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Patient profiling to tailor type 2 diabetes care

Dorijn Francisca Louise Hertroijs

Colofon

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Voor pap en mam

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CHAPTER 1

General introduction

The rise in chronic diseases

On a cold December night in 1799, George Washington, the first president of the United States, died at the age of 67 of an acute infectious disease believed to have been bacterial epiglottitis [1]. At that time, infectious diseases were the most common cause of death and a major healthcare challenge around the world [2]. No one alive then could have imagined the major advances in understanding and controlling infectious diseases that have since then been made [2, 3].

Although outbreaks of infectious diseases, such as Ebola and Zika virus, still exist, chronic diseases, such as type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD), have taken on a more prominent role [4, 5]. These diseases, characterized by a long development period and a prolonged course of illness [6, 7], are now the leading cause of death worldwide [8]. The increase in the prevalence of chronic diseases is mainly due to an increase in tobacco use and caloric intake, a diet rich in saturated fat, sugars and sodium, inadequate physical activity, and the ageing of the population [9-12]. The consequences of chronic diseases are not mild and include lower quality of life, functional impairment, and other health complications [6, 13]. Had George Washington lived in the current century, he would have most likely lived a longer, but not necessarily healthier life. For societies, chronic diseases are also very expensive. In the US alone, the five most prevalent chronic conditions caused an economic burden of 1.5 trillion dollars between 2008 and 2010 [14].

As the world experienced the epidemiological transition from infectious to chronic diseases, healthcare systems did not undergo major adjustments [4, 15, 16]. These systems were originally designed to deliver reactive and episodic care by diagnosing and treating, rather than preventing, acute illnesses. However, the treatment of chronic diseases requires proactive, continuous, and often multidisciplinary care [17]. Care that optimally supports patients in making important lifestyle changes and takes into account patients' interpersonal variation in disease development, management and impact [11, 18]. The best approach for providing such optimal care for people with chronic disease is, however, unclear. Therefore, the Dutch PROFILe project, which stands for *PROFiling people's healthcare needs to support Integrated, person-centered models for Long-term disease management*, started in 2014. The aim of this project was to develop and validate so-called 'patient profiles' as an instrument for tailoring chronic care management to the needs, preferences and abilities of patients. Type 2 diabetes mellitus was chosen as the starting point for profile development, because, due to its complications, it is a priority health problem in the Netherlands and a good model for other chronic diseases [19-21]. This dissertation describes the development and validation of the patient profiles. This first chapter introduces the topic of this dissertation, the aims and its outline.

Type 2 diabetes mellitus

Symptoms

Type 2 diabetes mellitus (from now on referred to as type 2 diabetes) is a complex and heterogeneous disorder that is characterized by an excess of glucose in the bloodstream [22]. This excess of glucose is caused by a resistance of the body to the effect of insulin and/or insufficient production of insulin, a hormone that is produced in the pancreatic islets and regulates the movement of glucose into body cells [23, 24]. Patients are diagnosed with type 2 diabetes when their fasting blood glucose values exceed 7.0 mmol/l on two different days or when their non-fasting blood glucose value exceeds 11.1 mmol/l in combination with symptoms related to hyperglycemia [25]. Type 2 diabetes often develops slowly. At diagnosis, patients who have type 2 diabetes may show little or no symptoms. Those patients who do have symptoms, typically experience polyuria, thirst, hunger, extreme fatigue, weight loss and a blurry vision due to elevated blood glucose levels [25].

Epidemiology and consequences of type 2 diabetes

According to the latest estimates, type 2 diabetes affects 451 million patients worldwide [26]. If no effective preventable measures are undertaken, the number of patients with type 2 diabetes is likely to increase to 693 million by 2045. Once “a disease of affluence”, it is now not only a common disease in high-income countries, but also in low- and middle income countries [27]. Asia is the epi-center of the epidemic, due to its large population, rapid economic development, and adoption of western lifestyle patterns [27, 28]. In the Netherlands, approximately one million patients live with type 2 diabetes, which is almost 6% of the total population [29, 30]. Type 2 diabetes disproportionally affects socially and materially disadvantaged people [31]. It is a major cause of morbidity and the 14th leading cause of disability-adjusted life years [32]. It is important for patients with type 2 diabetes to keep their blood glucose levels under control, as inadequate glycaemic control can lead to long-term complications [33]. The most common complication is CVD, which affects approximately 34% of patients with type 2 diabetes [34]. The hazard ratio for CVD is approximately twice as high for patients with type 2 diabetes compared with those without [35]. CVD accounts for as much as 75% of all mortality in type 2 diabetes. Other diabetes-related complications include chronic kidney failure, vision loss and lower-extremity amputations [19, 20, 36]. Furthermore, type 2 diabetes has been related to depression, lower quality of life and impaired physical fitness [37-39]. Treatment with glucose-lowering drugs, especially insulin, can have considerable side effects such as hypoglycemia, which is a very unpleasant experience for many patients further increasing the burden of disease [40].

Economic and societal burden

Type 2 diabetes does not only have a considerable impact on people’s health, but also places a heavy financial burden on society, health systems, individuals and employers. In high-income countries, the financial burden of type 2 diabetes mostly affects government or (public) health

insurance budgets, whereas in poorer countries, with limited health insurance coverage, much of the burden falls on the person with type 2 diabetes [41]. In the Netherlands, the total estimated economic burden of type 2 diabetes in 2016 was €5.9 billion [22]. Of course, many of these costs are directly related to medical care, such as primary and secondary care costs. However, more than half of the total costs of diabetes are indirect costs, such as income losses, lost work hours due to illness, welfare payment costs, and indirect costs due to complications.

Management of type 2 diabetes

Setting

As noted above, type 2 diabetes is a chronic disease that cannot be cured. However, with the right management, patients with type 2 diabetes can live a long and healthy life; this implies that patients need continuous care. In the Netherlands, more than 80-90% of people with type 2 diabetes are treated in primary care [42]. The majority (85%) of these patients has at least one diabetes consultation at a primary care practice per year, where they are treated by a team consisting of a general practitioner (GP) and a practice nurse (PN) or specially trained diabetes nurse [25, 42]. On average, these patients have 5.6 primary care consultations for type 2 diabetes per year [42]. Patients who are unable to reach individual treatment targets in primary care and/or have severe complications and/or comorbidities, need more complex diabetes management. These patients are treated in secondary care by a diabetes team, most often led by an endocrinologist/diabetologist [43].

In an attempt to change from reactive, episodic care for patients with chronic diseases to proactive, continuous care, a new funding system for chronic care based on bundled payments was formally introduced in the Netherlands in 2010 [44, 45]. Under this system, health insurers annually pay a single fee for the full 'bundle' of diabetes care per insured client to a new organizational construct in primary care: the care group (in Dutch: 'zorggroep'). A care group consists of care providers, such as GPs, PNs, dieticians, and – in some cases – endocrinologists, who are responsible for the delivery of chronic care to a specific patient population under a bundled payment contract [44]. The fee received per patient, which they freely negotiate with health insurers, covers a full range of care services for a fixed period, usually one year [44]. These services are codified in the Dutch Diabetes Federation Health Care Standard for type 2 diabetes [46], which focusses on the content, organization, and process of care. They are also in accordance with strict diabetes guidelines from the Dutch college of General Practitioners on type 2 diabetes, which guide healthcare providers in making adequate treatment decisions [25]. For example, a care group might receive €300 per year for a patient with type 2 diabetes. Within this budget, the patient receives four primary care consultations, a number of screenings and laboratory tests, and weight loss treatment from a dietitian. Care groups receive a higher budget for patients who, for example, need additional consultations or guidance in smoking cessation. There are approximately 130 care groups in

the Netherlands, which take care of the treatment of the majority of patients (85-90%) with type 2 diabetes [45, 47].

Treatment

Because an unhealthy lifestyle is an important risk factor of complications and insufficient glycaemic control, lifestyle improvement is usually the first advice from healthcare providers to patients with type 2 diabetes[25]. Previous studies have shown that weight loss and increased physical activity can lead to a marked decrease in hemoglobin A1c (HbA1c), which provides an estimate of the blood glucose level over the prior 2 to 3 months [48, 49]. Moreover, these lifestyle interventions have a beneficial effect on other CVD risk factors. When target values of HbA1c are not reached, oral glucose lowering drugs are prescribed. In the Netherlands, approximately 70% of the patients with type 2 diabetes use these drugs [29]. Insulin is used by approximately 25% of people with type 2 diabetes and is prescribed when oral glucose lowering drugs fail to decrease a patient's HbA1c below the target value [29, 50].

Self-management (support)

A large proportion of diabetes care is based on self-management, which is defined as the active participation of patients in their treatment [51]. Self-management activities for type 2 diabetes include day-to-day blood glucose monitoring for patients on insulin therapy, medication intake, consuming a healthy diet, being physically active, preventing hypoglycemia, coping with emotions, and dealing with the side effects of medication [52]. Healthcare providers should educate and support patients in obtaining and sustaining the knowledge, skills and confidence to self-manage their disease [25, 53]. In the guideline of the Dutch College of General Practitioners on type 2 diabetes, self-management support is a key element [25]. Providing high-quality self-management support is important, because it can improve patients' health-related behaviors [54] and self-efficacy, i.e. the belief in their ability to accomplish specific goals [55]. Subsequently this can lead to improved health- and/or functional status [54]. However, in reality, there is a limited degree of self-management support and patient involvement in practice in the Netherlands, as well as in many other countries in Europe [56, 57]. Healthcare providers often lack the time, skills and resources necessary to provide adequate self-management support- and education. Moreover, they are primarily trained to react to acute episodes of illness, and not to educate and support patients in maintaining their health and quality of life [56].

Quality of type 2 diabetes care

In the Euro Diabetes Index, most recently published in 2014, the Netherlands ranks second after Sweden in terms of quality of diabetes care [58]. This high rating is mainly due to an excellent multidisciplinary collaboration and coordination among healthcare providers [59]. Although Dutch diabetes care is considered to be of very high quality, it also has its drawbacks. One of the major drawbacks is that the care recommended in the care protocols is highly

standardized, based on the average patient with type 2 diabetes [25, 46]. Yet, the average patient does not exist. Patients with type 2 diabetes differ in glycaemic control, cardiovascular risk and socio-demographic characteristics, amongst many other factors. Yet, barring some exceptions for older patients, they all receive very similar diabetes care [25]. Not all patients seem to benefit from the current 'one-size-fits-all' approach, leading to differential treatment effects. Studies have for example shown that approximately 20 to 30% of patients with type 2 diabetes have insufficient glycaemic control [60-64]. This suggests that these patients might benefit from more intensive disease management, such as frequent and longer consultation visits. Vice versa, patients with adequate glucose levels might maintain these levels with less frequent consultation visits. These hypotheses were tested in two previous Dutch studies. In the first study, patients with type 2 diabetes treated in a hospital did not only receive usual care (e.g. three-monthly consultations with an endocrinologist and diabetes team), but also a diabetes passport, which included the results of medical examinations. The aim of the passport was to promote shared decision making, which is a method to establish mutually accepted treatment goals between a patient and healthcare providers [65]. Patients also attended educational meetings. After one year, the intervention seemed cost-effective for patients who had insufficient glycaemic control at the start of the study, but was not cost-effective for patients who had adequate glycaemic control. In the second study, the effectiveness of six-monthly consultations compared to three-monthly consultations, as stipulated in the care standard, was assessed in patients with adequately controlled type 2 diabetes and without a strong preference for their monitoring frequency [66]. After 18 months of follow-up, patients were equivalent to the three-monthly consultation group in terms of cardio metabolic control. Furthermore, 9 out of 10 patients were satisfied with the lower frequency of care. These findings suggest a shift towards more personalization of care.

Personalization of care

History

The personalization of care, defined as the tailoring of medical treatment based on individual patient characteristics, needs, and preferences [67, 68], is a concept that has received much attention over the past two decades, but is certainly not new. It was first described more than 2000 years ago as 'Ayurvedic medicine' in sacred texts from India [69]. Ayurveda, meaning 'science of life', is a traditional healing system that classifies people at birth into three subgroups based on their physical, physiological, and psychological characteristics. Individuals belonging to different subgroups, but displaying the same symptoms, may be treated differently. Thus, Ayurvedic medicine emphasizes the individual rather than the disease. Not much later, Hippocrates, a Greek physician, wrote: "it is far more important to know what person has the disease, than what disease the person has" [70]. He included patients' age and physique in the decision making process to prescribe drugs [71].

Even though, at the time, there was some emphasizes on the personalization of care, patients were used to, and perhaps also expected to, adopt the 'sick role' [72, 73]. In this role, first

described by Parsons in 1951, patients had very little autonomy and complied with the orders of healthcare providers in order to get well [74]. Healthcare providers acted to what they thought to be in the best interest of patients and were solely responsible for making all treatment decisions [75]. Until about 1960, this relationship between patients and healthcare providers was very common [73]. However, in the past several decades, the population has become increasingly educated and the emergence of the internet has made information about medical problems and treatment accessible for patients [72, 73]. Furthermore, the number of people with a chronic disease has increased: as part of their treatment, these patients have to make important behavioral and lifestyle changes (i.e. self-management) [8, 11]. Many patients are experts when it comes to embedding these changes in their daily lives [76]. This forces healthcare providers to discuss available treatment options with them and, as such, has increased the empowerment of patients [72, 73]. It has also made healthcare providers understand that patients have different care preferences, needs and abilities [72]. By incorporating shared decision-making, patient and healthcare providers are beginning to find a healthier balance of power [73], which has led to the growing popularity of care personalization.

The digitalization of health care is another reason for the increased popularity of the personalization of care. Since the mid-1980s, the capacity to produce, store and communicate digital data has exploded [77]. In health care, data from electronic health records, clinical trials and genomics, amongst others, have been compiled and analyzed to identify associations that would otherwise go unnoticed [78]. This so called 'big data' has the potential to improve clinical practice and patient care. It can detect genomic regions associated with a given trait in which disease-related genes are located, identify high-risk patients, and more precisely target treatment to their needs [61, 78, 79]. This type of personalization of care is often referred to as 'personalized care' or 'precision medicine' [80]. The use of the term precision medicine increased when the former president of the United States, Barack Obama, launched the Precision Medicine Initiative in 2015 [81]. The aim of this initiative is to predict the process of disease and to create personalized care by gaining more knowledge on the genetic variation in disease. For type 2 diabetes, efforts have been undertaken to unravel its genetic background by studying not only common gene variants, but also infrequent and rare variants [82]. To date, however, only 10-15% of the disease's heritability has been unveiled [23, 83].

Patient profiles

Since precision medicine based on a genotyping approach seems far away for the treatment of type 2 diabetes, shifting towards a phenotyping approach could be a more promising alternative. In this approach, patients' biomedical characteristics, such as blood pressure and BMI levels, as well as psychosocial characteristics, such as quality of life and social support, are identified and used to stratify patients into clinically relevant subgroups with similar care preferences, needs and abilities. In this dissertation, these subgroups are called 'patient profiles'. Stratifying patients into patient profiles can be used to develop optimal combinations of provider-led care and self-management support for each profile. For

example, for patients with increased care needs, the consultation frequency could be increased in combination with receiving group-based diabetes education and emotional support from a psychologist. This can help healthcare providers to translate concepts such as shared decision making and self-management into concrete care activities. There is increasing consensus that this approach could improve patients' health outcomes [67, 84-86]. Figure 1 shows the steps that need to be taken to stratify patients into patient profiles and adjust care accordingly.

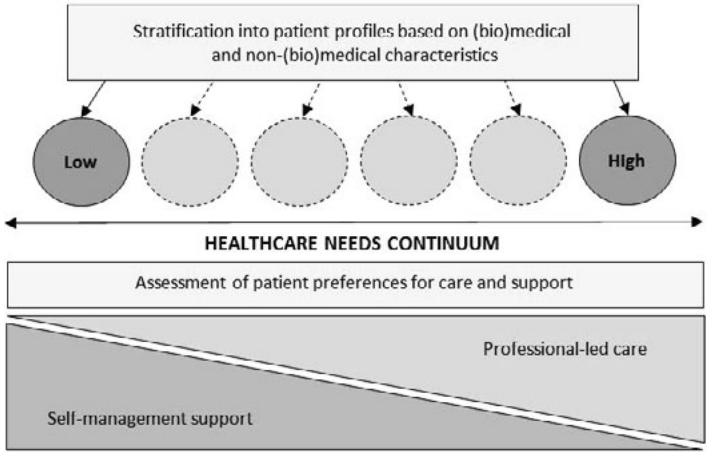

Figure 1. Framework for tailored chronic care management based on patient profiles

Patient profiling is related to the concept of 'mass customization', where goods and services are delivered with enough variety and customization that nearly everyone finds exactly what they want at costs close to those of mass production [87, 88]. Take Starbucks for example, which offers only a few products, but you can order them in many different ways. Mass customization has recently moved from products to healthcare services, with the goal to make care more cost-effective [89]. It constitutes a promising approach for achieving the so-called 'Triple Aim', which is a framework developed to optimize health system performance [90]. The first aim of the Triple Aim, improving patient experience, can be achieved by including patients' care preferences in treatment decisions. The second aim, improving the health of populations, can be achieved by including patients' care needs and abilities in treatment decisions. Reducing the per capita costs of health care, which is the final aim, can be achieved by providing the right care, to the right person, at the right time. Patient profiling aims to make care more personalized by identifying subgroups of patients who are more homogeneous than the population as a whole.

Aim and outline of the dissertation

At the initiation of the PROFILe project described in this dissertation, a tailored care approach for the treatment of type 2 diabetes was not structurally implemented in Dutch diabetes care, or even developed, due to two reasons. First, it was unclear which patient characteristics can be used to stratify patients into patient profiles. Second, it was unclear how type 2 diabetes care can be tailored to meet the care preferences, needs and abilities of the patients in each patient profile. Within this context, the overall aim of this dissertation was to develop and validate patient profiles as a tool to establish tailored care for patients with type 2 diabetes. Three objectives have been formulated:

1. To determine which health-, person-, and context-related patient characteristics are relevant for guiding tailored chronic care management
2. To determine how these characteristics can be combined into a scientifically robust and practicably feasible set of patient profiles
3. To assess the preferences and their determinants of patients with type 2 diabetes towards type 2 diabetes care

Chapter 2 provides a detailed description of the patient profiling approach. **Chapter 3** provides the results of a systematic literature review on patient-related effect modifiers that influence the outcomes of integrated care programs for type 2 diabetes in primary care. **Chapter 4** is a cross-sectional cohort study which gives insights into the relationship between patient characteristics and glycaemic control in patients with type 2 diabetes. In **Chapter 5** real world data from a Dutch diabetes care network are used to identify glycaemic control trajectories and build a model to predict these trajectories using patient characteristics. In the same chapter the findings of the prediction model are validated using real world data from another Dutch diabetes care network. In **Chapter 6** the opinions of HCPs and patients about relevant patient characteristics for estimating healthcare needs of patients with type 2 diabetes are assessed and compared. **Chapter 7** provides the results of a discrete choice experiment (DCE) on the preferences of patients with type 2 diabetes towards type 2 diabetes care. In **Chapter 8**, two different patient profiling approaches are discussed and compared. The final chapter discusses the main findings of the studies in this dissertation, provides a reflection on these findings, as well as methodological and theoretical considerations. Lastly, recommendations for clinical practice, future research and policy are presented.

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CHAPTER 2

Profiling patients' healthcare needs to support integrated, person-centered models for long-term disease management (Profile): research design

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Abstract

Background: This article presents the design of PROFILe, a study investigating which (bio)medical and non-(bio)medical patient characteristics should guide more tailored chronic care. Based on this insight, the project aims to develop and validate 'patient profiles' that can be used in practice to determine optimal treatment strategies for subgroups of chronically ill with similar healthcare needs and preferences.

