate screening. In total, about two-thirds of the study population were at high risk, most of them having hypertension or cardiovascular disease.

The stepwise glucose testing protocol of the Diabscreen study was well applicable in general practice (*Chapter 3*). It included a first capillary fasting plasma glucose (FPG) measurement from a portable blood glucose meter and, if indicated by the

result (>6.0 mmol/l [110 mg/dl]), a second one, and if indicated by that result (>6.0 mmol/l with at least one of the two measurements being ≥7.0 mmol/l [126 mg/dl]), a venous FPG. Response rates for both capillary measurements were high (about 90%), and the protocol's high positive predictive value (81%) resulted in a considerable reduction of patients in whom a venous FPG had to be assessed.

The yield of opportunistic targeted screening among high-risk patients in the Diabscreen study was fair, largely because of the stepwise protocol, and much higher than in low-risk patients; obesity alone was the best predictor of undiagnosed type 2 diabetes (*Chapter 4*).

The clinical findings of the Diabscreen study support the conclusion of a recent modelling study,[5] that the cost-effectiveness of screening for type 2 diabetes would be improved if screening was done opportunistically and by risk assessment before glucose testing (*Chapter 5*).

It was concluded that opportunistic screening in primary care, as proceeded in the Diabscreen study, was feasible. Middle-aged and older adults at high risk, especially those with obesity, can be targeted effectively. A well-kept EMR can be most helpful for identification of high-risk patients and also in supporting repeated screening. With systematic integration of diabetes screening into cardiovascular risk management, the number of high-risk patients to be opportunistically screened would be considerably reduced.

The partner's perspective

In a cross-sectional questionnaire study using the Brief Illness Perception Questionnaire (Brief IPQ),[6] the route to diagnosis of type 2 diabetes had a greater impact on the illness perceptions of partners than that of patients (*Chapter 6*). Partners of patients diagnosed through screening perceived greater consequences for their own life, had a stronger feeling that their patient-partners had control over their diabetes, were more concerned about their partners' diabetes, and believed that their patient-partners experienced more diabetes symptoms, compared with partners of patients who were diagnosed through clinical signs or symptoms.

Professionals involved in diabetes education and treatment should focus on and target the illness perceptions of partners, especially where screening is concerned. The Brief IPQ is a simple and effective tool with which to investigate these illness perceptions in daily practice.

Long-term effectiveness

The Diabscreen study follow-up confirmed the findings of earlier screening studies that opportunistic targeted screening for type 2 diabetes detects patients with higher cardiovascular disease (CVD) morbidity at baseline when compared with clinical diagnosis.[7,8] Despite this high cardiovascular risk in screen-detected

patients, the vascular event rates were low and did not differ significantly between the two groups after a mean follow-up of 7.7 years (*Chapters 7* and *8*).

Opportunistic targeted screening and guided care including cardiovascular risk management appears to improve long-term vascular outcomes in type 2 diabetes in primary care.

Methodological considerations

There are several methodological issues regarding screening studies, and many have already been addressed in the previous chapters of this thesis. Some important strengths and possible limitations are also worth discussing in this section.

Study setting

The major strength of this thesis was its primary care setting. Although many participants of the studies described in this thesis were recruited from general practices with an interest in diabetes care, these practices were normal community practices with a population and diabetes prevalence rates representative of the general Dutch population.9-14

In the Diabscreen study, high-risk patients were invited for screening during daily routine practice in the patients' local general practice by their own GP. Capillary blood samples were taken by the practice assistants in the patients' own practice, without any further support (eg, from trial nurses). Probably due to these factors, patients were highly willing to return in a fasting state for the capillary FPG measurement.

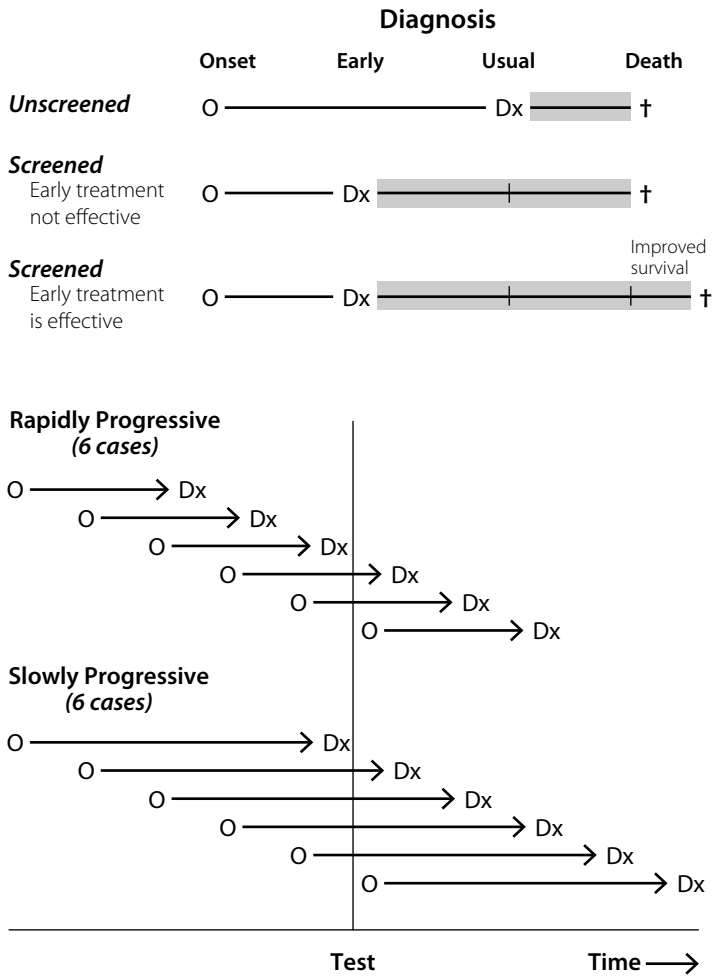
Because the Dutch system of primary healthcare provides for universal access and continuity of patient registration, data from the general practice's EMR could be used in a continuous screening programme, as well as in the follow-up study.