Methods/Design: PROFILe is a practice-based research comprising four phases. The project focuses on patients with type 2 diabetes. During the first study phase, patient profiles are drafted based on a systematic literature research, latent class growth modeling, and expert collaboration. In phase 2, the profiles are validated from a clinical, patient-related and statistical perspective. Phase 3 involves a discrete choice experiment to gain insight into the patient preferences that exist per profile. In phase 4, the results from all analyses are integrated and recommendations formulated on which patient characteristics should guide tailored chronic care.

Discussion: PROFILe is an innovative study which uses a uniquely holistic approach to assess the healthcare needs and preferences of chronically ill. The patient profiles resulting from this project must be tested in practice to investigate the effects of tailored management on patient experience, population health and costs.

Background

One of the greatest challenges for health systems and economic and social development in Europe is the rising burden of chronic disease [1]. Around 32 percent of Europeans is now chronically ill, with many – especially elderly – people suffering from multiple conditions at the same time [2]. Without action, the chronic disease epidemic in the region will continue to develop rapidly: diabetes prevalence, for example, is expected to increase by 12.6 million cases over the next 15 years [3]. Chronic conditions cause serious disability, lower quality of life and early mortality, and already consume 70 to 80 percent of healthcare budgets across Europe [1].

When it comes to managing chronic disease, thus far the trend in most countries is to treat conditions separately through multidisciplinary care teams using disease-specific guidelines [4]. While such one-dimensional disease management can lead to improved care quality and outcomes [5-8], its value is quickly decreasing in proportion to rising multimorbidity. For the growing group of patients living with a complex of (interrelated) chronic conditions – such as diabetes, cardiovascular disease, asthma and dementia – disease management means having several care teams working according to different guidelines [10]. This may lead to fragmented care, loss of responsibility among providers, and confusion or even harm for patients [9]. Recent studies of chronic care in Europe also point to overstandardised service provision, limited preventive action, and a lack of support for patients' self-management [4,10,11]. Overall, the return on investment in chronic disease management seems relatively poor: real improvements in population health are not always achieved and many patients remain dissatisfied about their care, while costs reach unprecedented levels [1,12].

In recent years, there is increasing consensus that better management of chronic conditions requires an approach centered on patients instead of on their primary diagnosed disease [10]. It has become clear that active participation and commitment of patients is critical for achieving any kind of chronic disease control. Hence, their personal healthcare needs and preferences must be taken into account in clinical decision-making. Such individualisation of care, while important for all chronically ill, is particularly relevant for people with type 2 diabetes [13]. Besides generally being considered the 'quintessential self-managed disease', type 2 diabetes is a highly heterogeneous condition both in pathogenesis and clinical manifestation [10]. This means that the 'typical' diabetes patient does not exist and standardised management is likely to yield differential treatment effects. Indeed, recent research in Germany and the Netherlands shows that unstable, high-risk diabetes patients benefit significantly more from disease management than patients with better disease control for whom such intensive treatment may have little added value [14,15]. Similarly, various large-scale international studies suggest that not all diabetes patients profit from intensive glucose- or blood pressure-lowering therapy, pointing towards characteristics like age, disease duration, comorbidities, and patient attitude as possible effect modifiers [10,13].

Taking into account patient characteristics – with the potential to modify treatment outcomes in chronically ill – in clinical decision-making is important to enable the *right care* to be

provided to the *right person* at the *right time*, with a focus on increased patient engagement, self-management and, ultimately, cost containment. However, thus far, it remains unclear which patient features should guide a more tailored approach to chronic care management and how these can be translated into a feasible tool to support professionals and patients in daily practice. This paper describes the design of a three-year, multiple-phase research project entitled '*PROFiling patients' healthcare needs to support Integrated, person-centered models for Long-term disease management (PROFILe)*', which seeks to fill this significant gap in knowledge and, in so doing, support more patient-centered, sustainable chronic care management in practice.

Research aims and questions

The PROFILe project aims to develop and validate a novel, practical instrument – in the form of patient profiles – that supports more tailored chronic care management in practice. Unique about the profiles to be developed is that they will combine (bio)medical and non-(bio)medical patient characteristics relevant for determining an optimal treatment strategy for subgroups of patients with similar care needs and preferences. The objective here is not to create a complex network of detailed patient features, but rather to identify a limited number of key characteristics that, when combined into profiles, can serve as an instrument to help tailor the general stipulations of chronic care standards and guidelines in a patient-driven manner. More specifically, the PROFILe project will answer the following research questions:

1. *Which (bio)medical and non-(bio)medical patient characteristics are (clinically) relevant for guiding tailored chronic care management?*
2. *How can those characteristics be combined into a scientifically robust and practicably feasible set of patient profiles?*
3. *What are patients' preferences for specific configurations of professional-led care and self-management support per developed patient profile?*

Although the objective of PROFILe is explicitly not to develop another disease-specific approach to chronic care management, type 2 diabetes (as primary diagnosis) is used as a starting point for profile development.

Methods/Design

Study design

PROFILe is designed as a practice-based, mixed-methods research comprising four phases, which are completed sequentially over a total period of 36 months. The project started in December 2014. Study design and phasing are shown in Figure 1. The research is conducted at Maastricht University in the Netherlands, in close collaboration with various stakeholders, and funded by Novo Nordisk. No ethical approval is needed for the research: as the data used are already available and patients are not physically involved in the research, the study is not subject to the Dutch Medical Research (Human Subjects) Act (WMO). PROFILe draws in considerable part on the 10-year, epidemiological Maastricht Study [16], which has previously

been approved by the medical ethical committee of Maastricht University Medical Centre (MUMC+) (NL31329.068.10) and the Netherlands Health Council under the Dutch Population Screening Act (Permit 131088-105234-PG).

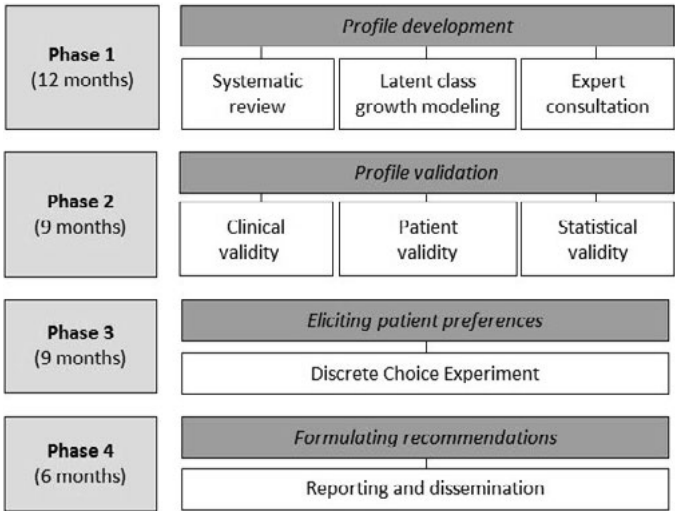

Figure 1. Study design and phasing

Setting

Over the past decade, diabetes has become a public health priority for the Dutch Ministry of Health [17]. Considerable resources have been and still are invested in reforming the content, organization and funding of diabetes management with the aim of improving care quality and outcomes for patients. According to Wensing et al. [18], the Dutch Ministry of Health regards diabetes as 'an ideal case for general policies for chronic illness care'. Indeed, some of the most important changes of late in Dutch chronic care management have started with pilots in diabetes care and were consequently rolled out to, for example, COPD care and vascular risk management [19]. Internationally, the Netherlands is regarded as a pioneer of high-quality diabetes care, ranking second after Sweden on the 2014 Euro Diabetes Index which compared diabetes management in 30 European countries [20].

In the Netherlands, the vast majority (85-90%) of patients with type 2 diabetes are managed by GPs in primary care [21]. Patients who need more complex management are treated in secondary care by a diabetes team led by an endocrinologist. According to the National Transmural Agreement (NTA) for type 2 diabetes [22], complex management concerns patients 'who are unable to reach individual treatment targets in primary care (and for whom there are valid grounds for expecting improvement in secondary care) and/or whose management is problematic due to severe complications or therapy resistant cardiovascular risk factors'. When patients are referred to secondary care, the endocrinologist assumes responsibility for their diabetes care, either indefinitely or until they can transition back to

general practice. The NTA specifies the formal criteria for referrals between primary and secondary care [22].

Because primary care is widely considered to be the most suitable medical home for chronically ill [23], and most Dutch type 2 diabetes patients are treated there, PROFILe will develop patient profiles specifically for the primary care setting. In recent years, Dutch primary care has undergone a considerable transformation as most GPs have gathered in so-called 'care groups'. These provider networks are similar to Accountable Care Organizations in the United States and Clinical Commissioning Groups in the United Kingdom [24,25]. Care groups first emerged in Dutch primary care in 2007 with the experimental introduction of a bundled payment system for integrated type 2 diabetes care. Quickly growing in number, there are now around 100 groups covering near to all Dutch regions and 85 to 90 percent of type 2 diabetes patients [26]. Annually, care groups negotiate a bundled payment contract with health insurers to organise, coordinate and provide the whole package of non-complex type 2 diabetes care for patients in their region. The care group is responsible for all patients covered by its bundled payment contract; GPs (and affiliated personnel, such as practice nurses) deliver care themselves and/or subcontract services from other providers, such as physical therapists, dieticians, laboratories, and, to a limited extent, medical specialists. The content of the care package is prescribed by a national standard for diabetes care developed by the Dutch Diabetes Federation, which stipulates, amongst others, that patients are seen in general practice at least four times annually, receive a specific number of tests and screening, and are offered education about their disease and self-management [24].

Although diabetes care in the Netherlands is viewed internationally as 'best practice', recent evaluations suggest there is room for further improvement. Most notably, the role that patients have in their care remains limited, with support interventions for self-management still largely in their infancy [11,19]. Another limitation is the high level of service standardisation based on the Dutch diabetes care standard, which – according to the Euro Diabetes Index – is followed 'so strictly that new ideas not accepted in the standard are shunned' [20].

Conceptual framework

Aim of the PROFILe project is to develop and validate a robust and feasible set of patient profiles that can be used in daily practice to support more patient-centered, tailored chronic care management. Although in essence, the patient profiles to be developed constitute a tool for case-mix classification – for which many other methods exist that have been studied extensively over the past years [28,29] – they will be unique in combining both (bio)medical patient features, such as disease duration and severity, and non-(bio)medical patient characteristics, like age, sex and educational level. Using non-(bio)medical characteristics for stratification purposes is assumed to provide better insight into patients' abilities for self-management of their chronic condition(s) and, in so doing, enables the intensity of professional-led care to be matched optimally to patients' actual care needs.

Figure 2 shows the conceptual framework underlying PROFILe, which draws upon the Population Health Conceptual Framework of the Care Continuum Alliance [30]. The figure illustrates that the ultimate goal of profiling is to enable patient subgroups to be aligned with interventions across the continuum of self-management support and professional-led care that match their established level of healthcare needs as well as their preferences for specific services. Thus, patients with a low level of healthcare needs – based on their (bio)medical and non-(bio)medical characteristics – might prefer support by a community nurse and/or incidental email contact with a primary care provider to manage their health. On the other end of the spectrum, those with a high-needs profile could favour regular monitoring in general practice combined with individual, nurse-led education. However, rather than assuming patients' likings for specific configurations of care and support, the PROFILe project will utilise a research method called 'discrete choice experimentation' to gain insight into the actual preferences of chronically ill patients for various attributes of chronic care management, such as the frequency of professional monitoring, central care giver, and methods and tools for self-management support. Moreover, as patients' perception of their illness is known to often differ from health professionals' assessment, the validity of the profiles will be tested against patients' own perceptions of their level of healthcare needs.

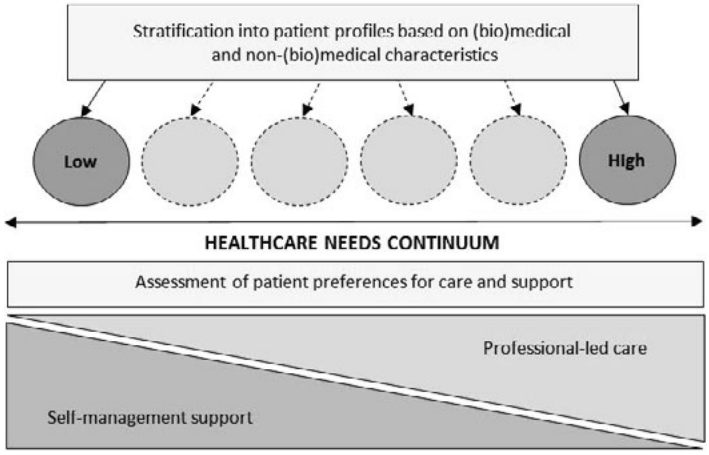

Figure 2. Framework for tailored chronic care management based on patient profiles

Data collection and analyses

The PROFILe project will combine a mixture of quantitative and qualitative data and analytic methods across four research phases.

Phase 1: Profile development

During the first research phase (12 months), the objective is to draft a robust and feasible set of patient profiles for tailoring type 2 diabetes management. Three research methods will be used to identify key patient characteristics influencing diabetes control and subsequently

combine those factors into real-valued prediction models: (a) systematic literature review; (b) latent class growth modeling; and (c) expert collaboration.

Systematic literature review

The systematic literature review is intended to gain insight into which bio(medical) and non-(bio)medical variables are potentially relevant for assessing the healthcare needs of type 2 diabetes patients. For this purpose, we will synthesise existing evidence about characteristics of patients that cause heterogeneity in the utilization and clinical outcomes of disease management strategies. In line with previous research [5-8], 'disease management' is operationalised as interventions targeting at least two of the four practice-level elements of the Chronic Care Model, that is, self-management support, delivery system design, decision support and clinical information [31].

Searches for English language empirical studies published between 1998 and 2015 will be conducted in PubMed, EMBASE and CINAHL using multiple groups of search terms related to type 2 diabetes, disease management, the Chronic Care Model, patient characteristics and relevant outcomes. The latter will include various measures of diabetes control and resource utilization. Included articles will be analysed descriptively; in addition, the two to three most consistently reported outcome variables across included articles will be meta-analysed to explain heterogeneity in disease management outcomes based on variation in patient characteristics.

Latent class growth modelling

In the second part of the profile development phase, quantitative data analyses will be conducted using a technique called latent class growth modelling (LCGM). LCGM is a type of cluster analysis that is increasingly employed in clinical research to capture heterogeneity between individuals in, for instance, treatment responses or disease patterns [32]. Using LCGM, subgroups of patients with distinct clinical trajectories over time can be identified and their characteristics determined [33].

Within PROFILe, LCGM will be applied to identify classes of type 2 diabetes patients with unique trajectories over the course of time in three measures of diabetes control, that is, HbA1c, LDL cholesterol and systolic blood pressure, as well as in a composite of these three measures. Longitudinal data on these and other relevant measures are collected from the Diabetes Patient Registry of the regional care group in Maastricht, which has been providing integrated type 2 diabetes care based on bundled payment contracts since 2007. Based on its achievements, the group was recently designated one of nine 'pioneer sites' in population (health) management in the Netherlands by the Minister of Health [34].

The Diabetes Patient Registry contains individual patient data registered during primary care visits from 2007 onward concerning a wide range of variables related to patient demographics, clinical status, and type and frequency of care provision. The study population will include all patients who entered the Diabetes Patient Registry at some point in time between January 2009 and December 2014 (N=~9,000). Based on the Diabetes Patient Registry data, models

with increasing numbers of classes will be run. Model fit and parsimony are assessed using the Bayesian Information Criterion and Lo-Mendell-Rubin Likelihood Ratio Test [32]. A standardised entropy score is calculated to determine the amount of ambiguity in class allocation [35]. Potential associations between various patient characteristics on the one hand and membership of a given class on the other will be explored using multinomial logistic backward regression analyses. All available determinants in the Diabetes Patient Registry will be analysed separately; correlations are assessed to test for co-linearity. Those determinants achieving a p-value <0.10 will be included simultaneously through a backward elimination method, resulting in a model that includes only significant ($p<0.05$) determinants.

In addition, multinomial logistic backward regression analyses will be conducted for a subsample of Diabetes Patient Registry patients, that is, those patients participating in the Maastricht Study [16]. This detailed epidemiological study, which started in 2010, focuses on the etiology and pathophysiology of type 2 diabetes, its classic complications (i.e. cardiovascular disease, nephropathy, neuropathy and retinopathy), and its emerging comorbidities, including cognitive decline, depression, and gastrointestinal, respiratory and musculoskeletal diseases [16]. During three to four 4-hour visits per participant, state-of-the-art imaging techniques and extensive biobanking are used to determine health status in a population-based cohort of 10,000 individuals enriched with type 2 diabetes patients. The latter are recruited from the Diabetes Patient Registry of the regional care group in Maastricht. An in-depth description of the design of the Maastricht Study can be found elsewhere [16]. Included in the multinomial logistic regression analyses are Maastricht Study participants with at least 24 months of registered data in the Diabetes Patient Registry prior to their inclusion in the Maastricht Study (N=~1,000), enabling combination of cross-sectional (Maastricht Study) data and longitudinal (Diabetes Patient Registry) data on the individual patient level. Compared to the Diabetes Patient Registry, the Maastricht Study adds extensive phenotype data as well as information on quality of life, lifestyle, socioeconomic and psychological features. These data will be used to place the latent classes developed based on the Diabetes Patient Registry data in a larger system of variables that may include hypothesised predictors not available in the Diabetes Patient Registry (e.g. education level) as well as potential long-term outcomes of latent class membership (e.g. quality of life) [36].

Expert and stakeholder consultation

Based on the combined findings from the literature review and LCGM analyses, a preliminary set of patient profiles is drafted by the research team in close collaboration with various stakeholders and scientific experts. These are represented in the project's Stakeholder Group, which includes representatives from patient organisations, provider associations, health insurers and policymakers, and the Scientific Advisory Board gathering (inter)nationally renowned experts in type 2 diabetes, disease management, case-mix classification and risk stratification. A priori, we assume phase 1 to result in three to eight draft patient profiles which, based on a limited number of pertinent (bio)medical and non-(bio)medical variables, describe relatively homogeneous classes of chronically ill in terms of their healthcare needs.

Phase 2: Profile validation

During phase 2 of the research (9 months), the aim is to validate the draft patient profiles focusing specifically on clinical validity, patient validity and statistical validity.

Clinical validity

To assess clinical (i.e. face) validity, that is, the extent to which health professionals consider the draft profiles as valid for assessing patients' healthcare needs, an electronic Delphi panel will be conducted with representatives of provider associations involved in type 2 diabetes management in the Netherlands. Relevant associations are the Dutch General Diabetes General Practitioners Advice Group (DiHAG), Diabetes and Nutrition Organization (DNO), Professional Organisation for Diabetes Care Providers (EADV), Diabetes Education Study Group (DESG), Royal Dutch Pharmacists Association (KNMP), Royal Dutch Society for Physical Therapy (KNGF) and the Dutch Internists' Association (NIV). The aim is to include two representatives from each Dutch association involved in structured diabetes management, so as to compose a balanced Delphi panel with sufficient professional expertise and mixed backgrounds.

The RAND/UCLA appropriateness method [37] will be used to design multiple Delphi rounds, including: (a) an online survey to assess experts preliminary scores of the profiles in terms of validity; (b) a face-to-face expert meeting to discuss individual scores and, where necessary and possible, increase group consensus; and (c) individual reassessment on a paper-based survey to produce final scores. Additional rounds may be added if insufficient consensus is reached after the face-to-face meeting. The focus of the Delphi study will be on the validity – according to healthcare professionals – of each separate patient characteristic identified as relevant during the first research phase, as well as on the validity of different combinations of these characteristics into patient profiles.