Biases in screening

Important biases that are frequently associated with (observational) screening studies can confound assessment of screening-test efficacy.[15]

In the Diabscreen study follow-up, the hazard curve of the primary outcome was higher for clinically diagnosed diabetes than for opportunistic targeted screening (*Chapter 7*). This might be explained by *lead-time bias*: the longer interval between diagnosis and development of complications in patients detected by opportunistic targeted screening might be due to earlier detection in the natural history of the disease, instead of earlier treatment (Figure 1 A).[15] The lower glucose levels at diagnosis and lower risk for retinopathy in screen-detected patients showed that screening detected patients at an earlier stage of disease.[16]

Figure 1 Lead-time bias (**A**) and length-time bias (**B**)



O = time of disease onset; Dx = diagnosis.
Lead time = interval between early diagnosis by screening and usual diagnosis by clinical signs or symptoms.
Lead-time bias = overestimation of survival duration among screen-detected vs clinically diagnosed patients.
Length-time bias = overestimation of survival duration among screen-detected patients due to relative excess of slowly progressing cases.

Patients with diabetes detected by screening also tend to show milder disease and slower progression, with better clinical outcomes after follow-up (*length-time bias*, Figure 1 B).[15] However, although a high-risk population was screened with a higher initial prevalence of ischemic heart disease, nephropathy and hypertension than in the clinical diagnosis group, vascular outcomes were similar between the groups upon follow-up (*Chapter 7*). Even adjusted hazard ratios were not significantly different between groups. The opportunistic targeted screening group may have developed diabetes complications caused by longer exposure to hyperglycemia as a result of a slower progression.

Furthermore, patients who volunteer for screening programmes are more health conscious and therefore more likely to have a better disease outcome even without screening (*selection bias*).[15] The initiation of screening during routine care, the targeting of patients with diabetes risk factors, and the high response rate of 90% (*Chapter 4*), all suggest that selection bias did not play a significant role in the Diabscreen study. However, clinically diagnosed patients were more often men and were generally younger than patients detected by opportunistic targeted screening. This difference may have been because only patients visiting the general practice were invited for screening, and younger men might be more likely to postpone a primary care consultation. Data analyses were adjusted for age and sex to account for this possible bias (*Chapter 7*).

A selection bias due to a selective allocation to a group or treatment by the patient's GP is also unlikely because patients were not randomized into a group but selected by the route to diagnosis (*Chapters 6* and *7*). Patients in both study groups (diagnosed by screening or by clinical signs or symptoms) were all treated according to the same practice guidelines during usual care.

Volunteer or self-selection bias cannot be entirely ruled out, however, because response rates were low and some baseline characteristics differed between the study groups (*Chapter 6*). Data analyses were adjusted for these differences to account for any possible bias.

To screen or not to screen: an ongoing debate

Screening for undiagnosed type 2 diabetes is still under debate and there is no definite answer yet to the question whether we should screen for type 2 diabetes or not.[17,18] Those who are opposed to screening suggest that a population approach to modifying cardiovascular risk factors would be better.[18] Changes to diet or physical activity levels will always be advisable for people who are overweight or sedentary, whatever their overall diabetes or cardiovascular risk score and whatever their glucose result, and focusing on diabetes risk alone ignores the additional benefits of weight loss and exercise. A recent modelling study suggests that it may be as

effective to treat on the basis of age alone as on the basis of a more complex risk assessment including blood pressure and cholesterol levels.[19] In England, the National Health Service has started the Health Check programme, which offers cardiovascular risk assessment including diabetes screening every five years to anyone between the ages of 40 and 74 years.[20] In the Netherlands, GPs can offer individual patients or the practice population from the age of 45 years a cardiovascular risk assessment, so-called Preventative Consultation, using a validated risk score including diabetes risk factors (eg, BMI and family history of type 2 diabetes).[21]

Others believe that screening for diabetes is feasible and cost-effective.[17] Screening followed by lifestyle interventions have been proven to be both effective and cost-effective in people with newly detected prediabetes and diabetes.[22] A recent modelling study concluded that screening is cost-effective when started between the ages of 30 and 45 years, with screening repeated every three to five years.[5] The British National Institute for Health and Clinical Excellence (NICE) has published guidance on identification and prevention of type 2 diabetes in people at high risk, making practical recommendations on risk identification using self-assessment risk scores or computer based risk scores in people aged 40 to 75 years followed by glucose or Hemoglobin A_{1c} testing.[23] The American Diabetes Association recommends three-yearly screening for undiagnosed type 2 diabetes in adults of any age with a BMI ≥25 and with additional risk factors, or starting at age 45 without these risk factors.[4] And the Dutch general practice guidelines for type 2 diabetes recommend three-yearly screening for type 2 diabetes in individuals aged 45 years or older with diabetes or cardiovascular risk factors, or with CVD.[2]

Recently, two population-based screening trials in high-risk individuals have reported important new findings. Intensive treatment between early detection by screening and clinical diagnosis was associated with a non-significant reduction in CVD among screen-detected individuals in the ADDITION-Europe trial after five years of follow-up.[24] The ADDITION-Cambridge trial showed that there was no significant difference in mortality between screening and control groups after ten years of follow-up.[25]

These finding are comparable to the findings in this thesis (*Chapter 7*), and might be taken as an argument against screening, suggesting that efforts in primary prevention among those at high risk for developing diabetes may be more important than early detection and treatment of undiagnosed diabetes.

On the other hand, it would have been expected that screen-detected patients with more pre-existing CVD would subsequently experience more CVD events, but they did not, probably because of cardiovascular risk management after diagnosis, which argues in favour of opportunistic targeted screening. Furthermore, observational follow-up data from the Diabscreen study showed a trend toward an

increasingly lower risk for a major CVD event in screen-detected type 2 diabetes, and significant differences may yet become apparent over time.

Clinical implications

The benefits of screening appear to be smaller than expected, but could be increased by combining diabetes screening with cardiovascular risk assessment and continuous or repeated screening. This asks for a dynamic process, in which the interaction between practice and practice population over time is directed at pro-actively assessing risk status and acting upon it.

In this respect, it is important to come back to the initial finding of the incompleteness of the GP's EMR at the start of the Diabscreen study in terms of diabetes risk status. Updating of information of individuals' health status and health risk should be seen as an integral part of pro-active diabetes risk and cardiovascular risk management. Individuals' risk status may change over time, as do scientific evidence and professional values of risk factors. The EMR should be a reflection of the best available information.

Future research

Further research is needed to investigate this thesis' findings in a larger setting and with a longer follow-up. The focus should be on long-term outcomes of cardiovascular risk management with integrated diabetes screening. Future studies should also estimate its cost-effectiveness and limitations. Furthermore, data on non-Caucasian individuals and on other less well known diabetes risk factors (eg, polycystic ovary syndrome[26]) may be investigated.

Key messages

The studies presented in this thesis have provided better insight in opportunistic targeted screening for type 2 diabetes in primary care. Five key messages can be formulated.

1. This thesis shows that opportunistic targeted screening for type 2 diabetes in primary care is feasible, and a well-kept electronic medical record with up-to-date cardiovascular risk profile can be most helpful for identification of high-risk patients and supportive in repeated screening.

2. Diabetes screening should be systematically integrated into cardiovascular risk management, so that opportunistic screening for type 2 diabetes can effectively target middle-aged and older adults with diabetes risk factors, in particular obesity. This asks for active management of information on individuals' risk status in the EMR to support screening and identification of those to benefit from it.

3. Professionals involved in diabetes education and treatment should focus on and target the illness perceptions of partners, especially where screening is concerned. The Brief Illness Perception Questionnaire is a simple and effective tool with which to investigate these illness perceptions in daily practice.

4. Opportunistic targeted screening and guided care including cardiovascular risk management appears to improve long-term vascular outcomes in type 2 diabetes in primary care, which is an important argument in favour of screening.

5. Future research should investigate long-term outcomes of cardiovascular risk management with integrated diabetes screening.

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Summary

Summary

This thesis addresses several aspects of opportunistic targeted screening for type 2 diabetes in primary care, which entails screening asymptomatic individuals at high risk for undiagnosed type 2 diabetes during regular healthcare consultations.

In *Chapter 1* the rationale and objectives of this thesis are described. Clinical guidelines recommend screening for undiagnosed type 2 diabetes in high-risk groups, assuming that this will prevent vascular complications. However, no direct supportive evidence exists, nor is there a standardized screening approach. Opportunistic targeted screening using clinical risk factor information from the electronic medical record (EMR) may be an efficient and continuous method of detecting undiagnosed type 2 diabetes during usual primary healthcare.

To investigate this screening approach, from the year 2000 to 2001 the Diabscreen study had been conducted. This was an opportunistic targeted screening programme for type 2 diabetes among patients aged 45-75 years in general practices in the Netherlands, using the general practitioner's (GP) EMR for risk assessment before glucose testing.

The first objective of this thesis was to evaluate the feasibility and yield of opportunistic targeted screening for type 2 diabetes in primary care. Secondly, to address the family perspective of screening, this thesis aimed to examine how the route to diagnosis of type 2 diabetes – through screening or by clinical signs or symptoms – affects illness perceptions in families, particularly in patients and their partners. The third objective was to assess the effectiveness on long-term vascular outcomes of opportunistic targeted screening for type 2 diabetes, compared with a clinical diagnosis.

In *Chapter 2* the design and results of the first steps of the Diabscreen study are described. Using a computerized cross-sectional analysis of diabetes risk factor information (diagnoses and medication) for each patient from the practices' EMR, the patient's risk for undiagnosed diabetes (high or low risk) was marked in the EMR. During a usual care consultation in the following year, the EMR reminded the GP to verify and, in the case of missing data, complete the patients' risk profile and to invite high-risk patients for a capillary fasting plasma glucose (FPG) measurement.

Of the population aged 45-75 years and not already known with diabetes, 28% had an EMR-based risk (hypertension, cardiovascular disease, lipid metabolism disorders and/or obesity). Additional risk assessment in those without an EMR-based risk showed that in 51%, greater than one risk factor was present, mainly family history of diabetes (51.2%) and obesity (59%). Ninety per cent of high-risk patients returned for the capillary FPG measurement.

These findings suggest that with additional risk assessment during consultation, the GP's EMR is valuable in identifying patients at high risk for undiagnosed type 2 diabetes, and that it is feasible to use this information to initiate screening.

In *Chapter 3* the stepwise glucose testing protocol of the Diabscreen study is evaluated. The protocol consisted of two capillary FPG measurements with a combination of two cut-off points (6.0 mmol/l and 7.0 mmol/l [110 mg/dl and 126 mg/dl]), and a venous FPG. All samples were taken in the patients' own general practice, by their own practice assistants. Plasma calibrated portable blood glucose meters were used for the capillary measurements. Patients with an initial value >6.0 mmol/l were invited for a second capillary FPG on another day. This was immediately followed by a venous sample if at least one of the capillary measurements was ≥7.0 mmol/l.