Patient validity

Given that patient profiles are intended to support more patient-centered management of type 2 diabetes, validation of the profiles by patients is also considered crucial. We will use a mixed-methods approach to test the validity of the draft profiles against patients' own views of their level of healthcare needs. The latter will be measured using the validated Problem Areas in Diabetes (PAID) questionnaire, which is a widely used, 20-item measure of emotional adjustment to life with diabetes [38]. A purposive sample of five to ten type 2 diabetes patients per draft patient profile will be selected from GP practices in Maastricht to participate in the profile validation.

The results of the PAID questionnaire form the input for an individual, in-depth follow-up interview, which aims to: (1) elaborate on patients' PAID scores by providing them the opportunity to tell their illness narratives; and (2) compare patients' own view of their level of healthcare needs with the profile chosen by the researchers. As the primary focus of patient validation is on the subjective experience of healthcare needs by the person who is chronically ill, a descriptive phenomenological approach is used for the interviews and analysis.

Phenomenology requires researchers to look at things in a new way without predispositions and prejudices, thus enabling fresh, rich and new understandings of existing phenomena [39]. A semi-structured interview guide will be used during the interviews to steer the conversation; the number and nature of questions can vary depending on the respondent's illness narrative. All interviews are audio-recorded. Data analysis will be conducted conform the descriptive phenomenological method using Hycner's 15-step framework [40], which starts with individual interview transcription and ultimately results in a composite summary of all interviews capturing the essence of the phenomenon under study as experienced by respondents.

Statistical validity

Finally, the statistical validity of the draft patient profiles – in particular, their generalisability to other settings – will be tested using quantitative data collected retrospectively from a different, larger cohort of patients than the one used for developing the profiles. This cohort will comprise a comprehensive selection of type 2 diabetes patients from the three remaining primary care groups in the Dutch province of Limburg (besides the one in Maastricht). Limburg is chosen as validation site because of its relatively poor population health compared to other provinces in the Netherlands, especially in terms of chronic disease prevalence [41].

Together, the three selected care groups cover an estimated population of approximately 65,000 to 70,000 individuals with type 2 diabetes. The groups' Diabetes Patient Registries will be used as source of retrospective data collection. Relevant parameters are identical to those used in research phase 1, that is, all routinely registered measures of patient demographics, clinical status, and type and frequency of care provision. Included in the validation sample are all adult (≥18 years) type 2 diabetes patients with at least 24 months of Diabetes Patient Registry data.

The generalisability of the draft profiles will be determined by assessing to which extent: (a) they cover the entire type 2 diabetes patient population in Limburg; (b) routine Diabetes Patient Registry data are sufficient to enable stratification into profiles and/or which additional data collection is necessary; and (c) identified trajectories and associations between patient characteristics and class membership are comparable. Based on the results of this research phase, the patient profiles will be adapted where necessary and finalised.

Phase 3: Eliciting patient preferences

The objective of the third PROFILe phase (9 months) is to provide insight into the patient preferences that exist per profile for specific configurations of diabetes care and support. For this purpose, a discrete choice experiment (DCE) will be conducted. Discrete choice experimentation is a validated, systematic approach for eliciting preferences, which has a strong theoretical basis in economic science and is increasingly used in international health systems to involve patients in health policymaking [42]. The technique is based on two assumptions: (a) that healthcare services can be described by their attributes; and (b) that an individual's valuation depends on the levels of these attributes. When determining an optimal

way to provide a service, such as tailored type 2 diabetes management, a DCE can be used to show how people are willing to trade between attributes.

The DCE to be conducted in this study will consist of five steps (see Table 1). First, five focus group discussions are held with purposive samples of four to eight type 2 diabetes patients per session. In selecting participants, we will ensure that each draft profile is represented by at least one person during each focus group discussion. Goal of the sessions is to select healthcare service attributes for inclusion in the DCE. Nominal group technique (NTG) will be used to prioritise attributes based on patients' preferences [43], with preliminary identification of potentially relevant attributes based on two sources: (1) the Dutch Diabetes Federation's care standard for type 2 diabetes [27]; and (2) the Dutch version of the Patient Assessment of Care for Chronic Conditions (PACIC) survey [44,45]. Examples of relevant attributes may include the frequency of professional monitoring, setting of care, involved providers, different methods and tools for self-management support, use of electronic applications, and so on.

Table 1. Steps of the discrete choice experiment (DCE) process and methods and sample size per step

DCE step	Method	Sample size
1. Attribute identification and selection	Focus group discussions (N=5) using the nominal group technique	4-8 respondents per focus group
2. Assigning levels to the attributes	Based on existing evidence (e.g. guidelines, protocols)	-
3. Developing scenarios	Based on chosen attributes and levels	-
4. Establishing preferences	Patient survey	50 respondents per profile
5. Data analysis	Regression analyses	50 respondents per profile

Second, levels are assigned to each of the identified attributes: the attribute 'frequency of monitoring', for instance, might have four levels (e.g. two, four, six or eight times per year). Third, scenarios are drawn up describing all possible service (or outcome) configurations given the attributes and levels chosen. For example, we could ask respondents to choose between these two scenarios: (a) to have four annual check-ups, with the nurse as central care giver; or (b) to have two annual check-ups, with the GP as central care giver. The number of scenarios to be developed will depend on the number of attributes and levels chosen.

Fourth, a patient survey is conducted to elicit patients' preferences for the developed scenarios. Although there is limited guidance on sample size calculations for DCE patient surveys, Pearmain et al. [46] suggest that sample sizes over 100 are a proficient basis for modeling preference data. Within this study, we aim for a larger sample size and will include

at least 50 respondents per draft profile. Thus, if the analyses in phases 1 and 2 result in a final set of six profiles, 300 patients will be needed to participate in the survey. Fifth, regression techniques are used to analyse patients' survey responses in general as well as focusing specifically on the level of heterogeneity in results between profiles.
The discrete choice experiment will be designed, conducted and analysed following published guidelines [42,47]. Respondents for the focus group sessions and survey will be selected from the Diabetes Patient Registry of the regional care group in Maastricht. Based on the findings from this research phase, recommendations will be formulated on how to tailor type 2 diabetes management to the developed and validated patient profiles. Moreover, the survey itself constitutes a project deliverable that can be used internationally to elicit patients' preferences for chronic care management.

Phase 4: Formulating recommendations
Aim of the final PROFILe phase (6 months) is to integrate the results of the three previous phases and derive evidence-based recommendations on which (bio)medical and non-(bio)medical patient characteristics should guide tailored chronic care management and how these can be combined into a robust and feasible profiling instrument for everyday practice. Explorations of the generalisability of findings to other conditions than type 2 diabetes will be an important focus in this phase. Findings are reported back to key stakeholders and disseminated to broader audiences in a variety of ways, including through scientific publications and conference contributions.

Discussion

This paper describes the design of the PROFILe project (2014-2017), a practice-based, mixed-methods research aiming to develop and validate a robust and feasible set of patient profiles for tailored chronic care management. It builds upon findings from the European collaborative DISMEVAL project, which was conducted between 2009 and 2012, and showed, amongst others, that current chronic disease management approaches in Europe tend to be highly standardised, insufficiently patient-centered, and result in differential – and often less than optimal – treatment effects across populations of chronically ill [48,49].
There is increasing consensus that better chronic care management requires a more patient-centered, tailored approach [10], which combines the advantages of maintaining a certain level of standardisation with the benefits of increased individualisation and patient participation. In business terms, this might be referred to as mass customisation, which is a service delivery trend adopted by major international companies, such as Levi's, Starbucks and Burger King. Mass customisation combines the flexibility and personalisation of custom-made service delivery with the low unit costs of mass production. In practical terms, the strategy is not about promising customers anything, anytime, anywhere and anyhow, but rather about differentiating services within a predetermined 'envelope of variety' ascertained from the client perspective [50].

PROFILe aims to support exactly such differentiation in chronic care management: patient profiles are intended as an instrument to segment the chronically ill population into subgroups with similar healthcare needs for whom – based on insight into their preferences – a range of matching care and support options can be developed. In the long run, tailored management based on patient profiles offers considerable potential for achieving Berwick's Triple Aim [51] of health system performance: (1) to improve patients' experience of care, by stimulating explicit inclusion of their healthcare needs and preferences in treatment decisions; (2) to improve population health and quality of life, by aligning patients with appropriate levels of treatment and self-management support; and (3) to reduce the per capita cost of care, by minimizing the over-, under- and misuse of healthcare resources that results, amongst others, from overly standardised service provision and a lack of patient self-management. In this respect, the PROFILe project fits within a broader health policy trend seen in many European countries, in which governments are rearranging healthcare services based on population health needs, and non-complex healthcare tasks and responsibilities are increasingly transferred back to patients and their families, not in the least for cost containment purposes [52].

An important strength of the PROFILe project is its use of a mixed-methods approach, combining quantitative and qualitative data and study techniques within and across research phases. In particular when investigating complex, multicomponent interventions, a mixed-methods design is increasingly viewed as superior to more classic methodological approaches such as the randomised controlled trial [53]. Another strong point of the study is the involvement of patients in multiple study phases and the use of innovative methods, such as discrete choice experimentation, in order to produce robust and meaningful findings that emphasise the patient perspective. Although more research has been and is being conducted internationally concerning individualisation of type 2 diabetes management [54,55], PROFILe is unique in its use of variables of non-(bio)medical nature for tailoring purposes. Given the strong impact that patients' personal circumstances have on their ability to self-manage and their level of treatment adherence [56], broadening the scope of individualisation beyond (bio)medical factors to also include demographic, socioeconomic and psychological aspects is a key forte of the PROFILe project.

There are also some limitations. Most notably, the disease-specific nature of the profiles to be developed – intended for patients with a primary diagnosis of type 2 diabetes – limits the generalisability of results and hampers development of a generic instrument for tailored chronic care management. However, there are two important arguments in favour of focusing on diabetes. First, because it is a priority health problem in the Netherlands, focusing on diabetes enables us to capitalise on the full potential that so-called 'big data' in electronic diabetes registries offer for personalising care [17]. Second, type 2 diabetes is widely considered to be a good model for chronic disease in general, in particular given its strong association with comorbidities [9,16], and is used as such in many countries' health policymaking efforts in chronic care, including in the Netherlands [18,57]. Another limitation concerns the setting of the study in primary care, which leads to exclusion of the 10 to 15%

most complex cases of type 2 diabetes – i.e. patients who are treated in secondary care in the Netherlands [21] – from our profiling efforts. Although the Dutch NTA for type 2 diabetes [22] seeks to ensure care continuity and safety during transitions between primary and secondary care, patients with complex type 2 diabetes might still benefit from a more tailored approach based on patient profiles. Hence, it is important to broaden the scope of future research efforts beyond primary care to include all patients with type 2 diabetes. A final limitation of the study is the lack of prospective evaluation of the effects of tailoring diabetes management based on patient profiles, for example in a randomised controlled trial, which is beyond the scope of this development and validation project. Following PROFILe, further research is necessary to gain detailed insight into the impact of tailored diabetes management on a range of measures related to the Triple Aim, including patient experience, population health and costs.

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CHAPTER 3

Relevant patient characteristics for guiding tailored integrated diabetes primary care: a systematic review

Published as

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Abstract

Aim: To identify which patient-related effect modifiers influence the outcomes of integrated care programs for type 2 diabetes in primary care.

Background: Integrated care is a widespread management strategy for the treatment of type 2 diabetes. However, most integrated care programs are not tailored to patients' needs, preferences and abilities. There is increasing consensus that such a patient-centered approach could improve the management of type 2 diabetes. Thus far, it remains unclear which patient-related effect modifiers should guide such an approach.

Methods: PubMed, CINAHL and EMBASE were searched for empirical studies published after 1998. A systematic literature review was conducted according to the PRISMA guidelines.

Findings: In total, 27 of 1,015 studies were included. Twenty-one studies measured the effects of integrated diabetes care programs on HbA1c and 3 on LDL-cholesterol, systolic blood pressure and health care utilization. Forty-nine patient characteristics were assessed as potential effect modifiers with HbA1c as an outcome, of which 46 were person or health-related and only 3 were context-related. Younger age, insulin therapy and longer disease duration were associated with higher HbA1c levels in cross-sectional and longitudinal studies. Higher baseline HbA1c was associated with higher HbA1c at follow-up in longitudinal studies. Information on context- and person-related characteristics was limited, but is necessary to help identify the care needs of individual patients and implement an effective integrated type 2 diabetes tailored care program.

Introduction

Diabetes is one of the most prevalent chronic conditions worldwide and a public health priority in many countries [1, 2]. In Europe, an estimated 9.8 million people suffer from diabetes; type 2 diabetes is responsible for 90% of cases. People with type 2 diabetes are at high risk for developing complications, such as cardiovascular disease and kidney failure, which in turn lead to increased healthcare costs[1, 2]. To prevent diabetes-related comorbidities and complications, and lower medical care expenditure for patients with type 2 diabetes, it is important to implement effective and efficient management strategies. An example of such a strategy is the implementation of integrated care. It aims to improve patient care and experience through improved coordination [3].

The implementation of integrated care programs is widespread in North America, Europe, and other parts of the world [3, 4]. However, most integrated care programs are not tailored to patients' needs and preferences, but rather highly standardized according to evidence-based guidelines for specific diseases, such as diabetes. Findings from recent studies suggest that not all patients benefit equally from such a standardized approach [5-7]. These studies report that patients with poorly controlled diabetes benefit mostly from intensive, provider-driven disease management, whereas patients with adequate glucose levels might maintain these levels independent of the type of care they receive.

In 2012, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recommended a more patient-centered approach for the management of type 2 diabetes [8]. In a patient-centered approach, care is tailored according to individual patient needs and preferences [8-11]. It draws on the concept of 'mass customization', where goods and services are delivered with enough variety and customization that nearly everyone finds exactly what they want [12]. Dividing the population based on healthcare needs creates groups that are more homogenous than the population as a whole. Hence, care offered to these groups will be more tailored to the patients' needs, while acknowledging that a certain amount of heterogeneity within the subgroups will remain.

There is increasing consensus that a patient-centered approach could improve the management of type 2 diabetes [8]. However, to date, it is unclear what the best method is for establishing patient-centered care [13]. Since intensive, provider-driven disease management is not beneficial to every type 2 diabetes patient, several studies have pointed towards patient characteristics – for example, number of co-morbidities, disease duration or attitude – as possible effect modifiers of treatment [8, 14-16]. These effect modifiers could be used to identify patients with different care needs and preferences, and subsequently serve as input to tailor treatment [17, 18] . However, it is unclear which effect modifiers should guide a more patient-centered approach. Therefore, the aim of this systematic review was to identify which patient effect modifiers influence the outcomes of integrated care programs for type 2 diabetes in primary care. These effect modifiers can help to segment the chronically-ill population into subgroups with similar healthcare needs for whom, based on insight into their needs and preferences, a range of matching care and support options can be developed.

This review is the first part of the research project entitled "PROFiling patients' healthcare needs to support Integrated, person centered models for Long-term disease management' (PROFIle)" [19]. The aim of this 4-year Dutch project is explicitly not to develop another disease-specific approach, but we use type 2 diabetes as starting point to develop, validate and test so-called 'patient profiles' as an instrument to support more patient-centered chronic care management in practice.

Methods

Data sources and searches

A systematic literature search according to PRISMA guidelines [20] was performed on PubMed, CINAHL and EMBASE databases in January 2015. Included were English- or Dutch-language randomized controlled trials (RCT), prospective and retrospective cohort- and cross-sectional studies which: [1] focused on integrated care (defined below) ; [2] included adult patients (≥18 years) with type 2 diabetes; [3] were set in primary care; [4] measured effects on 1 or more measures of diabetes management (HbA1c, LDL-cholesterol (LDL-c) and systolic blood pressure (SBP)) and/or health care utilization as outcome variables; and [5] included sub analyses with patient characteristics as independent variables. In line with previous research, integrated care was defined as interventions combining 2 or more components of the well-known Chronic Care Model (CCM) [21]. The CCM stresses the need for a more proactive healthcare system by focusing on 4 components: self-management support (e.g. patient education), decision support (e.g. evidence-based guidelines), delivery system design (e.g. care process) and clinical information systems (e.g. electronic registries) [22, 23]. Since the CCM was developed in 1998, only studies published in or after 1998 were included [24]. The search strategy included targeted terms related to diabetes, integrated care, CCM components, care outcomes and subgroup analyses based on patient characteristics. The complete search terms and search string can be found in Table 1. The snowball method was used to search for other relevant studies.

Study selection

Potentially relevant studies were retrieved from the electronic databases based on the inclusion criteria in 3 screening rounds. First, titles and abstracts were screened. The first 50 titles and abstracts were screened independently by 2 reviewers (DH and AE). More than 90% agreement was reached. Therefore, the remainder of the titles and abstracts were screened by 1 reviewer (DH). Second, the first 20 full texts were screened independently by 2 reviewers (DH and AE). Again, more than 90% agreement was reached and therefore, each reviewer independently screened half of the full texts. Third, the reference lists of the included studies were screened to obtain additional studies. Steps 1 and 2 of the study selection process were then repeated.

Data extraction and quality assessment

Descriptive data on studies were extracted by 1 reviewer (DH) between August and October 2015. Studies were coded for author names, year of publication, country, study design, length of follow up, population size, age, percentage of males and CCM components. In case of uncertainties, a group discussion was held with two other authors (AE and MB).

The Effective Public Health Practice Project Quality Assessment Tool (EPHPP) was used to assess the quality of the included studies [25]. This tool was chosen because it allows the assessment of different study designs. The studies were rated based on 6 domains: [1] selection bias; [2] study design; [3] confounders; [4] blinding; [5] data collection and [6] withdrawals and dropouts. Each domain was rated as 'strong', 'moderate' or 'weak'. A global rating was given based on the number of weak components.

Two reviewers (DH and MB) independently performed the quality assessment for each study. Disagreements were resolved via discussion conform EPHPP guidelines.

Data synthesis and analysis

The included studies were categorized according to: [1] the reported outcome(s) of interest (HbA1c, LDL-c, SBP and/or health care utilization); and [2] the type of patient characteristic(s) investigated in subgroup analyses. Characteristics were classified as person-related (predisposing)-, context-related (enabling)-, or health-related (illness level) characteristics according to Andersen and Newman's Behavioral Model of Health Service Use [26]. The model provides a theoretical framework for viewing health services utilization, taking into account both societal and individual characteristics. The model was chosen, because the individual characteristics can inform tailored care by, for example, helping determine the best intensity of care for the individual patient. Relationships between outcomes and characteristics were depicted as '+' for significant positive relationships, as '-'for significant negative relationships and as 'o' for non-significant relationships.

Results

Search results

In total, 1,374 studies were identified through electronic databases and by checking the references of the included studies. Figure 1 shows the flow diagram of the study selection. Most studies were excluded because none relevant outcomes were reported (n=453), and/or type of care was not integrated (n=257). After the title, abstract and full text screening, 27 studies were included [5, 27-52].