Fasting capillary and venous glucose values were highly correlated, with the latter being systematically higher. With response rates for both capillary measurements at about 90% and a positive predictive value for having undiagnosed type 2 diabetes of 81% (in 101 out of 125 patients the venous FPG was ≥7.0 mmol/l), the protocol was well applicable.

In *Chapter 4* the yield of the Diabscreen study was assessed. In addition to high-risk patients who were invited during usual care, a random sample of low-risk patients was contacted by mail for stepwise fasting glucose testing.

Ultimately, the screening yield (percentage of invited patients with undiagnosed type 2 diabetes) was much higher in high-risk than in low-risk patients (2.7% versus 0.4%; number needed to screen 37 versus 233). Obesity was the best predictor of undiagnosed type 2 diabetes (odds ratio 3.2).

The yield of opportunistic targeted screening was fair; obesity alone was the best predictor of undiagnosed diabetes. Opportunistic targeted screening for type 2 diabetes in primary care could target middle-aged and older adults with obesity.

Chapter 5 comments on a recent modelling study about the cost-effectiveness of screening for type 2 diabetes. This study concluded that the cost per quality-adjusted life-year would be improved if screening was done opportunistically and by risk assessment before glucose testing.

The clinical findings of the Diabscreen study clearly show that opportunistic screening in primary care is feasible. Middle-aged and older adults at high risk, especially those with obesity, can be targeted effectively. An EMR can be most helpful for identification of high-risk patients and also in supporting repeated screening, but this requires universal access and continuity of patient registration.

Chapter 6 focuses on the partner's perspective on screening. As most type 2 diabetes self-care occurs at home, beliefs or illness perceptions of in particular the partner regarding type 2 diabetes play an important role in adaptation to the disease and in disease outcome. In this chapter it was investigated how the route to diagnosis of type 2 diabetes, through screening or by clinical signs or symptoms, affects the illness perceptions of patients and their partners.

In a cross-sectional study, patients aged 40-75 years from general practices with a new diagnosis of type 2 diabetes (≤3 years), detected by either screening or clinical signs or symptoms, were enrolled. Patients and their partners each completed a postal Brief Illness Perception Questionnaire (Brief IPQ), and up-to-date clinical data were obtained from their GP.

The route to diagnosis did not appear to have a strong influence on patients' illness perceptions, but did influence illness perceptions of their partners. Partners of patients diagnosed through screening perceived greater consequences for their own life, had a stronger feeling that their patient-partners had control over their diabetes, were more concerned about their partners' diabetes, and believed that their patient-partners experienced more diabetes symptoms, compared with partners of patients who were diagnosed through clinical symptoms. Professionals in diabetes education and treatment should consider these differences in their approach to patient care.

In *Chapter 7* the Diabscreen study follow-up is described, assessing whether diagnosis of type 2 diabetes based on opportunistic targeted screening results in lower vascular event rates compared with diagnosis on the basis of clinical signs or symptoms.

Opportunistic targeted screening for type 2 diabetes detected patients with higher cardiovascular disease (CVD) at baseline when compared with clinical diagnosis, mainly ischemic heart disease (12.3% versus 3.9%). But the event rates of the primary endpoint (a composite of death from CVD, nonfatal myocardial infarction, and nonfatal stroke) were similar after 7.7 years (9.5% versus 10.2%).

Opportunistic targeted screening and guided care including cardiovascular risk management appears to improve long-term vascular outcomes in type 2 diabetes in primary care.

Chapter 8 contains the response to a comment on the Diabscreen study follow-up, presented in the previous chapter.

Together with a high response rate of 90% and a fair yield, it was shown that with the Diabscreen study's opportunistic targeted screening programme, using the EMR for risk assessment prior to glucose testing, diabetes screening in primary care can be performed systematically and continuously, as part of cardiovascular risk management.

Finally, in *Chapter 9*, the main findings of this thesis are summarized and reflected on. The main methodological issues of the studies and the ongoing screening debate are discussed. The chapter ends with clinical implications, recommendations for future research, and five key messages.

II

Samenvatting

Samenvatting

Dit proefschrift richt zich op het opsporen van nog niet ontdekte diabetes type 2 in de huisartsenpraktijk (*primary care*) door middel van gerichte, opportunistische screening (*opportunistic targeted screening*). Hierbij worden mensen met een verhoogd risico op diabetes maar zonder diabetesklachten of -verschijnselen, tijdens een spreekuurbezoek vanwege een andere vraag of klacht, uitgenodigd voor een diabetestest, zoals een meting van de bloedsuiker (bloedglucose).

In *Hoofdstuk 1* worden de achtergrond en doelen van dit proefschrift beschreven. Diabetes mellitus ('suikerziekte'), kortweg diabetes genoemd, is een stofwisselingsziekte waarbij het lichaam de bloedglucose niet meer in evenwicht kan houden en deze te hoog wordt. Hierdoor kan in de loop van de jaren schade ontstaan aan de kleine bloedvaten, met als gevolg bijvoorbeeld uitval van de nieren (nefropathie) en slechtziendheid (retinopathie), maar ook schade aan de zenuwen (neuropathie) met vooral gevoelsstoornissen en risico op wonden aan de voeten. Dit worden microvasculaire complicaties genoemd. Daarnaast hebben mensen met diabetes een verhoogd risico op het krijgen van schade aan de grotere bloedvaten en het hart, met als gevolg zogenaamde macrovasculaire complicaties – hart- en vaatziekten zoals een hartinfarct of herseninfarct – of overlijden.

Er zijn verschillende typen diabetes, elk met een verschillende oorzaak en meestal ook met een eigen behandeling. Dit proefschrift is gericht op diabetes type 2. Negen van de tien mensen met diabetes hebben dit type, waarvan de meesten worden behandeld in de huisartsenpraktijk. Diabetes type 2 werd vroeger 'ouderdomssuiker' genoemd, maar tegenwoordig krijgen ook steeds meer jonge mensen het. Diabetes type 2 ontstaat doordat er te weinig van het hormoon insuline, nodig voor de opname van bloedglucose, in het lichaam aanwezig is. Bovendien is het lichaam vaak ongevoeliger voor insuline (insulineresistentie). Bij diabetes type 2 kan het jaren duren voordat mensen er klachten van krijgen (bijvoorbeeld dorst en vaak plassen). Intussen kunnen er al wel complicaties ontstaan. Diabetes type 2 komt steeds meer voor, vooral door vergrijzing en de toename van het aantal mensen met overgewicht en obesitas.

Diabetesrichtlijnen adviseren te screenen op onontdekte diabetes type 2 in hoogrisicogroepen, bijvoorbeeld mensen met obesitas (ernstig overgewicht) of hoge bloeddruk, omdat vroege behandeling mogelijk complicaties kan voorkomen. Hiervoor is echter nog geen bewijs geleverd. Ook is er geen standaard afspraak hoe te screenen. Gerichte, opportunistische screening aan de hand van het risicoprofiel in een elektronisch patiëntendossier zoals dat van de huisarts (H-EPD genoemd), kan een efficiënte manier zijn om nog niet ontdekte diabetes type 2 tijdens gewone spreekuurbezoeken op te sporen.

Om dit wetenschappelijk te onderzoeken, is van 2000 tot 2001 Diabscreen uitgevoerd. Deze studie onderzocht het opsporen van nog onontdekte diabetes type 2 onder 45- tot 75-jarige hoogrisicopatiënten door middel van opportunistische screening in Nederlandse huisartsenpraktijken verbonden aan het Universitair Medisch Centrum St Radboud Nijmegen (Netwerk Academische Huisartspraktijken Nijmegen CMR NMP, kortweg NMP, van de afdeling Eerstelijnsgeneeskunde). Ook praktijken van het RegistratieNet Huisartspraktijken (RNH) van het Maastricht Universitair Medisch Centrum en enkele praktijken verbonden aan het VU medisch centrum Amsterdam deden mee.

Het eerste doel van dit proefschrift was om de uitvoerbaarheid (*feasibility*) en effectiviteit op basis van de opbrengst (*yield*) van opportunistische screening naar diabetes type 2, gericht op hoogrisicogroepen in de huisartsenpraktijk, te evalueren. Het tweede doel was om te onderzoeken of de manier van opsporen van diabetes type 2 – via screening of naar aanleiding van klachten – invloed heeft op de ideeën of gedachten over de ziekte bij zowel de patiënt als bij zijn/haar partner, ook wel ziektepercepties (*illness perceptions*) genoemd. Het derde en laatste doel was het vaststellen van de effectiviteit op lange termijn (*long-term effectiveness*) van opportunistische screening onder hoogrisicopatiënten, waarbij na de diagnose diabetes type 2 het ontstaan van microvasculaire en macrovasculaire complicaties in de screeningsgroep is vergeleken met het ontstaan daarvan in een groep patiënten met diabetes, ontdekt naar aanleiding van klachten.

In *Hoofdstuk 2* worden de opzet en resultaten van de eerste stappen van Diabscreen beschreven. Op basis van in het H-EPD beschikbare informatie (diagnosen en medicatie) werd aan alle 45- tot 75-jarigen in de onderzoekspraktijken een risicolabel toegekend: hoog risico (één of meer risicofactoren) of laag risico. Geholpen door een geautomatiseerde signalering op het beeldscherm van de huisarts, werd gedurende een jaar tijdens gewone spreekuurcontacten dit risico door de huisarts gecontroleerd en zo nodig aangepast. Patiënten met een hoog risico werden uitgenodigd om via een capillaire meting (vingerprik) de nuchtere bloedglucose te laten bepalen.

Van de populatie 45- tot 75-jarigen zonder al bekende diabetes, had 28% één of meer risicofactoren voor onontdekte diabetes in het H-EPD (hoge bloeddruk, hart- of vaatziekte, verhoogd cholesterol en/of obesitas). Van de laagrisicopatiënten bleek bij navraag tijdens het spreekuur 51% alsnog risicofactoren te hebben, vooral diabetes in de familie (ouders, broer en/of zus; 51.2%) en obesitas (59%). De opkomst voor de nuchtere bloedglucosemeting was hoog: 90%.

Het H-EPD bleek goed bruikbaar bij het identificeren van patiënten met een hoog risico voor onontdekte diabetes. Als risicoprofielen goed worden bijgehouden en aangevuld – vooral bij diabetes in de familie en obesitas – kan met het H-EPD

screening naar diabetes tijdens gewone spreekuurcontacten snel en effectief in gang worden gezet en regelmatig worden herhaald.