Table 1. Search terms and search string

#	Category	Search terms
1	Diabetes	Diabetes OR diabetes mellitus OR diabetic patient OR type 2 diabetes OR type 2 diabetes mellitus OR T2DM OR NIDDM
2	Integrated care	Integrated care OR disease management OR disease state management OR comprehensive healthcare OR comprehensive health care OR shared care OR coordinated care OR case management OR chronic care model OR primary care OR primary health care OR outpatient clinic OR outpatient services OR primary health care OR primary healthcare OR primary health clinics OR general practice OR family practice OR community care
3	CCM – self-management support	Self-management OR self-management support OR self-care OR patient-centeredness OR patient-centered care OR behavioral support OR motivational support OR self-management education OR patient education
4	CCM – delivery system design	Delivery system design OR care pathway OR critical pathway OR individualized care OR clinical case management OR medicines management OR medication management OR comorbidities management OR health literacy OR cultural sensitivity OR practice nurse OR care team OR health care team Or healthcare team OR patient care team OR personalized care OR personalized management OR individualized management OR multidisciplinary care team OR tailored care OR tailored support OR multidisciplinary care
5	CCM – decision support	Decision support, clinical reminders, clinician reminders, patient reminders, provider education, reminder systems, individualized care plans, individual care plans
6	CCM – clinical information system	Clinical information system, clinical information systems, clinical registry, health information system, health information systems, health information technology, electronic registry, clinical reminders, clinician reminders, patients reminders, provider feedback, performance monitoring, ICT device, patient portal, patient registry, diabetes registry, telemonitoring, telehealth, teleassistance, telehomecare, videoconferencing, mobile phone
7	Outcome measures	Glycemic control, glycaemic control, diabetic control, diabetes control, diabetes status, Charlson Comborbidity Index, resource use, health care use, health care utitlity, service use, resource utility, service utility
8	Sub group analysis	Factor, predictor, predictive factor, determinant, patient characteristic, patient characteristics, patient feature, patient features, patient dynamics, subgroup, subgroups, segment, strata, classes
9	Complete search string	#1 AND (#2 OR (#3 AND #4) OR (#3 AND #5) OR (#3 AND #6) OR (#4 AND #5) OR (#4 AND #6) OR (#5 AND #6)) AND #7 AND #8

CCM: Chronic Care Model

Quality assessment

The methodological quality of the included studies can be found in supplementary Table S1. The domains with the most 'weak' ratings were confounders (n=10), blinding (n=9), and selection bias (n=9). Almost all studies (n=25) scored high on the domain data collection. The overall study quality was strong for 4 studies, moderate for 11 studies and low for 12 studies. Most studies with low quality had a cross-sectional study design and did not report on or adjust for possible confounders.

Study- and sample characteristics

Of the included studies, 9 (33.3%) were retrospective cohort studies, 7 (25.9%) cross-sectional studies, 7 (25.9%) (randomized) controlled studies, and 4 (14.8%) prospective cohort studies. Table 2 shows that the median follow-up duration for retrospective cohort-, prospective cohort-, and randomized controlled studies (n=20) was 15 months (range 6 to 112). The median sample size consisted of 376 individuals (range 80 to 105,056) with an average age of 60.0 years (range 50.5 to 70.9); the percentage of male subjects ranged from 31.3 to 68.0. Table 2 also provides an overview of the CCM components implemented in each study. Eight studies included all 4 components of the CCM model. The CCM component delivery system design was included in most studies (n=25), followed by self-management support (n=20). Of the studies that included the components delivery system design, most introduced a care team (n=13), followed by regular follow-up visits (n=8). Self-management support was mostly realized through individual educational sessions on diabetes, health and nutrition (n=14).

Outcome variables

HbA1c

Eighteen uncontrolled studies – including prospective-, retrospective-, and cross-sectional cohort designs – measured the effects of integrated care programs on HbA1c. In addition, 7 studies compared the influence of patient characteristics on the effectiveness of integrated diabetes care programs between intervention- and control groups. In total, 51 patient characteristics were assessed as potential effect modifiers of the relationship between integrated care and HbA1c. The results will be presented according to study design. For RCTs all characteristics assessed by this study design will be discussed. Due to the high number of characteristics assessed by the cross-sectional-, retrospective-, and prospective cohort studies, only characteristics assessed by 3 or more studies will be presented.

(Randomized) controlled trials. Five RCTs and 2 CTs compared the influence of patient characteristics on the effectiveness of integrated diabetes care programs on the HbA1c level between intervention- and control groups (Table 3). In total 8 patient characteristics were evaluated as potential modifiers.

Sex and age were the person-related characteristics evaluated as potential effect modifiers. Three studies assessed sex as a potential modifier, of which two found that women in the intervention group had statistically significant lower HbA1c values at follow-up compared to women in the control group [40, 51]. For men, no statistically significant difference was found. The third study did not find a statistically significant relationship [39]. Age was assessed by 2 studies. Both found that younger patients receiving integrated diabetes care had statistically significantly lower HbA1c values at follow-up compared to patients receiving usual care [39, 43].

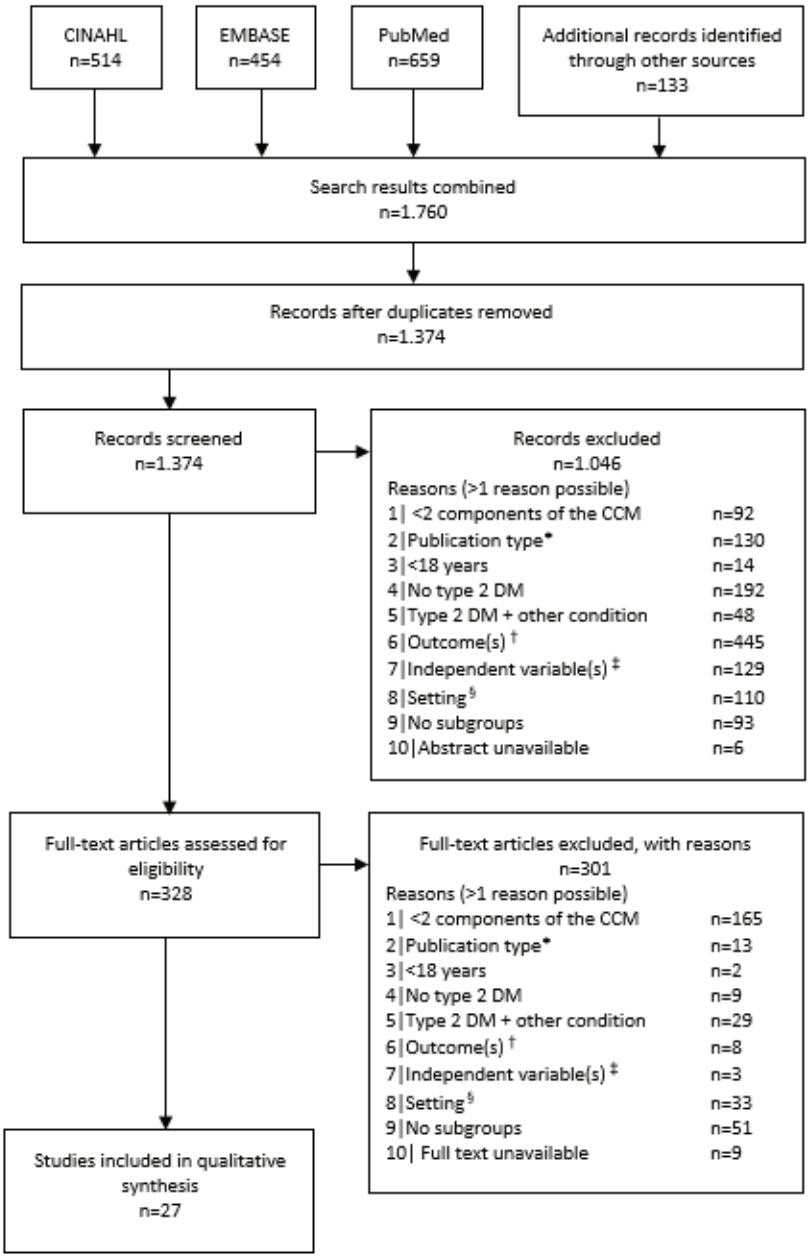

Figure 1. Flow diagram of the study selection

*qualitative-, or mixed-method studies; †any outcome other than HbA1c, LDL-cholesterol, blood pressure or health care utilization; ‡Independent variable is not a person-, context-, or health-related patient characteristic (e.g. healthcare provider characteristics); §setting is not a primary care setting (e.g. hospital).

Table 2. Study and sample characteristics

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Al Omari et al. (2009)	JOR	CS	NA	337	54.1(11.3)	52.1	Regular group counselling with the presence of family physicians, nurses, pharmacists and dieticians Leaflets related to diabetes	Care team (doctor and diabetic nurse) Regular follow-up: patient has to see the physician to take the prescription on a monthly basis		
Benoit et al. (2005)	USA	RC	24	573	55.4(10.1)	31.3		The nurse educator is the case manager Nurse educator identifies individual service and access needs of patients Nurse communicates with the primary care physician regarding clinical issues.	Nurse educator follows up on missed patient appointments Diabetes electronic medical system (DEMS) software	
Cardenas-Valladolid et al. (2012)	ES	PC	24	23,488	69.7(14.5)	48.4	Interventions focused on drug therapy compliance, change in lifestyle, health education and self-management		Computerized clinical record(CCR)	

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
De Fine Olivarius et al. (2009)	DK	PC	66	581	64.7(55.7-73.2)	51.9	Individualized goal setting	Follow-up every 3 months annual screening for diabetic complications	Annual descriptive feedback reports on individual patients.	Clinical guidelines supported by annual half-day seminar
Elissen et al. (2012)	NL	RC	20-24	105,056	65.7(11.9)	?	National Diabetes Care Standard includes general modules on information, education and self-management support, smoking, cessation, physical activity, nutrition and diet	Care team (GP, practice nurse)	Shared diabetes patient registry	Defined frequency of GP visits, regular foot and eye examinations, laboratory testing
El-Kebbi et al. (2003)	USA	RC	5-12	2,539	55.0(12.0)	44.0	Education program emphasizing lifestyle modifications and self-management skills offered to all patients at their initial visit and projects 6 to 8 return visits within the first year	Patients cared for by a team of nurse providers, physicians, dietitians, podiatrists, and a social worker		If glycemic goals are not met after the first 1 to 2 months, pharmacologic therapy is started or advanced according to a stepped-care protocol for intensification of therapy

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
De Alba Garcia et al. (2006)	Mex	CS	NA	796	60.5(10.8)	38.6	Diabetes and nutrition education Diabetes- and exercise support groups	Care team (physicians, nutritionist and psychologist)		
Groeneveld et al. (2001)	NL	RCT	12	I: 91 C: 155	I: 62.7(11) C: 62.3(10)	I: 34.1 C: 46.4	Counseling by a diabetes educator (nurse) and dietician at the 'Diabetes Service', a monitoring and advisory service	Care team consisting of diabetes educator (nurse), dietician and GP Patients were called up and reviewed every 3 months. If insulin was started contacts were more frequent		GP responsible for implementation of therapeutic advice of the Diabetes Service
Kellow, Savige and Khalil (2011)	AUS	RC	60	272	62.1(11.6)	49.0	Diabetes education at the health service diabetes education department	Care team (GP, diabetes educator). Diabetes educator referred patients for additional optometry, podiatry and dietetic appointments as required		
LeBlanc et al. (2015)	USA	RC	12	14,430	63 (55.0-76.0)	52.5			Electronic medical record system	Evidence based treatment guidelines

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Liu et al. (2013)	CH	CS	NA	960	68.3(10.4)	39.6		Health management Follow-up every 3 months		Community diabetes prevention and treatment guidelines provide glycemic control targets
Luijks et al. (2015)	NL	PC	60	610	63(12.5)	48.2		Routine 3-monthly check-up visits	Electronic medical record system	
Mold et al. (2008)	UK	RC	11	646	<50: 16.4% 50-59: 18.3% 60-69: 31.1% ≥70: 34.2%	54.3	Dietary advice is offered at each consultation	Care team (GP, practice nurse) Patients initially see the GP and are then referred to the practice nurse	Electronic medical record system	
Moreira et al. (2015)	Brazil	RCT	12	I: 40 C: 40	I: 50.0(6.5) C: 50.3(7.3)	I: 40 C: 30	Educational activities focused on providing orientation about physical activities, healthy diet, monitoring campillary glycemia, and acute and chronic complications	Quarterly nursing consultations, bimonthly educational group activities. When necessary referral for a consultation with a primary healthcare physician, nurse, nephrologist, pharmacist, and nutritionist. Home visits and phone contacts on a monthly basis with the case manager		

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Nielsen et al. (2006)	DK	RCT	72	I: 459 C: 415	Median I: 63.0 (53.8 – 71.4) C:63.7 (65.6-71.6)	I: 48.8 C: 52.3	Individualized goal setting	Follow-up every 3 months annual screening for diabetic complications	Annual descriptive feedback reports on individual patients	Clinical guidelines supported by annual half day seminar
Óstgren et al. (2002)	SWE	CS	NA	376	HbA1c<6.5: 69.6(10.4) HbA1c≥6.5: 70.9(9.8)	50.5	Structured education program.	Specially trained nurses, supervised by the physician. Team also included a dietician and a podiatrist.		Structured treatment program, including annual check-up at hypertension and diabetes outpatient clinic including examinations concerning vision, peripheral sensibility of vibration and peripheral pulsation and laboratory tests
Quah et al. (2013)	SG	CS	NA	688	62.2 (11.1)	44.0		Routine 3-monthly visit to polyclinics	Diabetes database	

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Quinn et al. (2016)	USA	RCT	12	118	Age < 55 yrs: I: 47.3(6.8) C: 47.5(7.5) Age≥55 yrs: I: 59.0(2.9) C:59.5(2.8)	Age < 55 yrs: I: 37.3 C: 62.1 Age≥55 yrs: I:68.0 C: 37.0	Mobile diabetes management software application, which allowed patient to enter diabetes self-care data on a phone and receive automated, real-time messages that were educational, behavioral, motivational and specific to the entered data Electronic diabetes self-care action plan	Patients could communicate with 'virtual' case managers on the phone or electronically	Quarterly online reports that summarized patients' glycemic and metabolic control, etc.	Clinical guidelines

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Robinson et al. (2009)	USA	PC	18	315	64.4(15.8)	41.9	Self-monitoring of blood glucose, foot care, diet and exercise modification, diabetes education resources, and participation in planned visits, were addressed through individual and small group appointments with members of the care team and through population-based quality improvement projects All patients in the intervention group were targeted for individual coaching in self-management activities by the NP or pharmacy student	Care team consisting of medicine resident, nurse practitioner students and pharmacy students All participated in chronic illness curriculum Patients seen in individual 30-minute appointments by 1 or more of the team members Follow up appointments were scheduled	An electronic clinical information system supplied clinical data	Care team participates in 60-minute didactic presentation, 30-minute clinical discussion session focusing on patient management and quality improvement Weekly presentation topic covered various aspects of diabetes care

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Rothman et al. (2003)	USA	RC	6	138	57.0 (23-87)	41.0	Diabetes education: 1-hour educational session	Three pharmacists participated in the program. Referrals for ophthalmology, nutrition, and podiatry also were suggested to the patient and provided when appropriate All recommendations discussed with primary care provider	Computer database Patients were contacted approximately every 2 weeks through phone calls, letters, or pharmacy visits	Algorithms for titrating insulin and metformin
Rothman et al. (2004)	USA	RCT	12	I:98 C:95	I low literacy: 57 (10.5) I high literacy: 51 (13.1) C low literacy: 59 (10.4) C high literacy: 56 (10.9)	I low literacy: 45 I high literacy: 35 C low literacy: 47 C high literacy: 42	One to one educational sessions including counseling and medication management Communication individualized depending on patients literacy status	Intensive diabetes management from 3 clinical pharmacist practitioners and a diabetes care coordinator (DCC)	Patients contacted every 2-4 weeks by telephone or in person by pharmacist or DCC	Application of evidence based treatment algorithms to help manage glucose and cardiovascular risk

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Sperl-Hillen and O'Connor (2005)	USA	RC	112	5,610-7,650	59 - 61	52-54	Nurses provided diabetes education and self-management training	Diabetes education nurses work closely with primary care physicians	Patient registry. Nurses use the registries to guide 'active outreach' to high-risk patients not in metabolic control or missing recommended tests	Drug formulary facilitated use of sulfonylureas, metformin, insulin, fibrates, and HMG-CoA reductase inhibitors
Taweepolcharoen et al. (2006)	TH	CS	NA	1,510	58.8(10.9)	34.6	Group diabetes education supervised by registered nurses and dieticians	Clinic is served by 3 groups of working physicians, consisting of faculty members, family medicine residents and service GPs. There are also registered nurses and dieticians		

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Trief et al. (2006)	USA	CT	12	1,665	70.8 (6.6)	37.2	Nurse case manager provided diabetes education	Nurse case manager provides, under the supervision of an endocrinologist, treatment planning and consultation to PCPs who maintained decision authority for their patients A separate team of trained research nurses conducts physical and psychological assessments at baseline and 1-year follow-up	Intervention subjects received a home telemedicine unit, i.e. a web-enabled computer used to upload blood pressure and blood glucose measurements, to videoconference with a nurse case manager and dietician, and to access individualized graphic data displays and educational materials	
Uitewaal et al. (2004)	NL	RC	24	T: 106 D:90	T: 50.5(7.5) D: 55.3(8.2)	T: 43.3 D: 51.1		4 visits to the GP per year Blood glucose and weight are measured at every visit. Other blood measures and feet and eye inspection every year	Computer based patient records	Guideline recommending 4 visits to the GP per year

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Uitewaal et al. (2005)	NL	CT	12	I: 53 C: 51	I: 50.6(9.3) C: 53.5(6.2)	I: 40 C: 38	Culturally acceptable and ethnic specific diabetes program for Turkish diabetes patients, consisting of 7 individual education sessions and 3 group sessions Program was based on 3 principles: peer education, tailoring and the Health Education Model	Individual sessions consisting of 4 sessions with the educator and patient together and 3 'triangle' sessions with the GP, educator and patient present, to discuss 3-monthly assessment of glycemic control and cardiovascular risk factors Patients were encouraged to have 1 of the individual sessions with the dietician and 1 with the partner present, although this was not obligatory	Computer based patient records	

Study characteristics				Sample characteristics			Chronic Care Model (CCM)			
							Description of components			
Study	**Country**	**Study design**	**Follow-up (months)**	**N**	**Age (sd or range)**	**Sex (% male)**	**Self-management support**	**Delivery system design**	**Clinical information systems**	**Decision support**
Whaba et al. (2007)	USA	CS	NA	136	59.7(15.2)	51.5	Individual care plan Self-monitoring of blood glucose	Care team (dietitian, DM nurse educator and physician) Referred patients to ophthalmologic and podiatric evaluations as soon as the diagnosis of DM was made Regular follow-up	Patient prescribed a glucose meter and advised to keep a diary of those readings to share with the physician at each office visit	Plan of care developed specifically for the patient's clinical condition Laboratory tests were conducted at least twice a year Compliance with diet and medications was assessed at each visit A DM flow sheet was created for each patient to keep track of the laboratory values, medications, and immunizations

AUS: Australia; Mex: Mexico; Jor: Jordan; USA: United States of America; ES: Spain; DK: Denmark; NL: the Netherlands; CH: China; UK: United Kingdom; SWE: Sweden; SG: Singapore; TH: Thailand; RC: retrospective cohort; CS: cross sectional; PC: prospective cohort.

Three context-related characteristics were evaluated as potential effect modifiers of the relationship between integrated diabetes care programs and HbA1c: literacy status, income, and number schooling years. Literacy status was assessed by 1 study [46], which found that patients in the intervention group with low literacy status (≤ 6th grade) had statistically significant lower HbA1c values at follow-up compared to patients with low literacy status receiving usual care. Monthly income and number of schooling years were also each assessed by one study. Patients with lower monthly income (≤$118.26) and ≤4 years of schooling at baseline receiving integrated diabetes care had significantly lower HbA1c values at follow-up compared to patient receiving usual care [39].