In *Hoofdstuk 3* wordt het volledige stapsgewijze protocol voor bloedglucosemetingen in Diabscreen geëvalueerd. Dit bestond uit maximaal twee capillaire metingen met een draagbare bloedglucosemeter, zo nodig gevolgd door afname van veneus (aderlijk) bloed uit de arm van de patiënt voor een laboratoriummeting. De bloedglucosemeters waren, zoals inmiddels standaard bij alle bloedglucosemeters, veneus gekalibreerd (afgesteld), waardoor automatisch veneuze waarden werden weergegeven. Bij een eerste nuchtere bloedglucose hoger dan 6,0 mmol/l, werd de patiënt uitgenodigd voor een tweede nuchtere meting op een andere dag. Als de tweede bloedglucose ook hoger was dan 6,0 mmol/l én als ten minste één van de twee metingen hoger was dan 7,0 mmol/l, werd meteen veneus bloed afgenomen. Alle bloedafnamen en alle capillaire metingen werden bij patiënten uitgevoerd in de eigen huisartsenpraktijk door een van de eigen praktijkassistentes. Capillaire en veneuze bloedglucosewaarden kwamen goed overeen, waarbij de veneuze waarden systematisch iets hoger waren. Voor beide capillaire metingen was de opkomst hoog: ongeveer 90%. Met een positief voorspellende waarde van 81% (101 van de 125 patiënten met te hoge capillaire waarden hadden een veneuze bloedglucose van 7,0 mmol/l of hoger, overeenkomend met diabetes) bleek het protocol goed bruikbaar voor het opsporen van onontdekte diabetes.

In *Hoofdstuk 4* is de effectiviteit van Diabscreen vastgesteld op basis van het aantal gevonden nieuwe mensen met diabetes. Hiervoor werd als controlegroep een steekproef van laagrisicopatiënten uitgenodigd voor de bloedglucosemetingen.

Uiteindelijk had in de hoogrisicogroep 2,7% diabetes type 2 en in de laagrisicogroep slechts 0,4%. Om één nieuwe patiënt met diabetes te vinden, moesten slechts 37 hoogrisicopatiënten worden uitgenodigd voor screening, tegen 233 laagrisicopatiënten (*number needed to screen* 37 respectievelijk 233). Mensen met obesitas (BMI >27) hadden een drie keer grotere kans op het hebben van onontdekte diabetes type 2 dan mensen met een normaal gewicht (odds ratio 3,2), waarmee obesitas de beste voorspeller voor onontdekte diabetes type 2 bleek te zijn.

Opportunistische screening op basis van het risicoprofiel in het H-EPD bij 45-plussers is effectief bij hoogrisicopatiënten, vooral met overgewicht of obesitas, maar niet zinvol zonder aanvullende risicofactoren.

Hoofdstuk 5 bevat een commentaar op een recente studie die de kosteneffectiviteit van screening naar diabetes type 2 met theoretische modellen had berekend. De studie adviseerde opportunistisch te screenen in hoogrisicogroepen.

De resultaten van Diabscreen onderschrijven dit model en laten zien dat opportunistische screening in de huisartsenpraktijk goed uitvoerbaar is en dat dit effectief is onder 45-jarige en oudere hoogrisicopatiënten, zeker als ze obesitas hebben.

Hoofdstuk 6 richt zich op de partner van de patiënt met nieuw ontdekte diabetes. De partner heeft invloed op het omgaan met de ziekte door de patiënt en uiteindelijk ook op ziekte-uitkomsten. Onderzocht werd of de ziektepercepties (*illness perceptions*) van zowel patiënt als zijn/haar partner anders zijn na een diagnose door screening dan na een diagnose op basis van diabetesklachten.

Patiënten van 40 tot 75 jaar oud met maximaal 3 jaar bekende diabetes werd, net als hun partner, gevraagd een korte vragenlijst over ziektepercepties in te vullen (de Nederlandstalige versie van de *Brief Illness Perception Questionnaire,* IPQ-K(ort); www.uib.no/ipq of www.ziekteperceptie.nl). Medische gegevens werden bij hun huisarts opgevraagd.

Vooral bij partners had de manier van opsporen van diabetes type 2 – via screening of naar aanleiding van klachten – invloed op de ziektepercepties. Partners van patiënten met diabetes ontdekt door screening hadden sterker het gevoel dat de diabetes invloed had op hun eigen leven, hadden vaker de opvatting dat hun partner met diabetes de ziekte goed onder controle had terwijl de patiënt dat zelf niet altijd vond, waren meer bezorgd over de diabetes van hun partner, en dachten meer dat hun partner klachten had van de diabetes, dan partners van patiënten met diabetes ontdekt door klachten.

Professionals in de diabeteszorg zouden zich meer bewust moeten zijn van deze verschillen. Ze zijn eenvoudig vast te stellen door gebruik te maken van een vragenlijst zoals de IPQ-K.

In *Hoofdstuk 7* wordt een vervolgstudie op Diabscreen beschreven, met gegevens tot gemiddeld ruim zeven jaar later. Er is onderzocht of de diagnose diabetes type 2 door gerichte, opportunistische screening onder hoogrisicopatiënten tot minder vaatcomplicaties heeft geleid dan na een diagnose diabetes type 2 bij patiënten met diabetesklachten.

Patiënten opgespoord bij screening bleken bij diagnose vaker al een hart- of vaatziekte te hebben dan patiënten uit de klachtengroep, vooral ischemische hartziekten (12,3% respectievelijk 3,9%). Maar desondanks was na gemiddeld 7,7 jaar het percentage opgetreden macrovasculaire complicaties (met name sterfte door een hart- of vaatziekte, niet-fataal hartinfarct of niet-fataal herseninfarct) in beide groepen gelijk (9,5% respectievelijk 10,2%). Ook het percentage nieuwe microvasculaire complicaties was vergelijkbaar.

Opportunistische screening naar diabetes type 2 onder hoogrisicogroepen gevolgd door cardiovasculair risicomanagement lijkt de vasculaire uitkomsten van diabetes type 2 na bijna acht jaar te hebben verbeterd, maar een duidelijk effect is mogelijk pas zichtbaar na een nog langer vervolg.