Three health-related characteristics were evaluated as potential effect modifiers of the relationship between integrated diabetes care programs and HbA1c: fasting blood glucose (FBG), depression and DM duration. Each characteristic was assessed by 1 study. Patients with high FBG (>10 mmol/L) at baseline receiving integrated diabetes care had significantly lower HbA1c levels at follow-up compared to patients receiving usual care [33]. For patients with a FBG ≤10 mmol/L no significant difference was found in HbA1c levels at follow-up between the intervention and control groups. Depression was not an effect modifier of the association between integrated diabetes care programs and HbA1c [49]. Patients with a DM duration <5 years receiving integrated diabetes care had significantly lower HbA1c levels at follow-up compared to patients receiving usual care [39].

No RCTs assessed context-related characteristics as potential effect modifiers of the relationship between integrated diabetes care programs and HbA1c.

Prospective –and retrospective cohort studies. Eleven prospective –and retrospective cohort studies measured the effects of integrated diabetes care programs on HbA1c (Tables 4 and 5). Three studies compared the change in HbA1c between levels of patient characteristics [5, 45, 47]. The other 8 studies compared HbA1c levels at follow-up between levels of patient characteristics [28, 29, 31, 32, 38, 44, 53, 54]

Most examined person-related characteristics were age (n=11) and sex (n=9). In 7 studies the effect of integrated diabetes care programs on HbA1c differed significantly across ranges of age: younger patients had higher HbA1c levels at follow-up compared to older patients (n=5) and experienced greater change from baseline in HbA1c (n=2) [5, 28, 32, 38, 47, 53, 54]. As to the latter, the direction of the measured change in HbA1c differed: one study found a significant improvement [47] and the other a significant increase [5] in HbA1c. Age was not a significant effect modifier in the other 4 studies [29, 31, 44, 45]. The effect of integrated care on HbA1c did not differ between men and women in 8 studies [28, 31, 32, 44, 45, 47, 53, 54]. In 1 study females had significantly higher HbA1c levels at follow-up compared to males [29].

Most examined health-related characteristics were medication use (n=8), baseline HbA1c (n=7), and duration of type 2 diabetes (n=6). The effect of integrated diabetes care programs on HbA1c was different for people on insulin therapy. These patients had higher HbA1c levels at follow-up compared with patients on diet and/or oral therapy in 5 studies[28, 31, 32, 38, 54] and less desirable changes in HbA1c from baseline [47]. In two studies the relationship

between integrated diabetes care programs and HbA1c did not differ between types of medication [45, 53]. In the studies assessing baseline HbA1c, patients with higher baseline HbA1c levels had higher HbA1c levels at follow-up (n=3) [28, 32, 54], but did have greater improvements in HbA1c from baseline (n=3) [5, 45, 47] compared to patients with lower baseline HbA1C levels. In one study baseline HbA1c was not a significant effect modifier [53]. The effect of integrated diabetes care programs on HbA1c differed significantly across ranges of diabetes duration in 5 studies. Patients with longer diabetes duration had significantly higher HbA1c levels at follow-up compared to patients with shorter diabetes duration (n=5) [5, 28, 32, 38, 54]. In one study a significant opposite effect was found [45].

Health insurance status was assessed by 4 studies. It did not seem to significantly modify the observed effect of integrated care on HbA1c in 3 studies [28, 44, 45]. Patients with no health insurance coverage had less desirable changes in HbA1c than those with health insurance coverage [47]. No other context-related characteristics were examined by the included studies.

Cross-sectional studies. In total, 6 cross-sectional studies measured the modifying effect of patient characteristics on the relationship between integrated diabetes care programs and HbA1c (Tables 4 and 5).

Most examined person-related characteristics were age (n=6), body mass index (BMI) (n=6) and sex (n=5). Four studies of integrated care programs found non-significant associations between age and HbA1c [27, 30, 41, 48]. In 2 studies significant associations were found: in these studies, younger patients had higher HbA1c levels [52, 55]. The effect of integrated diabetes care programs on HbA1c did not significantly differ between levels of BMI in all studies [27, 30, 41, 48, 52, 55]. The effect on HbA1c did also not differ between men and women in 4 studies [27, 30, 52, 55]. In 1 study females had significantly higher HbA1c levels compared to males [48].

Most examined health-related characteristics were duration of type 2 diabetes (n=6) and medication use (n=4). The effect of integrated care programs on HbA1c differed significantly across ranges of diabetes duration in 4 studies [27, 30, 48, 55]. Patients with longer diabetes duration had higher HbA1c levels compared to patients with shorter diabetes duration in these studies. In 2 studies diabetes duration was not a significant effect modifier [41, 52]. The effect of integrated care programs on HbA1c was also different for people on insulin therapy. These patients had higher HbA1c concentrations compared with patients on diet and/or oral therapy in 3 studies [27, 30, 55]. In 1 study type of medication was not a significant effect modifier [52].

No context-related characteristics were assessed by 3 or more studies.

Table 3. Subgroup intervention effects on HbA1c

Study	Variables entered in multivariate regression model	Global quality rating	Person-related characteristics					
			Female	**Male**	**Lower age[1]**	**Higher age[2]**		
Nielsen et al. (2006)	Clustering effect at the general practitioner level, interaction between age and baseline HbA1c, DM duration, BMI, number of DM related consultations, interaction between the patients' physical activity level, antidiabetic medication and dietary habits	weak	-	O				
Uitewaal et al. (2005)[3]	Baseline HbA1c, sex, age, DM duration, DM medication, indicators of DM care	weak	-	O				
Moreira et al. (2015)	N/A	weak	O	O	-	O		
Quinn et al. (2016)	Study group, time, age, all two-way interactions and three way interaction	moderate			-	-		
			Context-related characteristics					
			Low literacy status	High literacy status	**Monthly income ≤$118,26**	**Monthly income >$118,26**	**≤4 years of schooling**	**>4 years of schooling**
Rothman et al. (2004)	Baseline HbA1c, age, race, sex, income, DM medication, DM duration, income	weak	-	O				
Moreira et al. (2015)	N/A	weak			-	O	-	O

			Health-related characteristics					
			FBG > 10 mmol/L	**FBG ≤ 10 mmol/L**	**Depression Yes**	**Depression No**	**DM duration <5 years**	**DM duration ≥5 years**
Groeneveld et al. (2001)	N/A	weak	-	O				
Trief et al. (2006)	Baseline HbA1c, ethnicity, age, sex, marital status, years of education, DM duration, insulin use, smoking, co-morbidity, Clustering effect at the general practitioner level	weak			O	O		
Moreira et al. (2015)	N/A	weak					-	O

Abbreviations: FBG: fasting blood glucose; N/A: not applicable

o: No significant relationship between the characteristic with HbA1c for people in the intervention group compared to usual care;

-: Significant negative relationship between the characteristic with HbA1c for patients in the intervention group compared to usual care.

[1] lower age = ≤52 years (Moreira et al. 2015), <55 years (Quinn et al. 2016); [2] higher age = >52 years (Moreira et al. 2015), ≥55 years (Quinn et al. 2016);

[3] intervention and control groups only consisted of patients with a baseline HbA1c >7%.

Table 4. Relationship between HbA1c and person-related- and context-related characteristics

Study	Variables entered in multivariate regression model	Global quality rating	Person-related characteristics							Context-related characteristic
			Socio-demographics					Lifestyle		
			Age	Sex*	Ethnicity	Marital status†	Education	BMI	Smoking	Health insurance
Prospective cohort studies										
Cardenas-Valladolid et al. (2012)	Age, sex, DM medication	moderate	o	+						
De Fine Olivarius et al. (2009)	Age, sex, BMI, HbA1c baseline, SBP, TC, urinary albumin	moderate	o	o				o		
Retrospective cohort studies										
Benoit et al. (2005)	A1c, time, age, TC, DM duration, Medication	strong	-	o	o‡			o	o§	o‖
Sperl-Hillen and O'Connor (2005)	Age, sex, baseline HbA1c, DM medication, depression, co-morbidities, PC physician variable (age, sex, specialty), diabetes educator visits, pharmacy coverage	weak	+	o						-¶
Elissen et al. (2012)	N/A	weak	-						+#	
El-Kebbi et al. (2003)	Year of presentation, age, sex, ethnicity, BMI , DM duration, baseline HbA1c, DM medication, no. of interval visits, follow-up duration	strong	-	o	o**			+		
LeBlanc et al. (2015)	Age, sex, DM duration, DM medication, Charlson comorbidity index	strong	-	o						
Kellow, Savige and Khalil (2011)	Age, sex, OGTT, HbA1c, TC, HDL, TG, LDL/HDL ratio, weight change, body weight	moderate	-	o				o	o††	

Study	Variables entered in multivariate regression model	Global quality rating	Person-related characteristics							Context-related characteristic
			Socio-demographics					Lifestyle		
			Age	Sex*	Ethnicity	Marital status†	Education	BMI	Smoking	Health insurance
Retrospective cohort studies										
Mold et al. (2008)	N/A	moderate	-		+‡‡					
Robinson et al. (2009)	N/A	weak	o	o	o§§	o				oǁǁ
Rothman et al. (2003)	Age, sex, ethnicity, education, insurance, BMI, HbA1c, DM medication, hypertension medication, hypercholesterolemia medication, recent diagnosis of DM, DM duration	moderate	o	o	o¶¶		o##	o		O***
Cross-sectional studies										
Al Omari et al. (2009)	DM medication, DM duration	weak	o	o				o	o†††	
De Alba Garcia et al. (2006)	Age, sex, marital status, education, BMI, smoking, follow diet, glucose, family history of DM, DM duration, DM medication, SBP, DBP, TC, TG	weak	o	o		o	o‡‡‡	o	o§§§	
Ostgren et al. (2002)	Age, sex, waist-hip ratio, TG, β-cell function	weak	o					o		
Quah et al. (2013)	Age, sex, ethnicity, marital status, occupation, housing type, DM duration, DM medication, compliance to medication, self-monitoring, BMI	moderate	-	o	oǁǁǁǁ	o	o¶¶¶	o	o###	
Taweepolcharoen et al. (2006)	Age, sex, DM duration, BMI, BP, fasting glucose, TG, HDL, LDL	weak	o	+				o		
Whaba et al. (2007)	Age, DM duration, BMI, DM medication, hypertension, hyperlipidemia	moderate	-	o				o		

Abbreviations: TG: triglycerides; DM: diabetes mellitus; BMI: body mass index; HbA1c: hemoglobin A1c; PC: primary care; BP: blood pressure; TG; triglycerides; HDL: high density lipoprotein; LDL: low density lipoprotein; OGTT: oral glucose tolerance test; TC: total cholesterol; SBP: systolic blood pressure; N/A: not applicable

+: positive significant relationship; 0: non-significant relationship; -: significant negative relationship
*0=male, 1=female;
†0=not married, 1=married;
‡0=Hispanic, black and white, 1=Asian;
§0=current smoker, 1=past smoker, 2=never smoker;
||0=insured, 1=County Medical Services, 3= uninsured;
¶0=pharmacy coverage; 1=no pharmacy coverage;
#0=current smoker, 1=none smoker/previous smoker;
**0=others, 1=African American;
††0=non-smoker, 1= current smoker;
‡‡0=white, 1=black Caribbean/African;
§§0=white, 1=Asian, 2=black, 3=other;
||||0=insured, 1=uninsured;
¶¶0=black, 1=others;
##0=less than high school, 1=high school or higher
***0=Medicaid or pharmacy assistance programs, 1= no Medicaid or pharmacy assistance program
†††0=current smoker; 1=past and none smoker;
‡‡‡0=none. 1=incomplete primary, 2=completed primary; 3=primary;
§§§0=smoker, 1=none smoker;
|||||0=Chinese, 1=Malay, 2=Indian, 3=others;
¶¶¶0=no formal education, 1=formal education;
###0=none smoker, 1=past smoker, 2=current smoker.

Table 5. Relationship between HbA1c and health-related characteristics

Study	Variables entered in multivariate regression model	Global quality rating	Health-related characteristics										
			HbA1c	SBP	DBP	TC	HDL	LDL	TG	# providers visits	DM duration	Medication*	# comorbidities
Prospective cohort studies													
Cardenas-Valladolid et al. (2012)	Age, sex, DM medication	moderate											
De Fine Olivarius et al. (2009)	Age, sex, BMI, HbA1c baseline, SBP, TC, urinary albumin	moderate		o		o						+	
Retrospective cohort studies													
Benoit et al. (2005)	A1c, time, age, TC, DM duration, Medication	strong	+	o	o	+	o			o	+	+	
Sperl-Hillen and O'Connor (2005)	Age, sex, baseline HbA1c, DM medication, depression, co-morbidities, PC physician variable (age, sex, specialty), diabetes educator visits, pharmacy coverage	weak	+									+	o
Elissen et al. (2012)	N/A	weak	+								+		+
El-Kebbi et al. (2003)	Year of presentation, age, sex, ethnicity, BMI , DM duration, baseline HbA1c, DM medication, no. of interval visits, follow-up duration	strong	+							-	+	+	
Kellow, Savige and Khalil (2011)	Age, sex, OGTT, HbA1c, TC, HDL, TG, LDL/HDL ratio, weight change, body weight	moderate	o	o	o	o	o	o	o			o	o
LeBlanc et al. (2015)	Age, sex, DM duration, DM medication, Charlson comorbidity index	strong	+								+	+	
Mold et al. (2008)	N/A	moderate								-	+	+	

Study	Variables entered in multivariate regression model	Global quality rating	Health-related characteristics										
			HbA1c	SBP	DBP	TC	HDL	LDL	TG	# providers visits	DM duration	Medication*	# comorbidities
Retrospective cohort studies													
Robinson et al. (2009)	N/A	weak											
Rothman et al. (2003)	Age, sex, ethnicity, education, insurance, BMI, HbA1c, DM medication, hypertension medication, hypercholesterolemia medication, recent diagnosis of DM, DM duration	moderate	+								-	o	
Cross-sectional studies													
Al Omari et al. (2009)	DM medication, DM duration	weak				o	o	o	o		+	+	
De Alba Garcia et al. (2006)	Age, sex, marital status, education, BMI, smoking, follow diet, glucose, family history of DM, DM duration, DM medication, SBP, DBP, TC, TG	weak		o	o	o			o	o	+	+	
Ostgren et al. (2002)	Age, sex, waist-hip ratio, TG, β-cell function	weak		-	-	o			+		o		
Quah et al. (2013)	Age, sex, ethnicity, marital status, occupation, housing type, DM duration, DM medication, compliance to medication, self-monitoring, BMI	moderate									+	+	o
Taweepolcharoen et al. (2006)	Age, sex, DM duration, BMI, BP, fasting glucose, TG, HDL, LDL	weak					o	o	o		+		
Whaba et al. (2007)	Age, DM duration, BMI, DM medication, hypertension, hyperlipidemia	moderate									o	o	o

Abbreviations: HbA1c: hemoglobin A1c; OGTT: oral glucose tolerance test; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; DM: diabetes mellitus; BMI: body mass index; PC: primary care; BP: blood pressure; N/A: not applicable
+: positive significant relationship; 0: non-significant relationship; -: significant negative relationship; 0=no insulin, 1=insulin.

LDL-cholesterol

Three prospective –and retrospective cohort studies measured the effect of integrated diabetes care programs on LDL-c. The RCTs and cross-sectional studies included in this review did not measure this effect. In total, 11 patient characteristics were assessed by the studies. Only those results that were assessed by at least 2 studies will be discussed.

Prospective –and retrospective cohort studies. The person-related characteristic age was examined by 3 studies [5, 44, 47]. The relationship between age and LDL-c was inconsistent: a negative and positive as well as a non-significant relationship were found.

The modifying effect of baseline LDL-c on the relationship between integrated diabetes care programs and changes in LDL-c over baseline was assessed by 2 studies [5, 47]. Both found that patients with higher baseline LDL-c had greater LDL-c improvements.

No context-related characteristics were assessed by the included studies.

Systolic blood pressure

Four retrospective - and prospective cohort studies measured the effect of integrated diabetes care programs on SBP. In total, 9 patient characteristics were assessed by the studies. Only those results that were assessed by at least 2 studies will be discussed.

Retrospective cohort –and prospective cohort studies. Age was measured by 3 studies [5, 38, 44]. These studies found that higher age was associated with higher SBP at follow-up [38, 44] and greater improvement [5]. The modifying effect of ethnicity on integrated care programs and SBP was measured by 2 studies [38, 44].The effect was unclear, as results were inconsistent between these studies. Four other characteristics were assessed, 1 context-related-, and 3 health-related characteristics, by 1 study each.

Health care utilization

Health care utilization was assessed by 3 studies: 1 RCT [40], 1 retrospective cohort study [50], and 1 cross-sectional study [36]. Together they measured the modifying effect of integrated care programs and health care utilization for 5 person-related characteristics, 1 context,- and 1 health-related characteristic. Most examined characteristic was sex, which was measured by 2 studies [36, 40]. Nielsen et al. found that females in the intervention group had statistically significant more GP consultations per year compared to females in the control group [40]. For males, no difference was found. Liu et al. found that the effect of integrated diabetes care programs on health care utilization was different between males and females [36]. Females had higher utilization of community health centers compared to males.

Discussion

This paper presents a literature review on relevant patient characteristics for guiding tailored integrated type 2 diabetes care in primary care. HbA1c was considered an outcome in 93% of the 27 studies identified. Many different patient characteristics were investigated by these studies. Findings indicate that the effect of integrated primary care programs on HbA1c differs significantly according to a number of person and health-related characteristics. Younger age, longer disease duration, higher baseline HbA1c and insulin therapy were associated with higher HbA1c levels. Health insurance status, living situation and income were the only context-related characteristics in the included studies and were not frequently assessed.

Compared to HbA1c, LDL-c, SBP and health care utilization were included far less. It was found that higher baseline LDL-c lead to greater LDL-c improvement. Patients with higher age had higher SBP levels at follow-up as well as greater improvements in SBP compared to younger patients. The relationship between integrated care and health care utilization seemed to be modified by sex: women had more consultations per year compared to men.

Several factors might explain the elevated HbA1c levels in a subset of patients with type 2 diabetes. Younger patients tend be more non-adherent to oral medication therapy and experience less profound diabetes-related health problems than older patients [56] [57]. The latter might cause them to believe that a pro-active attitude towards their disease is less important. Moreover, younger patients and/or those with longer disease duration undergo a more rapid decline in beta cell function and pancreatic insulin secretion, resulting in the need for a more complex and intensive drug therapy [27, 53, 58, 59]. Higher HbA1c levels for patients on insulin therapy compared to patients on diet and/or oral therapy could be due to a delayed start or low intensity of insulin therapy [32, 60, 61]. Furthermore, maintaining glycemic control, while minimizing hypoglycemia and sticking to a diet might be difficult [55, 62].

High HbA1c at baseline also seemed to be predictive of later HbA1c. First, type Type 2 diabetes is a heterogeneous disease in both pathogenesis and clinical manifestation [8], thus a high HbA1c at baseline and at follow-up could be due to decreased insulin sensitivity, secretion and β-cell dysfunction [63]. Second, unhealthy lifestyle habits, such as low physical activity, and a diet rich in carbohydrates have been associated with less glycemic control [8, 64]. Changing these lifestyle factors is easier said than done, making it difficult for patients to improve their glycemic control.

Several factors could explain the differences in levels of LDL-c, SBP and health care utilization between levels of patient characteristics. Prescription of statins usually follows when LDL-c level is 2.5 mmol/l or higher, possibly leading to greater improvements in LDL-c for those patients with high baseline LDL-c levels [65]. The higher SBP levels at follow-up for older patients may be due to less stringent treatment targets [66, 67]. The greater health care utilization by women compared to men might be explained by the difference in perception of illness between men and women. According to some studies, it is more culturally and socially accepted for women to be ill than it is for men [68].

Overall, our results indicate the need to implement integrated diabetes care programs specifically tailored to the needs, values and preferences of younger patients and to those on insulin therapy, with longer disease duration and/or higher HbA1c levels and older patients with high SBP levels. These effect modifiers can help to provide the right care to the right person at the right time. At this moment, not every patient with these characteristics receives such care. Current practice might therefore not be suitable for all patients. Lack of motivation, family-support and feeling burned-out from managing diabetes are reported barriers to optimal self-management [69]. To tackle these barriers, diabetes treatment programs should take them into account by, for example, providing shared decision making and simple and specific instructions and advice, involving family members and offering online consultations or evening primary care opening hours. In addition to patients who find it difficult to keep their diabetes under control, there is a large group of patients who does manage to control their diabetes [5, 6]. For these patients, fewer visits to primary care might have similar outcomes and thus should be taken into consideration by both the GP and the patient. Allowing care givers to provide care based on patient characteristics constitutes a promising approach for achieving the so called 'Triple Aim' by: [1] improving patient experience, by including patients' care needs, preferences, and abilities in treatment decisions; [2] improving population health and quality of life, by supporting tailored diabetes care; and [3] reducing the per capita cost of diabetes care, by reducing the over-, under- and misuse of health care services [70].

This review has several limitations that should be taken into account. First, given the scarceness of studies assessing the differences in the effect of integrated diabetes care programs on diabetes control measures by levels of patient characteristics, it was decided to include RCTs, prospective-, and retrospective cohort studies. However, this introduced significant heterogeneity and made it impossible to conduct a meta-analysis. Second, quality of the studies was weak for most studies. This was mainly due to the cross-sectional study design of more than one third of the studies and the use of less robust statistical methods. Fortunately, it is unlikely that these studies altered the results, as their findings were similar to those of the other, more robust studies. Third, very few context- and person-related characteristics were analyzed. Studies performed in a non-integrated diabetes care setting, found that context-related characteristics, such as socioeconomic status and social network, are associated with measures of diabetes control and are likely to be strong predictors of diabetes control [71, 72]. Person-related characteristics, such as low mastery and low self-efficacy, have been related to negative health outcomes [73, 74]. Traditionally, researchers and care providers have looked at diabetes from a mostly biomedical viewpoint, which might explain the relatively scarce collection of context- and person-related characteristics in routinely collected individual patient data [15].

The current review provides a good understanding of which characteristics can help to identify patients with different health care needs and preferences. However, to implement an effective integrated type 2 diabetes tailored care program, it is necessary to know which context- and person-related characteristics are important to identify patients. Furthermore,

implementation of an effective tailored diabetes care program is only possible by taking into account the care preferences of patients and caregivers. In the next phase of the PROFILe project [19], data rich in non-health-related characteristics will be analyzed to assess which of these are predictors of diabetes control measures and a discrete choice experiment will be conducted to gain knowledge on patients' care preferences as a first step towards patient-centered diabetes care.

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Supplementary material

Supplementary Table S1. Quality of included studies

Study	Study design	Selection bias	Study design	Confounders	Blinding	Data collection	Drop-outs	Global
Al Omari et al. (2009)	CS	+	-	-	o	+	NA	-
Benoit et al. (2005)	RC	+	o	+	o	+	NA	+
Cardenas-Valladolid et al. (2012)	PC	+	o	+	o	+	-	o
De Fine Olivarius et al. (2009)	PC	+	o	+	-	+	+	o
Elissen et al. (2012)	RC	o	o	-	+	+	-	-
El Kebbi et al. (2003)	RC	o	o	+	+	+	NA	+
De Alba Garcia et al. (2006)	CS	-	-	+	-	+	+	-
Groeneveld et al. (2001)	RCT	o	+	-	-	+	o	-
Kellow, Savige and Khalil(2011)	RC	o	o	o	+	+	-	o
LeBlanc et al (2015)	RC	o	o	+	+	+	NA	+
Liu et al. (2013)	CS	+	-	o	-	o	NA	-
Luijks et al. (2015)	PC	+	o	+	o	+	+	+
Mold, While and Forbes (2008)	RC	o	o	-	+	+	NA	o
Moreira et al. (2015)	RCT	-	+	-	o	+	+	-
Nielsen et al. (2006)	RCT	-	+	+	-	+	-	-
Ostgren et al. (2002)	CS	+	-	-	-	+	NA	-
Quah et al. (2013)	CS	o	-	+	o	o	NA	o
Quinn et al. (2016)	RCT	o	+	-	o	+	o	o
Robinson et al. (2009)	PC	-	o	-	-	+	-	-
Rothman et al. (2003)	RC	-	o	+	o	+	+	o
Rothman et al. (2004)	RCT	o	+	+	-	+	+	o
Sperl Hillen and O'Connor (2005)	RC	+	-	o	o	+	+	o

Study	Study design	Selection bias	Study design	Confounders	Blinding	Data collection	Drop-outs	Global
Taweepolcharoen et al. (2006)	CS	+	-	-	+	+	NA	-
Trief et al. (2006)	CT	-	o	+	+	+	+	o
Uitewaal et al. (2004)	RC	-	o	-	o	+	NA	-
Uitewaal et al. (2005)	CT	-	+	+	-	+	+	-
Whaba and Chang (2007)	CS	-	o	o	o	+	NA	o
Sum (+/o/-)		9/9/9	6/14/7	13/4/10	7/11/9	25/2/0	9/2/5	4/11/12

Abbreviations: CS: cross-sectional; RC: retrospective cohort; PC: prospective cohort; RCT: randomized controlled trial; CT: controlled trial.
+: strong; o: moderate; -: weak.

CHAPTER 4

Differences in biopsychosocial profile of diabetes patients by level of glycaemic control and health-related quality of life: a cross-sectional study

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Abstract

Aims: Tailored, patient-centred innovations are needed in the care for persons with type 2 diabetes mellitus (T2DM), in particular those with insufficient glycaemic control. Therefore, this study sought to assess their biopsychosocial characteristics and explore whether distinct biopsychosocial profiles exist within this subpopulation, which differ in health-related quality of life (HRQoL).

Methods: Cross-sectional study based on data from The Maastricht Study, a population-based cohort study focused on the aetiology, pathophysiology, complications, and comorbidities of T2DM. We analysed associations and clustering of glycaemic control and HRQoL with 38 independent variables (i.e. biopsychosocial characteristics) in different subgroups and using descriptive analyses, latent class analysis (LCA), and logistic regressions.

Results: Included were 840 persons with T2DM, mostly men (68.6%) and with a mean age of 62.6 (±7.7) years. Mean HbA1c was 7.1% (±3.2%); 308 patients (36.7%) had insufficient glycaemic control (HbA1c>7.0% [53 mmol/mol]). Compared to those with sufficient control, these patients had a significantly worse-off status on multiple biopsychosocial factors, including self-efficacy, income, education and several health-related characteristics. Two 'latent classes' were identified in the insufficient glycaemic control subgroup: with low respectively high HRQoL. Of the two, the low HRQoL class comprised about one-fourth of patients and had a significantly worse biopsychosocial profile.

Conclusions: Insufficient glycaemic control, particularly in combination with low HRQoL, is associated with a generally worse biopsychosocial profile. Further research is needed into the complex and multidimensional causal pathways explored in this study, so as to increase our understanding of the heterogeneous care needs and preferences of persons with T2DM, and translate this knowledge into tailored care and support arrangements.

Introduction

Diabetes care in the Netherlands is widely regarded as a 'best practice' [1] and several developments were pivotal in shaping this care model. In 2003, an evidence-based standard for generic care for type 2 diabetes mellitus (T2DM) was established by the Netherlands Diabetes Federation – an umbrella organisation of diabetes care professionals, patients and researchers – providing the norm for high-quality, multidisciplinary diabetes care [2].
Another important change followed in 2007, when a bundled payment system was introduced allowing health insurers to contract the different components of generic diabetes management as an integrated care programme, based on the diabetes care standard [3-5]. Their main contracting partners in primary care are care groups, i.e. networks of general practitioners (GPs) comparable to Clinical Commissioning Groups (CCGs) in the United Kingdom. As part of their contract with health insurers, care groups assume clinical and financial responsibility for integrated diabetes care delivery and coordination [6]. Today, there are around 115 care groups with an integrated diabetes care contract, covering 85 percent of the approximately 900,000 Dutch citizens with diagnosed T2DM [6,7].

Since care groups emerged in Dutch primary care, many studies have been conducted to assess the quality of diabetes care provided by these groups. According to a recent evaluation [6], relevant process and outcome indicators have improved over the years in most groups and now seem to be stabilising. For example, a relatively steady share of around two-thirds of patients has sufficient glycaemic control (glycated haemoglobin (HbA1c) levels ≤7.0% [53 mmol/mol]) [6]. Within the limitations of current practice, it seems unlikely that this percentage will increase much further: both the former report [6] and the Euro Diabetes Index [1] showed that in general, Dutch GPs strictly adhere to the care standard, suggesting that the outcomes achieved represent near-optimal results.

The existence of plateau values in processes and outcomes points towards a need for further innovation: the current, highly standardised care approach leaves a considerable subgroup – about a third of patients with diagnosed T2DM, i.e. roughly 300,000 people in the Netherlands [6,7] – unable to adequately manage glycaemic control. In the long-term, these patients have a higher risk of microvascular and macrovascular complications, and lower health-related quality of life (HRQoL) [8]. The phenomenon of differential treatment effects is not unique to Dutch diabetes care: multiple studies in different countries have recently shown that 'one-size-fits-all' diabetes management does not actually fit for all patients [9,10]. It remains unclear, however, which biopsychosocial factors are associated with more or less promising treatment outcomes.
The present study hypothesises that there is a broad range of patient characteristics influencing the ability of individuals to self-manage, their need for professional treatment and support, and, ultimately, their level of glycaemic control and HRQoL. In a first step towards leveraging these characteristics to develop more person-centred, tailored diabetes care, this study aims to: (1) gain insight into the biopsychosocial characteristics of patients with insufficient glycaemic control, as opposed to patients with sufficient control; and (2) explore

whether distinct biopsychosocial profiles can be identified within the group of patients with insufficient glycaemic control, which are associated with different HRQoL. For the latter purpose, an explorative latent class analysis (LCA) was conducted. The study was based on a comprehensive subset of phenotyping data from the population-based The Maastricht Study.

Materials and Methods

Study design and study population

We conducted a cross-sectional study based on data from The Maastricht Study, an observational prospective population-based cohort study in the region of Maastricht in the southern part of the Netherlands. The rationale and methodology have been described previously [11]. In brief, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of T2DM, and is characterised by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years, and living in the Maastricht region. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency.

For this study, cross-sectional data were used from the first 975 participants with T2DM in The Maastricht Study, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of three months. Participants were included in the present study if they were previously diagnosed with T2DM by a health professional (i.e. prior to participating in The Maastricht Study) and had an HbA1c measurement conducted at The Maastricht Study research centre. No further in- or exclusion criteria were used.

The Maastricht Study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Definition of dependent and independent variables

The study was conducted in two steps, which differed in terms of the dependent variable. First, to gain insight into differences in patients' biopsychosocial characteristics by level of glycaemic control, we used participants' HbA1c level as dependent variable. Although there is growing interest in, amongst others, glycated albumin and fructosamin as alternative markers of glycaemic control, HbA1c remains the gold standard biomarker of glycaemia [12]. It has been used as a universally accepted means for monitoring glycaemic control for more than three decades [13].

We dichotomised HbA1c based on the norm values in the Dutch diabetes care standard [2]. Thus, subgroups represented sufficient glycaemic control (HbA1c≤7.0% [53 mmol/mol]) versus insufficient glycaemic control (HbA1c>7.0% [53 mmol/mol]).Second, we explored whether there are distinct biopsychosocial profiles within the patient subgroup with

insufficient glycaemic control, which differ in terms of HRQoL. Several HRQoL measures were used as dependent variable, given the potential effect of insufficient glycaemic control on HRQoL and the importance of this outcome to patients [8]. As LCA requires a categorical dependent variable, we dichotomised summary scores from three surveys focused on various domains of HRQoL: PAID, EQ-5D-3L and SF-36. The 20-items PAID (Problem Areas in Diabetes) survey assesses diabetes-related emotional distress; a sum score of 40 – indicating severe distress at the level of 'emotional burnout' – was used for dichotomisation [14]. Based on the EQ-5D-3L questionnaire, five binary variables were defined illustrating the presence or absence of problems related to mobility, self-care, usual activities, pain/discomfort and anxiety/depression [15]. Participants' SF-36 scores were aggregated into two summary measures of HRQoL, i.e. the Physical (PCS) and Mental Component Summary (MCS) scores [16]. The Dutch PCS and MCS norm scores – i.e. 50 and 42 points, respectively – were used as cut-off points for dichotomisation [17].

In both steps, independent variables comprised a comprehensive set of biopsychosocial characteristics considered potential predictors of health outcomes (in this case, glycaemic control and HRQoL) in patients with T2DM. To structure these characteristics in a meaningful way, we used Andersen and Newman's Behavioural Model of Health Service Use [18]. Given the strong reported associations between glycaemic control, HRQoL and health service use [19,20], we assumed that applying this model could provide relevant insights for tailoring diabetes care. Anderson and Newman [18] distinguish three categories of individual determinants of health service use: person-related, context-related and health-related factors.

Person-related characteristics

Person-related (or predisposing) characteristics determine people's personal predisposition to use health services [18]. The variables in this category were: age (in years), sex (male/female), smoking behaviour, alcohol consumption, self-reported physical activity (in hours/week), mastery, self-efficacy and social adequacy. Smoking behaviour was categorised as non-, former or current smoker. Alcohol consumption was classified as none, low (≤7 glasses/week for women; ≤14 glasses per week for men) or high (>7 glasses/week for women; >14 glasses per week for men) based on the 2006 Health Council of the Netherlands guidelines for a healthy diet [21]. Self-efficacy and mastery are measures of a person's control beliefs: where self-efficacy is a person's belief that he is able to perform a (desired) action or behaviour, mastery refers to his belief that his actions matter for outcomes.[22] We measured self-efficacy by the sum of items scores on the Dutch adaptation [23] of the validated, 16-item Self-Efficacy Scale of Sherer et al. [24]: higher scores suggest more self-efficacy. Mastery was defined as participants' sum score on seven items of the Pearlin Mastery Scale, with higher total scores indicating a greater sense of personal mastery [25]. Social adequacy was measured using a shortened version (15 items) of the Dutch Personality Questionnaire, which was recoded so that higher sum scores indicate greater social adequacy [26].

Context-related characteristics

Context-related (or enabling) factors are largely socioeconomic variables that facilitate or hamper a person's service use and might affect glycaemic control [18]. Four enabling factors were analysed: household income (in euros per month), educational level, employment status and marital status. Household income was 'equivalised' using the Organisation for Economic Co-operation and Development (OECD) square root scale to reflect differences in needs between households of different size [27]. Hence, the median value of the income class to which a given household belonged was divided by the square root of household size. Income classes ranged from <€750 to ≥€5000 per month, with each subsequent class representing a €250 income increase. Education was dichotomised as low/medium (elementary education, preparatory secondary vocational education, senior general secondary education or senior secondary vocational education) versus high (pre-university, higher professional or academic education) based on a participant's highest completed type of education. With regard to employment status, two categories were distinguished: employed persons (self-employed/entrepreneurs, employees and civil servants) versus not employed persons (disabled, unemployed, rentiers, retirees, homemakers and others). Marital status could be either with partner (married or registered partners, or living together) or without partner (unmarried, widow(er), divorced, or other).

Health-related characteristics

The third category concerns health-related (or illness-level) factors, which – according to Anderson and Newman [18] – are the strongest predictors of health service use. Variables in this category were: diabetes duration (in years), diabetes-related complications, depression, HRQoL, and medication use, as well as multiple clinical measures determined by physical examination (i.e. weight, waist circumference, body mass index (BMI), and systolic and diastolic blood pressure) or laboratory assessment (i.e. HbA1c, total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides).

Four diabetes-related complications were assessed – i.e. cardiovascular disease, neuropathic pain, retinopathy and chronic kidney disease – as described elsewhere [28,29]. Based on the Patient Health Questionnaire (PHQ) instrument for screening, diagnosing and measuring severity of depression, we categorised depression as: (1) no or minimal depressive symptoms (score 0-9); (2) minor depression (score 10-14); or (3) major depression (≥15) [30,31]. Besides the dichotomised HRQoL measures described earlier, a weighted overall HRQoL score was calculated from the EQ-5D-3L items, ranging from -0.33 to 1.00 on the basis of a Dutch validation study [15]. Medication use was categorised as none, oral and injectable (non-insulin) pharmacological agents (i.e. alfaglucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide 1 analogues, and/or sulphonylurea derivatives), or insulin (with/without oral and injectable (non-insulin) pharmacological agents).

Statistical analyses

Descriptive analyses were conducted to assess the biopsychosocial profile of diabetes patients by level of glycaemic control (HbA1c ≤7.0% [53 mmol/mol] vs >7.0% [53 mmol/mol]) in terms of the 38 included independent variables. Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. Missing data were assumed to be missing at random and not imputed. Depending on the nature of the independent variables, different statistical tests were used to measure associations with glycaemic control. Thus, for continuous variables, independent samples t-tests were used; for binary and categorical variables, group comparisons were performed by chi-squared test and one-way ANOVA, respectively. A p-value <0.05 was set as level of significance. Analyses were conducted using IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY).

LCA, also known as finite mixture modelling, was used to explore the existence of biopsychosocial profiles in the insufficient glycaemic control subgroup (HbA1c >7.0% [53 mmol/mol]), which differ in HRQoL. First, a one-class model was applied, after which the number of classes was sequentially increased up to a five-class model. To decide on the most parsimonious and best-fitting model, the Bayesian Information Criterion (BIC) was used for comparison across models, where the lowest value indicates the best fit [32]. The Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) was also used to compare fit between neighbouring models. A significant p-value (p<0.05) indicates an improvement in fit for inclusion of one or more classes [32]. Entropy was used to determine the quality of classification. Higher entropy values indicate less ambiguity in class allocation [33]. LCA models were fitted using Mplus, version 7.3 [34]. Based on the results of the LCA, posterior probability of belonging to a given 'latent class' was determined for each patient and used as dependent variable in univariable logistic regression analyses to examine significant differences in biopsychosocial profile between HRQoL classes. Odds ratios (ORs) with 95% confidence intervals (CIs) were obtained using STATA version 14 [35].

Results

Of The Maastricht Study participants with T2DM, 840 persons met the inclusion criteria. The study flowchart is included in Supplement 1 (S1 Fig). Mean age of the study population was 62.6 (±7.7) years. Males were overrepresented (68.6%). Mean HbA1c level was 7.1% (±3.2%) [54 (±12) mmol/mol]. Based on the Dutch diabetes care standard [2], 532 patients (63.3%) had sufficient glycaemic control (HbA1c≤7.0% [53 mmol/mol]), whereas 308 patients (36.7%) had insufficient control (HbA1c>7.0% [53 mmol/mol]).

Biopsychosocial characteristics of diabetes patients by level of glycaemic control

Table 1 shows the distribution of person-related characteristics across subgroups. Patients with sufficient glycaemic control had a significantly higher level of self-efficacy compared to those with insufficient control (59.4±8.2 vs. 58.1±8.3; p=0.047). There were no differences

between subgroups in age, sex, smoking status, alcohol consumption, physical activity, mastery or social adequacy.