Hoofdstuk 8 vermeldt de reactie op een ingezonden commentaar op het vervolgonderzoek op Diabscreen.

De auteurs van het commentaar hadden recent gerapporteerd over een eigen onderzoek over dit onderwerp. In een gerandomiseerde, gecontroleerde trial (RCT) was het percentage sterfgevallen na populatiescreening naar diabetes type 2 vergeleken met dat percentage na een diagnose op basis van klachten. Na tien jaar was er tussen de twee groepen geen significant verschil in totale sterfte of sterfte door hart- en vaatziekten. De auteurs menen dat een RCT de beste onderzoeksmethode is voor deze vergelijking, maar erkennen dat, zolang de kosteneffectiviteit van screening naar en vroege behandeling van diabetes nog onzeker is, het waarschijnlijk nog het meest efficiënt is om opportunistisch op diabetes te screenen onder hoogrisicogroepen op basis van al bekende risicofactoren.

Hoewel het vervolg op Diabscreen geen RCT was maar een pragmatische, observationele studie, zijn de langetermijnuitkomsten wel vergelijkbaar met de genoemde RCT en laten ze zien dat op basis van het cardiovasculaire risicoprofiel zoals bekend bij de huisarts, hoogrisicogroepen tijdens een toevallig spreekuurbezoek kunnen worden opgespoord en/of als onderdeel van cardiovasculair risicomanagement kunnen worden gescreend op onontdekte diabetes type 2.

Ten slotte worden in *Hoofdstuk 9* de belangrijkste bevindingen van dit proefschrift besproken. De belangrijkste methodologische beperkingen komen aan bod, en de voor- en tegenargumenten van diabetesscreening worden bediscussieerd. Na enkele aanbevelingen voor de dagelijkse praktijk en voor nieuw onderzoek eindigt het hoofdstuk met een opsomming van de vijf kernboodschappen van dit proefschrift:

1. Opportunistische screening naar onontdekte diabetes type 2 is goed uitvoerbaar in de huisartsenpraktijk, waarbij het elektronisch patiëntendossier goed bruikbaar is voor het identificeren van hoogrisicogroepen, mits risicoprofielen worden bijgehouden en aangevuld.

2. Diabetesscreening behoort systematisch te zijn geïntegreerd binnen het cardiovasculair risicomanagement, terwijl opportunistische screening naar diabetes type 2 het meest effectief is bij 45-plussers met overgewicht of obesitas.

3. Professionals in de diabeteszorg zouden vaker moeten letten op de ziektepercepties van partners van patiënten met diabetes, zeker bij diabetes ontdekt door screening. Ziektepercepties zijn eenvoudig vast te stellen door gebruik te maken van een korte vragenlijst zoals de IPQ-K.

4. Opportunistische screening naar diabetes type 2 onder hoogrisicogroepen gevolgd door cardiovasculair risicomanagement lijkt de vasculaire uitkomsten op langere termijn te verbeteren, wat een belangrijk argument is voor screening.

5. Nieuwe studies zouden langetermijnuitkomsten van cardiovasculair risicomanagement met geïntegreerde diabetesscreening moeten onderzoeken.

III

Dankwoord

Dankwoord

Begin 2003 – ik zat in het eerste jaar van mijn huisartsopleiding – kreeg ik een e-mail van Wim de Grauw, huisarts en onderzoeker van de (toen nog) afdeling Huisartsgeneeskunde van het UMC St Radboud Nijmegen. Ik kende hem nog van mijn wetenschappelijke stage in 2000. Zowel de goede sfeer op de afdeling als het doen van onderzoek waren goed bevallen en smaakten naar meer. Bij een lopend project was nu een vacature ontstaan voor de onderzoeker en Wim vroeg of ik geïnteresseerd was. Na een gesprek met hem en projectleider Eloy van de Lisdonk, besloot ik de uitdaging aan te gaan. Het werd een zogenaamd aiotho-traject (arts in opleiding tot huisarts en onderzoeker), waarbij ik de rest van mijn huisarts-opleiding zou combineren met promotieonderzoek. Het onderzoek zou na de opleiding worden afgerond en de verwachting was dat ik in januari 2006 klaar zou zijn. Hoe anders is het gelopen...
Het onderzoek was lastiger dan gedacht en de financiering bleek eindig. Er ging veel (vrije) tijd zitten in het vinden van een eigen lijn in het onderzoek en in het in goede tijdschriften gepubliceerd krijgen van de artikelen. Hierdoor maar ook door de nodige life events (mijn echtgenote ontmoet, verhuisd en gaan samenwonen, huisarts geworden, verloofd, eigen praktijk, getrouwd, weer verhuisd, twee kinderen gekregen) werd het al snel 2013. Maar nu kan ik eindelijk zeggen: het 'boekje' is af! Nou ja, alleen het dankwoord dan nog. Hiervoor kan ik dan wel terugkijken op tien bijzondere en boeiende jaren.

Ik had dit project niet kunnen uitvoeren en vooral niet kunnen afronden zonder de hulp en steun van velen.
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Zoals ik hierboven al heb vermeld, is de combinatie huisarts en onderzoeker niet makkelijk, zeker de laatste jaren waarin ik in mijn vrije tijd aan het onderzoek moest werken. Dit was niet mogelijk geweest zonder mijn part-time werk in mijn eigen huisartsenpraktijk in Ede, die ik, na een jaar in loondienst te zijn geweest, sinds 2008 samen heb met mijn collega en maat Inge Meekes. Inge, bedankt dat je me na die ene gezamenlijke nachtdienst hebt benaderd om mee te solliciteren toen je collega met pensioen ging. Bedankt voor de prettige samenwerking in onze maatschap. Ook veel dank aan praktijkassistentes Bettina, Melissa, Irene en Linda, oud-praktijkassistente Rosanne en praktijkondersteuners Nely en Tia voor jullie werk, gezelligheid en (meestal...) begrip. Ook bedank ik al onze huisartsen in opleiding die de afgelopen jaren bij ons hebben gewerkt.