Table 1. Person-related patient characteristics by glycaemic control.

Characteristic	N	HbA1<=7.0% [53 mmol/mol] (N=532)	HbA1c >7.0% [53 mmol/mol] (N=308)	Total (N=840)	p-value
Age (years)	840	62.9±7.6	62.3±7.7	62.6±7.7	0.26
Sex	840				0.29
Men		*358 (67.3%)*	*218 (70.8%)*	*576 (68.6)*	
Women		*174 (32.7%)*	*90 (29.2%)*	*264 (31.4)*	
Smoking status	809				0.29
Never		*151 (29.5%)*	*73 (24.5%)*	*224 (27.7)*	
Former		*276 (54.0%)*	*172 (57.7%)*	*448 (55.4)*	
Current		*84 (16.4%)*	*53 (17.8%)*	*137 (16.9)*	
Alcohol consumption	809				0.27
None		*153 (29.9%)*	*100 (33.6%)*	*253 (31.3)*	
Low		*264 (51.7%)*	*155 (52.0%)*	*419 (51.8)*	
High		*94 (18.4%)*	*43 (14.4%)*	*137 (16.9)*	
Physical activity (hours/week)	672	12.1±7.7	11.8±8.0	12.0±7.8	0.57
Self-efficacy	672	59.4±8.2	58.1±8.3	58.9±8.2	0.047*
Mastery	680	25.6±4.8	25.2±5.0	25.5±4.9	0.27
Social adequacy	673	3.6±3.7	3.5±3.7	3.6±3.7	0.75

Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. *Significant at the P<0.05 level.

Table 2 shows the context-related characteristics of patients by HbA1c level. The sufficient glycaemic control subgroup had a significantly higher mean equivalent income (in euros) than the subgroup with insufficient control (1,899±906 vs. 1,736±763; p=0.03). Moreover, there were significantly more high-educated persons and fewer low-educated persons among those with sufficient glycaemic control (p=0.047). No subgroup differences were identified with regard to employment or marital status.

Table 2. Context-related patient characteristics by glycaemic control.

Characteristic	N	HbA1<=7.0% [53 mmol/mol] (N=532)	HbA1c >7.0% [53 mmol/mol] (N=308)	Total (N=840)	p-value
Equivalent income (euros)	551	1,899±906	1,736±763	1,841±861	0.03*
Educational level	809				0.047*
Low/medium		*373 (72.9)*	*235 (79.1)*	*608 (75.2)*	
High		*139 (27.1)*	*62 (20.9%)*	*201 (24.8)*	
Employment status	694				0.75
Not employed		*306 (68.6)*	*173 (69.8)*	*479 (69.0)*	
Employed		*140 (31.4)*	*75 (30.2)*	*215 (31.0)*	
Marital status	816				0.40
No partner		*109 (21.1)*	*71 (23.7)*	*180 (21.4)*	
Partner		*407 (78.9)*	*229 (76.3)*	*636 (77.9)*	

Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. *Significant at the P<0.05 level.

As to health-related characteristics (Tables 3-5), patients with insufficient glycaemic control had a significantly longer mean duration of diabetes (11.1±8.0 vs. 6.9±5.9 years; p<0.001), as well as a higher prevalence of cardiovascular disease (34.1 vs. 25.9%; p=0.014), neuropathic pain (24.7 vs. 18.0%; p=0.025), retinopathy (7.7 vs. 3.3%; p=0.007) and chronic kidney disease (50.0 vs. 37.7%; p<0.001).

HRQoL was reduced in the insufficient glycaemic control subgroup compared to patients with sufficient control. Thus, mean PAID scores indicated higher diabetes-related emotional distress (15.3±15.2 vs. 9.3±11.6; p<0.001) and there was a significantly higher percentage of patients at an emotional burn-out level, as indicated by a PAID score ≥40 (9.7 vs. 2.7%; p<0.001). Moreover, mean summary scores on all domains of HRQoL measured by the EQ-5D-3L and SF-36 were significantly lower among patients with insufficient glycaemic control, as was the overall EQ-5D-3L index score.

Medication use was different between subgroups (p<0.001): in particular, the percentage of patients on insulin was greater in patients with insufficient glycaemic control compared to those with sufficient control (50.0 vs. 11.7%). In terms of clinical measures, patients with insufficient glycaemic control differed significantly from their counterparts in terms of weight (91.6±17.7 vs. 87.1±15.2; p<0.001), waist circumference (108.9±14.6 vs. 105.1±12.6; p<0.001), BMI (30.9±5.3 vs. 29.5±4.7; p<0.001) and triglycerides (1.8±1.1 vs. 1.7±0.9; p=0.047).

Table 3. Health-related patient characteristics by glycaemic control (continuous variables)

Characteristic	N	HbA1<=7.0% [53 mmol/mol] (N=532)	HbA1c >7.0% [53 mmol/mol] (N=308)	Total (N=840)	p-value
Diabetes duration	663	6.88±5.89	11.13±7.96	8.5±7.0	<0.001*
Diabetes-related distress (PAID)	710	9.3±11.6	15.3±15.2	11.6±13.4	<0.001*
EQ-5D-3L index score	791	0.86±0.20	0.83±0.19	0.85±0.20	0.05*
SF-36 Physical component score (total)	785	47.24±9.47	44.69±10.56	46.3±9.9	0.001*
SF-36 Mental component score (total)	785	53.11±8.79	51.55±9.44	52.5±9.0	0.02*
HbA1c (% [mmol/mol])	840	6.5±2.5 [47±4]	8.1±3.2 [65±12]	7.1±3.2 [54±12]	NA
Total cholesterol (mmol/l)	840	4.3±0.9	4.3±0.9	4.3±0.9	0.34
LDL cholesterol (mmol/l)	840	2.3±0.8	2.2±0.8	2.3±0.8	0.29
HDL cholesterol (mmol/l)	840	1.3±0.3	1.2±0.4	1.2±0.4	0.09
Triglycerides (mmol/l)	840	1.7±0.9	1.8±1.1	1.7±0.9	0.047*
Weight (kg)	838	87.1±15.2	91.6±17.7	88.7±16.3	<0.001*
Waist circumference (cm)	838	105.1±12.6	108.9±14.6	106.5±13.5	<0.001*
BMI (in kg/m^2)	838	29.5±4.7	30.9±5.3	30.0±5.0	<0.001*
Systolic blood pressure (mmHg)	840	142.3±17.8	141.9±17.8	142.2±17.8	0.755
Diastolic blood pressure (mmHg)	840	77.1±9.5	76.3±9.5	76.8±9.5	0.265

Continuous variables are presented as means and standard deviations (SD). *Significant at the P<0.05 level.

Table 4. Health-related patient characteristics by glycaemic control (binary variables)

Characteristic	N	Category	HbA1<=7.0% [53 mmol/mol] (N=532)	HbA1c >7.0% [53 mmol/mol] (N=308)	Total (N=840)	p-value
Cardiovascular disease	817	*No*	371 (74.1)	193 (65.9)	564 (71.0)	0.01*
		Yes	130 (25.9)	100 (34.1)	230 (29.0)	
Neuropathic pain	781	*No*	405 (82.0)	216 (75.3)	621 (79.5)	0.025*
		Yes	89 (18.0)	71 (24.7)	160 (20.5)	
Retinopathy	762	*No*	472 (96.7)	253 (92.3)	725 (95.1)	0.01*
		Yes	16 (3.3)	21 (7.7)	37 (4.9)	
Chronic kidney disease	816	*No*	325 (61.1)	147 (50.0)	472 (57.8)	0.001*
		Yes	197 (37.7)	147 (50.0)	344 (42.2)	
Diabetes-related distress (PAID)	710	*PAID score <40*	430 (97.3)	242 (90.3)	672 (94.6)	<0.001*
		PAID score ≥40	12 (2.7)	26 (9.7)	38 (5.4)	
EQ-5D-3L Mobility problems	796	*No*	356 (70.5)	186 (63.9)	542 (68.1)	0.055*
		Yes	149 (29.5)	105 (36.1)	254 (31.9)	
EQ-5D-3L Self-care problems	795	*No*	486 (96.4)	271 (93.1)	757 (95.2)	0.04*
		Yes	18 (3.6)	20 (6.9)	38 (4.8)	
EQ-5D-3L Usual activities problems	796	*No*	430 (85.3)	217 (74.3)	647 (81.3)	<0.001*
		Yes	74 (14.7)	75 (25.7)	149 (18.7)	
EQ-5D-3L Pain/discomfort	796	*No*	303 (60.1)	155 (53.1)	458 (57.5)	0.05*
		Yes	201 (39.9)	137 (46.9)	338 (42.5)	
EQ-5D-3L Anxiety/depression	796	*No*	430 (85.3)	229 (78.4)	659 (82.8)	0.01*
		Yes	74 (14.7)	63 (21.6)	137 (17.2)	
SF-36 Physical component score	*785*	*PCS≥50*	267 (53.6)	113 (39.4)	380 (48.4)	<0.001*
		PCS<50	231 (46.4)	174 (60.6)	405 (51.6)	
SF-36 Mental component score	785	*MCS≥42*	446 (89.6)	244 (85.0)	690 (87.9)	0.06
		MCS<42	52 (10.4)	43 (15.0)	95 (12.1)	

Binary variables are presented as frequencies and valid percentages. *Significant at the P<0.05 level.

Table 5. Health-related patient characteristics by glycaemic control (categorical variables)

Characteristic	N		HbA1<=7.0% [53 mmol/mol] (N=532)	HbA1c >7.0% [53 mmol/mol] (N=308)	Total (N=840)	p-value
Depression	716	*No/minimal symptoms*	432 (93.3)	227 (89.7)	659 (92.0)	0.23
		Minor depression	19 (4.1)	15 (5.9)	34 (4.7)	
		Major depression	12 (2.6)	11 (4.3)	23 (3.2)	
Glucose-lowering medication	839	*None*	66 (12.4)	10 (3.2)	76 (9.1)	<0.001*
		Oral and injectable (non-insulin)	403 (75.9)	144 (46.8)	547 (65.2)	
		Insulin	62 (11.7)	154 (50.0)	216 (25.7)	

Categorical variables are presented as frequencies and valid percentages. *Significant at the P<0.05 level.

HRQoL in patients with insufficient glycaemic control: biopsychosocial profiles

Among patients with insufficient glycaemic control (HbA1c >7.0% [53 mmol/mol]; N=308), LCA was used to explore the existence of distinct biopsychosocial profiles, which differ in terms of HRQoL. LCA models were run with one to five classes. The model fit indices showed that the two- and three-class models had the best fit (S1 Table). The two-class model was chosen for further analysis, because of little distinction in patterns and item probabilities between class 2 and class 3, as well as the small percentage of patients in class 3 based on most likely class membership (4.9%).

Fig 1 shows the item response probability plot for the final two-class model. Values on the y-axes represent the likelihood, by class, of patients experiencing problems related to included HRQoL domains. Two distinct classes were identified: patients with 'low' HRQoL (28.6%; N=88) versus patients with 'high' HRQoL (71.4%; N=220). Classes differed most in the probability of experiencing problems with usual activities, anxiety and physical functioning, which was greater for patients with low HRQoL (~70-90%; Fig 1). On the other hand, the chance of problems with self-care and pain, as well as for severe diabetes-related distress (PAID score ≥40), was relatively low and comparable in both classes, although consistently greater in the low HRQoL class. The likelihood of mobility issues was around 50% in the low HRQoL class versus circa 25% in the high HRQoL class.

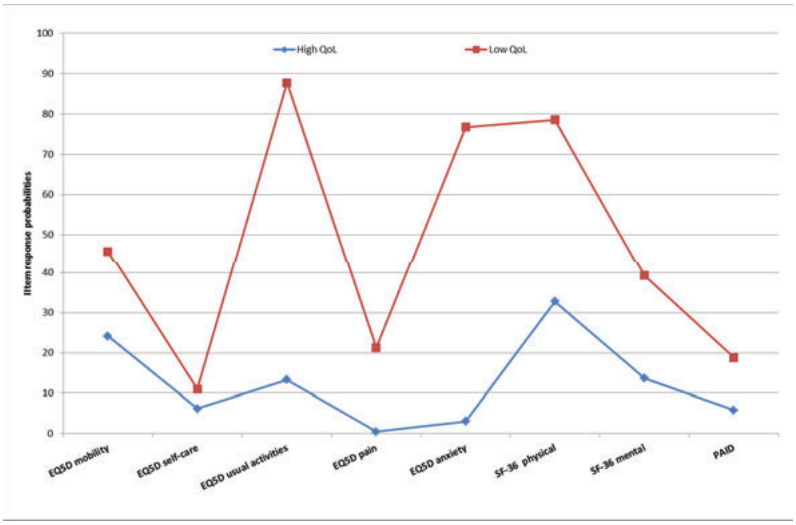

Figure 1. Two-class model for HRQoL in patients with insufficient glycaemic control (HbA1c>7.0% [53 mmol/mol]).

High HRQoL class, N=220 (71.4%); low HRQoL class, N=88 (28.6%)

Tables 6-8 summarize the biopsychosocial characteristics of the identified HRQoL classes and show which characteristics were associated with HRQoL-based class membership (high HRQoL class is used as reference category). With regard to person-related characteristics, women had higher odds than men to be in the low HRQoL class (OR 2.32; 95% CI 1.36-3.94; p=0.002), as did current smokers compared to non-smokers (OR 2.24; 95% CI 1.03-4.88; p=0.04). Other person-related factors associated with greater odds of being in the low HRQoL class were no versus low or high alcohol consumption, less than 7 hours of physical activity per week versus 14 hours or more, and lower mastery, self-efficacy and social adequacy (Table 6).

Apart from marital status, all context-related characteristics (Table 7) were significantly different between HRQoL classes. Lower equivalent income was associated with higher odds of being in the low HRQoL class (OR 0.10; 95% CI 0.10-0.10; p=0.007), as was a low or medium educational level (OR 2.28; 95% CI 1.12-4.67; p=0.02) and unemployment (OR 8.05; 95% CI 3.23-20.10; p<0.001).

As for health-related characteristics (Table 8), a diabetes duration of ≥10 years relative to <5 years was associated with higher odds for the low HRQoL class (OR 2.41; 95% CI 1.13-5.13; p=0.02). Patients with cardiovascular disease, neuropathic pain or chronic kidney disease also had significantly higher odds to be in the low HRQoL class, as did patients with minor or major depression (ORs ranging from 2.08 to 6.21). Medication-wise, use of insulin instead of no or other diabetes medication was associated with higher odds for the low HRQoL class (OR 1.98; 95% CI 1.19-3.30; p=0.009). Of the clinical measures, higher HbA1c, BMI, weight or waist circumference was associated with greater odds of belonging to the low HRQoL class (ORs from 1.02 to 1.12).

Table 6. Person-related characteristics of T2DM patient across different classes of HRQoL.

	N	Category	Biopsychosocial characteristics		OR (95% CI)	p-value
			High HRQoL class (N=220)	*Low HRQoL class (N=88)*	*Low HRQoL class*	
Age (years)	308	*41 – 49*	20 (9.1)	3 (3.4)	Reference	
		50 – 64	108 (49.1)	41 (46.6)	2.50 [0.70-8.91]	0.16
		65 – 76	92 (41.8)	44 (50.0)	3.11 [0.87-11.07]	0.08
Sex	308	*Male*	167 (75.9)	51 (58.0)	Reference	
		Female	53 (24.1)	37 (42.0)	2.32 [1.36-3.94]	0.002*
Smoking status	298	*Never*	56 (26.4)	17 (19.8)	Reference	
		Former	124 (58.5)	48 (55.8)	1.25 [0.66-2.37]	0.50
		Current	32 (15.1)	21 (24.4)	2.24 [1.03-4.88]	0.04*
Alcohol consumption	298	*None*	58 (27.4)	42 (48.9)	Reference	
		Low	120 (56.6)	35 (40.7)	0.40 [0.23-0.96]	0.001*
		High	34 (16.0)	9 (10.5)	0.31 [0.13-0.74]	0.008*
Physical exercise	240	*<7 h/w*	48 (27.6)	28 (42.4)	Reference	
		7-13 h/w	66 (37.9)	20 (30.3)	0.53 [0.27-1.05]	0.07
		≥14 h/w	60 (34.5)	18 (27.3)	0.48 [0.23-0.98]	0.04*
Mastery	242		174±26.3	68±22.4	0.48 [0.36-0.65]	<0.001*
Self-efficacy	238		59.6±7.8	54.3±8.6	0.92 [0.88-0.96]	<0.001*
Social inadequacy	240		172±3.1	68±4.5	1.11 [1.03-1.20]	0.006*

Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. *Significant at the P<0.05 level.

Table 7. Context-related characteristics of T2DM patient across different classes of HRQoL.

	N	Biopsychosocial characteristics		OR (95% CI)	p-value
		High HRQoL class (N=220)	*Low HRQoL class (N=88)*	*Low HRQoL class*	
Equivalent income	195	1837±791	1499±640	0.10 [0.10-0.10]	0.007*
Educational level (*Low/medium*)	297	159 (75.7)	76 (87.4)	2.28 [1.12-4.67]	0.02*
Employment status (*Unemployed*)	248	109 (61.2)	64 (91.4)	8.05 [3.23-20.10]	<0.001*
Marital status (*No partner*)	300	46 (21.6)	25 (28.7)	1.42 [0.80-2.51]	0.23

Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. *Significant at the P<0.05 level.

Table 8. Health-related characteristics of T2DM patient across different classes of HRQoL.

	N	Category	Biopsychosocial characteristics		OR (95% CI)	p-value
			High HRQoL class (N=220)	*Low HRQoL class (N=88)*	*Low HRQoL class*	
Diabetes duration	251	*<5 years*	52 (28.9)	11 (15.5)	Reference	
		5-9 years	42 (23.3)	18 (25.4)	2.04 [0.86-4.84]	0.11
		≥ 10 years	86 (47.8)	42 (59.2)	2.41 [1.13-5.13]	0.02*
Cardiovascular disease	293		61 (29.5)	39 (45.3)	2.08 [1.23-3.52]	0.006*
Neuropathic pain	287		36 (17.8)	35 (41.2)	3.26 [1.85-5.76]	<0.001*
Retinopathy	274		12 (6.1)	9 (11.7)	2.09 [0.83-5.24]	0.12
Chronic kidney disease	294		93 (44.3)	54 (64.3)	2.48 [1.46-4.21]	0.001*
Depression	253	*No/minimal*	170 (94.4)	57 (78.1)	Reference	
		Minor depression	6 (3.3)	9 (12.3)	4.31 [1.44-12.87]	0.009*
		Major depression	4 (2.2)	7 (9.6)	6.21 [1.74-22.18]	0.005*
Glucose-lowering medication (*Insulin*)	308		100 (54.0)	54 (61.3)	1.98 [1.19-3.30]	0.009*
HbA1c (% [mmol/mol])	308		8.0±3.1 [64±10]	8.4±3.5 [68±15]	1.03 [1.01-1.05]	0.009*
Total cholesterol (mmol/l)	308		4.2±0.9	4.3±0.9	1.07 [0.82-1.39]	0.62
LDL cholesterol (mmol/l)	308		2.3±0.8	2.2±0.8	0.94 [0.68-1.30]	0.70
HDL cholesterol (mmol/l)	308		1.2±0.4	1.2±0.4	0.97 [0.51-1.83]	0.93
Triglycerides (mmol/l)	308		1.8±1.1	2.0±1.1	1.21 [0.96-1.52]	0.11
Weight (kg)	301		90.2±16.7	94.4±17.9	1.02 [1.00-1.03]	0.04*
Waist circumference (cm)	303		107. 2±13.5	113.8±16.3	1.03 [1.01-1.05]	0.001*
BMI (kg/m^2)	308		30.1±4.7	33.0±6.2	1.12 [1.06-1.18]	<0.001*
Systolic blood pressure (mmHg)	308		142.8±17.9	139.8±17.5	0.99 [0.98-1.01]	0.23
Diastolic blood pressure (mmHg)	308		76.8±9.3	75.3±9.8	0.98 [0.95-1.01]	0.17

Continuous variables are presented as means and standard deviations (SD); binary and categorical data as frequencies and valid percentages. *Significant at the P<0.05 level.