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als papa moest werken achter de computer. Gelukkig maakten jullie lieve lach en vele knuffels het allemaal weer goed. Ik ben blij dat we nu weer meer samen kunnen gaan doen!

Lieve Iti-Marije, *partners matter!* Partners zijn belangrijk! Ik ben dan wel aan mijn promotietraject begonnen voordat ik je kende, maar afronden was niet gelukt zonder jouw steun en toeverlaat. Dankzij jou kon ik op mijn vrije woensdag naar Nijmegen om daar te werken aan mijn proefschrift, terwijl jij ons gezin onder je hoede nam. En dat deed je ook al die weekenden en vakantiedagen waarop ik thuis moest werken. Daarnaast ging je ook nog door met de verzorging van je vader. Niet voor niets heb ik 'ons' beeld in het prachtige Italiaanse Cinque Terre opgenomen op de omslag van dit proefschrift. Heel veel dank voor alles. Ik kijk ernaar uit meer tijd met jou en ons gezin te kunnen doorbrengen!

Erwin Klein Woolthuis
mei 2013

IV

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About the author

Erwin Klein Woolthuis was born on November 12, 1974 in Deventer, a city in the eastern part of the Netherlands. He grew up there as well. In 1993 he completed his high school at the Alexander Hegius Public School (nowadays Etty Hillesum Lyceum) in Deventer and was admitted to study medicine at the Radboud University Nijmegen. After two years he joined the Nijmegen Student Rowing Club Phocas, of which he was a full-time board member from 1997 to 1998. On December 22, 2000 he passed his medical finals.

He then worked as a resident at the Bernhoven hospital in Veghel until the start of his GP vocational training at the Radboud University Nijmegen Medical Centre in March 2002.

In September 2003 he started combining vocational training with research training and became one of the first GP medical research trainees (aiotho in Dutch) at the Department of Primary and Community Care of the Radboud University Nijmegen Medical Centre.

In 2005 he completed his vocational training, after which he worked as a GP in several general practices and out-of-hours GP clinics, while continuing his research. The results of that research are described in this doctoral (PhD) thesis.

Since 2007 he has been working together with GP Inge Meekes in their joint general practice in Ede, a city in the center of the Netherlands. The practice participates in education, in particular the GP vocational training, and in research programmes of the Radboud University Nijmegen Medical Centre.

The author is a member of the Dutch GP expert group on diabetes (DiHAG) and of the European Association for the Study of Diabetes (EASD), and is working as a diabetes expert in primary care in the Gelderse Vallei region.

He is also a board member of the District of Groot Gelre of the Royal Dutch Medical Association (KNMG) and of the Gelderse Vallei cooperative union of GPs.

Erwin Klein Woolthuis is married to Iti-Marije Klein Woolthuis-Smits. Together they have two sons: Sander and Jasper.

Over de auteur

Erwin Klein Woolthuis werd geboren op 12 november 1974 in Deventer. Daar groeide hij ook op. Hij behaalde in 1993 zijn gymnasiumdiploma aan de Openbare Scholengemeenschap Alexander Hegius (tegenwoordig Etty Hillesum Lyceum) in Deventer. Dankzij een gunstige loting kon hij aansluitend geneeskunde gaan studeren aan de Radboud Universiteit Nijmegen (toen nog Katholieke Universiteit Nijmegen). Na twee jaar werd hij lid van de Nijmeegse Studenten Roeivereniging Phocas, waarvan hij van 1997 tot 1998 met een universitaire beurs een jaar full-time bestuurslid was. Op 22 december 2000 is hij geslaagd voor zijn artsexamen.
Daarna werkte hij als arts-assistent in ziekenhuis Bernhoven in Veghel tot de start van zijn huisartsopleiding aan het Universitair Medisch Centrum St Radboud Nijmegen in maart 2002.
In september 2003 kreeg hij de mogelijkheid om de huisartsopleiding te combineren met promotieonderzoek als één van de eerste aiotho's (arts in opleiding tot huisarts en onderzoeker) bij de afdeling Huisartsgeneeskunde (nu Eerstelijnsgeneeskunde) van het Universitair Medisch Centrum St Radboud.
In 2005 werd hij huisarts, waarna hij als waarnemend huisarts heeft gewerkt in diverse huisartsenpraktijken en huisartsenposten. Daarnaast deed hij het promotie-onderzoek, waarvan de resultaten in dit proefschrift zijn beschreven.
Sinds 2007 werkt hij samen met huisarts Inge Meekes in hun gezamenlijke huis-artsenpraktijk in Ede. Deze praktijk biedt als Nijmeegse Universitaire Huisarts-praktijk stageplaatsen voor de opleiding geneeskunde en de huisartsopleiding van het Universitair Medisch Centrum St Radboud. Daarnaast neemt de praktijk regelmatig deel aan wetenschappelijk onderzoek.
De auteur is lid van de Diabetes Huisartsen Advies Groep (DiHAG) en de European Association for the Study of Diabetes (EASD), en is werkzaam als kaderhuisarts diabetes voor de zorggroep Gelderse Vallei.
Hij is tevens bestuurslid van district Groot Gelre van de Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst (KNMG) en van de coöperatieve vereniging Huisartsen de Gelderse Vallei.
Erwin Klein Woolthuis is getrouwd met Iti-Marije Klein Woolthuis-Smits. Samen hebben ze twee zonen: Sander en Jasper.