Discussion

Findings from this study suggest that significant differences exist in biopsychosocial characteristics between subgroups of diabetes patients by level of glycaemic control. Most characteristics were health-related, including HRQoL, complications, medication, and BMI. Of the assessed person- and context-related characteristics, self-efficacy respectively income and education level differed between glycaemic control subgroups, albeit modestly. Identified associations were consistently negative: a worse status on any of the significant variables was associated with less glycaemic control. Zooming in further on the insufficient glycaemic control subgroup, we identified two distinct patient classes in terms of HRQoL: one with a low probability of HRQoL problems and one with a higher probability of such problems. A broad range of biopsychosocial factors was associated with low HRQoL class membership, including lower levels of mastery, self-efficacy and social adequacy, lower income and education levels, longer disease duration, presence of various complications, and insulin use.

In 2012, the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) published a position statement on hyperglycaemia management in T2DM, which described the need to individualise treatment targets and strategies [8]. Yet in most countries, diabetes management remains highly standardised and does not comprehensively account for heterogeneity within the diabetes population [36,37]. Our findings support the need for more individualised management, by showing that patients with insufficient glycaemic control differ considerably from those with sufficient control. Differences exist not only in health-related variables, as emphasised by the EASD and ADA, but also on a psychosocial and socioeconomic level. Particularly lower self-efficacy, income and/or education levels seem to be associated with less glycaemic control. This is supported by previous research demonstrating the effects of self-efficacy on diabetes self-management and, consequently, glycaemic control [38]. Increasing evidence supports the notion that people's control beliefs are a fundamental mechanism underlying socioeconomic differences in health [39-41]. This might be particularly true for T2DM patients, as recent work suggests that among chronically ill, control beliefs are even more important determinants of HRQoL than social support or income [42].

To our knowledge, this is the first LCA among T2DM patients with insufficient glycaemic control. Findings suggest that in terms of HRQoL – described as an outcome that 'actually matters to patients' [43] – distinct classes exist within this subgroup: about a quarter of patients has serious problems in multiple HRQoL domains, whereas the others do not (yet) experience any limitations. This finding might partly explain why previous studies into the relation of glycaemic control with HRQoL, which did not account for 'latent subclasses', have found weak and inconsistent associations [44,45]. Looking at the specific domains in which problems were most likely to occur, i.e. with usual activities, anxiety and physical functioning, diabetes-related complications might be important predictors of low HRQoL. Indeed, previous research suggests that complications are more strongly associated with HRQoL than HbA1c, and that even minor complications can have a significant impact on HRQoL [46,47]. Given their higher complication rates and longer disease duration, it is not surprising that patients with insufficient glycaemic control – particularly those with low HRQoL – were more likely to use

insulin. However, the overrepresentation of insulin users in this class might also suggest that insulin is an inadequate 'last resort' for some patients.

Patients with low versus high HRQoL in the insufficient glycaemic control subgroup also differed in person- and context-related characteristics – more profoundly even than when comparing patients by level of glycaemic control. Here again, control beliefs might mediate socioeconomic health differences. Living with diabetes poses many challenges for patients in areas like nutrition, glycaemic monitoring and medication adherence, which tend to become increasingly difficult and burdensome as glycaemic control deteriorates [48]. However, the knowledge, skills, confidence and means – both financially and socially – needed to adequately respond to these challenges are not distributed equally among the population, which might contribute to differences in HRQoL among those with insufficient glycaemic control. Indeed, estimates from the United Kingdom show that morbidity from diabetes-related complications is more than three times higher among the less well-off compared to the wealthiest [49].

This study has a number of strengths and limitations. We drew on the comprehensive phenotyping approach of The Maastricht Study [11] and used a relatively large sample size, allowing for the investigation of multiple subgroups and classes. Although there is no formal benchmark for adequate sample size in LCA, Finch and Bronk [50] concluded – based on a number of simulation studies – that 500 participants is 'a worthy goal in practice'. In terms of methods, LCA is a sophisticated analytic technique, which allowed us to improve understanding of previously unobserved subgroups in the diabetes population. An important advantage of LCA over traditional types of cluster analysis is its probability-based classification, which better captures uncertainty [51]. Given the complex and difficult to differentiate interactions that might exist between many of the included variables, investigating causal relations via multivariable analysis was beyond the scope of this explorative study. On one hand, this is a limitation of the study, as it precludes any conclusions about which patient characteristics are the strongest predictors of insufficient glycaemic control and/or low HRQoL, and which are confounders. On the other hand, our univariable exploration of a broad range of possibly relevant characteristics provides a sound basis for more targeted, hypothesis-driven future investigations of causal relations using multivariable models, and is in line with the biopsychosocial paradigm that is gaining increasing traction in health care [52]. Univariable analyses also enabled us to maintain a relatively large overall sample size, despite missing values in some independent variables. A final limitation relates to the relative underrepresentation of people with severe diabetic complications in The Maastricht Study. As a result, the study sample may be healthier than the average diabetes population, which could mean that some of the associations measured between patient factors and health outcomes are underestimations.

In conclusion, this explorative study shows that insufficient glycaemic control, particularly in combination with low HRQoL, is associated with a generally less positive biopsychosocial profile. Further studies, especially multivariable analyses, are needed to better understand the complex and multidimensional causal pathways between relevant biopsychosocial characteristics of T2DM patients and their health outcomes. Perhaps even more importantly, we need to learn more about the self-perceived care needs and preferences of different patient subgroups, and how we can meet them with well-aligned care and support strategies. With regard to the latter, a large-scale study is currently being conducted in the Netherlands

('PROFILe'), which builds on the findings of the present study to develop an instrument supporting more tailored, person-centred chronic care [53] The first results of PROFILe are expected in 2017.

Supplementary material

S1 Table. Statistical criteria for latent class models with 1 to 5 latent classes.

Number of Classes	BIC[a]	LMR-LRT[b]	Entropy	Percentage patients per class based on most likely class membership
1	2.292.709	NA	NA	100
2	2140.802	-1123.434*	0.757	71.4-28.6
3	2164.218	-1021.695*	0.803	67.5-27.6-4.9
4	2196.614	-1007.618	0.793	47.4-29.2-18.5-4.9
5	2235.191	-998.030	0.821	46.7-29.2-14.0-6.5-3.6

[a]Bayesian Information Criterion; [b]Lo-Mendell-Rubin Likelihood Ratio Test; *Significant at the P<0.05 level.

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CHAPTER 5

A risk score of BMI, glycated haemoglobin and triglycerides predicts future glycaemic control in type 2 diabetes

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Abstract

Aim: To identify, predict and validate distinct glycaemic trajectories among patients with newly diagnosed type 2 diabetes treated in primary care, as a first step towards more effective patient-centred care.

Material and methods: We conducted a retrospective study on two cohorts using routinely collected individual patient data in primary care practices from two large Dutch diabetes patient registries. Participants included newly diagnosed, adult patients with type 2 diabetes between January 2006 and December 2014 (n = 10,528, development cohort; n = 3,777, validation cohort). Latent growth mixture modeling (LGMM) identified distinct glycaemic 5-year trajectories. Machine learning models were built to predict the trajectories with easily obtainable patient characteristics in daily clinical practice.

Results: Three different glycaemic trajectories were identified: 1) stable, adequate glycaemic control (76.5% of patients); 2) improved glycaemic control (21.3% of patients) and 3) deteriorated glycaemic control (2.2% of patients). Similar trajectories could be discerned in the validation cohort. BMI, HbA1c and triglycerides were the most important predictors of trajectory membership. The predictive model, trained on the development cohort, had a receiver operating characteristic area under the curve (ROC-AUC) of 0.96 in the validation cohort, indicating excellent accuracy.

Conclusions: The developed model can effectively explain heterogeneity in future glycaemic response of patients with type 2 diabetes. It can therefore be used in clinical practice as a quick and easy tool to provide tailored diabetes care.

Introduction

Archibold Garrod is considered the founding father of precision medicine. In 1931, he was the first to recognize interpersonal variation in disease development and impact. Garrod noted that "individual cases of any particular disease are not exactly alike; they resemble rather the drawings made from the same model by individual members of a drawing class" [1]. Nowadays, precision medicine is becoming more popular, due to an increase in electronic clinical data and decline of genome sequencing costs.[2, 3] In 2012, former UK Prime Minister David Cameron initiated the 100,000 Genomes Project and in 2015 former US president Barack Obama launched the Precision Medicine Initiative [4, 5]. The aim of both initiatives is to predict the process of disease and to create personalized patient care by gaining more knowledge on genetic variation in disease.

Thus far, significant advances have been made, such as the discovery of certain genetic variations that are linked to the effectiveness of a drug or specific genes that predict cancer ris [6, 7]. Nevertheless, the implementation of precision medicine based on solely genomics has proven to be difficult for certain diseases, such as type 2 diabetes. Recently, new efforts have been undertaken to unravel the genetic background of type 2 diabetes by studying not only common gene variants, but also infrequent and rare variants [8]. To date, only 10% of its heritability has been unveiled, which has been referred to as a "geneticist's nightmare" by some experts [9]. Consequently, precision medicine based on a genotyping approach is still far away for type 2 diabetes. Shifting to a phenotyping approach of precision medicine seems a more promising alternative, in particular in the short-term, to improve patients' health outcomes [10, 11]. The US National Institutes of Health defines precision medicine as an emerging approach for disease treatment and prevention that takes into account not only individual variability in genes, but also a patient's environment and lifestyle [12]. Currently, such a phenotyping approach to precision medicine is only sparsely adopted in evidence-based guidelines for diabetes treatment. Barring some exceptions for persons of older age, these guidelines are usually highly standardized [13, 14].

As a first step towards more patient-centred care, the purpose of this study was threefold: a) to identify subgroups of people with newly diagnosed type 2 diabetes with distinct glycaemic trajectories; b) to predict trajectory membership using patient characteristics that are commonly assessed in diabetes primary care; and c) to validate these findings in a different cohort of patients with type 2 diabetes.

Research design and methods

Study design and patients

In this retrospective cohort study, patients were selected using the electronic health records (EHR) of two large Dutch diabetes care networks (DCN) that routinely collect individual patient data and have been frequently used for research [15-19]. General Practitioners (GP) and practice nurses from the participating practices recorded these data in the EHRs from the start

of diabetes diagnosis. They use the information in the EHRs for the treatment and follow-up of their patients and as proof that they provided the care as agreed upon with health insurers for declaration purposes. Therefore, it can be considered accurate. Patients from both DCNs received managed diabetes primary care based on the Netherlands Diabetes Federation Care Standard [13], which describes the norm for generic multidisciplinary diabetes care.

The first DCN, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC),[20] was used as development cohort and contained the anonymous longitudinal health records of 93,981 adult (≥18 years) patients with type 2 diabetes from 731 primary care practices in the city of Rotterdam, northern, north-western and eastern parts of the Netherlands. The data in the current study were collected during the yearly visits between 1 January 2006 and 31 December 2013. Those patients with a new diagnosis of type 2 diabetes during the study period and with at least one HbA1c measured +/- three months from diagnosis (baseline) were selected for further analysis.

The second DCN, the regional care group ZIO [18], was used as validation cohort. The ZIO database contained the anonymous longitudinal health records of 11,833 adult (≥18 years) patients with type 2 diabetes from 95 primary care practices in Maastricht, in the south of the Netherlands. Data were collected and registered in the EHRs between 1 January 2009 and 31 December 2014. The inclusion criteria were the same as for the development cohort.

Both cohorts were open and dynamic, and patients were followed from diagnosis until the end of the study period or until censoring because no more HbA1c measurements were available (due to death, no show or change of practice). Patients' date of entry into the study (baseline) was fixed at their registered date of diagnosis of type 2 diabetes.

No ethical approval was needed for the study: as the data used were already available and patients were not physically involved in the research, the study is not subject to the Dutch Medical Research (Human Subjects) Act (WMO).

Outcome

The outcome of interest was glycaemic control trajectories, based on HbA1c values during a maximum of 4 (development cohort) or 5 years (validation cohort). Baseline HbA1c values were included if measured +/- three months from diagnosis. Follow-up HbA1c values were included if measured a year from the previous HbA1c measurement with a deviation of +/- three months.

Predictors

The baseline patients' characteristics were used as potential predictors for an individual's glycaemic trajectory membership. Characteristics included baseline age, sex and race, which was categorized into a binary variable of Caucasian or non-Caucasian, since participants were mainly Caucasian; non-Caucasian included Moroccan, Turkish, black African, Indian, Indonesian, and non-Indian in the development cohort and black, Indian, and other Asian in the validation cohort. HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile (LDL, HDL, total cholesterol and triglycerides), and BMI were also included as

baseline characteristics if measured +/- three months from diagnosis. Urinary albumin-to-creatinine ratio (ACR), presence of heart failure (only reported in development cohort), smoking (yes/no) and alcohol consumption (≤3 glasses/day or >3 glasses/day) were included as baseline characteristics if measured +/- 12 months from diagnosis. Patient reported history of CVD in family members <60 years (yes/no) was included in the analysis if obtained at any point before diagnosis or maximum 12 months after diagnosis.

Outliers - most likely due to errors in recording - were removed based on cutoff points determined by diabetologists (MB and NS).

Statistical methods

To systematically identify latent trajectories of glycaemic control, latent growth mixture modeling (LGMM) was used. This method allows for the clustering of patients into an optimal number of growth trajectories [21]. Full information maximum likelihood (FIML) was used as a missing data estimation approach [22]. A protocol, as recommended previously [23, 24], was followed to identify the best LGMM model. A series of latent class growth analysis (LCGA) and LGMM models were estimated. LCGA assumes no within class variance, whereas LGMM freely estimates the within class variance [23]. The best model was determined by comparing the model fits of a progressive number of trajectories. Fit indices included the Akaike Information Criterion (AIC) [25], Bayesian Information Criterion (BIC) [26] and the Lo-Mendel-Rubin-likelihood ratio test (LMR-LRT) [27]. Lower values of the AIC and BIC, and/or a significant result on the LMR-LRT indicate a better model fit in terms of the number of trajectories. To determine model classification performance, entropy was used. Higher entropy values indicate less ambiguity in trajectory allocation [28]. The usefulness and clinical interpretation of each trajectory model was also taken into account. Analyses were performed using Mplus version 7.1. [29] and are reported according to the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist [24]. Baseline characteristics were assessed for the development- and validation cohorts. Significant differences between cohorts were determined using two-sample t-tests and x^2. Analysis of variance (ANOVA) and chi-square tests were used to identify significant differences between glycaemic control trajectories within each cohort. To gain insight into the influence of glucose lowering drugs and insulin on the patterns of the trajectories, the percentage of patients with oral glucose lowering drugs and/or insulin prescriptions was compared at baseline and at each follow-up year between the trajectories of the development cohort using Chi-square tests.

For the development and validation of the prediction model, only patients with no missing baseline values were included. A five-fold cross validation was performed in the development cohort. Since there is no consensus on the best performing classifier, several machine learning classification methods were used [30]. The correlations between SBP and DBP, lipid profile characteristics, and CVD characteristics were calculated using the Spearman- (for non-normally distributed variables) and Pearson (for normally distributed variables) correlation coefficients. If there was a significant correlation coefficient ≤-0.4 or ≥0.4 between two potential predictors, only one potential predictor was included in the analysis to avoid over-

adjustment. To examine the generalizability of the developed prediction model, an external validation was computed in the validation cohort. Receiver operating characteristic (ROC) curves were generated to show the discrimination of the models. To examine the agreement between predicted and observed trajectory membership, calibration slopes were produced. Diagnostic values (sensitivities and specificities) and prognostic values (positive predictive values (PPV), and negative predictive values (NPV)), were also calculated.

For further details regarding the analyses see supplementary material (eMethods).

Results

Description of the development – and validation cohorts

The initial development cohort included 20,414 patients who were diagnosed with type 2 diabetes between January 1 2006 and December 31 2013. Of these, 10,528 patients had a baseline HbA1c measurement and were included in the analysis. The group of patients without a baseline HbA1c measurement had significantly higher LDL levels (3.0 versus 2.9 mmol/l, 95% CI 0.05 – 0.14, p-value <0.001) and a lower percentage of women (46.9 versus 48.4%; 95% CI 0.2% to 3.0%, p-value = 0.031). Other characteristics did not differ. The mean age of the included patients in the development cohort was 62.9 (SD 12.7) years and 51.6% were men (table 1).

The initial validation cohort included 4,164 patients who were diagnosed with type 2 diabetes between January 1 2009 and December 31 2014. Of these, 3,337 adult patients had a baseline HbA1c measurement and were therefore selected for inclusion in the analysis. The group of patients without a baseline HbA1c measurement were significantly older (64.9 versus 63.7 years, 95% CI 0.3 – 2.1, p-value=0.009) and had a lower percentage of CVD in the family (19 versus 24.2%, 95% CI 1.4% to 8.0%, p-value = 0.008). Other characteristics did not differ. The mean age of the included patients in the validation cohort was 63.7 years (SD 12.2) and 52.3% were men (table 1).

In both the development- and validation cohort, date of diagnosis (and inclusion into the study) differed considerably between patients: some patients were, for example, diagnosed in 2009 and others in 2013, resulting in a variable follow-up. Due to this variable follow-up, 78.7% of the patients in the development cohort did not have a HbA1c measurement after 4 years of follow-up and 72.9% did not have a HbA1c measurement after 5 years of follow-up in the validation cohort (Supplemental Table S1). It was therefore decided to restrict follow-up in the development cohort to 4 years and in the validation cohort to 5 years. The median number of HbA1c measurements during the research period was 2 (interquartile range 2) in the development cohort and 3 (interquartile range 3) in the validation cohort.

Table 1. Baseline patient characteristics of the development cohort and the validation cohort

	Development cohort*	Validation cohort*	p-value
N	10,528	3,337	
Age (years) (sd)	62.9 (12.7)	63.7 (12.2)	0.001
Not recorded	0	0	
Male sex	5433 (51.6)	1744 (52.3)	<0.001
Not recorded	0	0	
Ethnic group†			0.797
Caucasian	6669 (95.3)	2913 (95.5)	
Non-Caucasian	330 (4.7)	137 (4.5)	
Not recorded	3539	287	
Smoking status†			<0.001
Non-smoker	7748 (80.1)	2065 (74.8)	
Current smoker	1928 (19.9)	695 (25.2)	
Not recorded	852	577	
BMI (kg/m^2) (sd)	30.4 (5.5)	30.6 (6.1)	0.073
Not recorded	4443	595	
Alcohol consumption†			0.308
<3 glasses/day	6029 (76.3)	3147 (94.6)	
≥3 glasses/day	1876 (23.7)	178 (5.4)	
Not recorded	2623	12	
HbA1c (mmol/mol) (sd)	53.0 (15.3)	56.9 (18.8)	<0.0001
Not recorded	0	0	
HbA1c (%) (sd)	7.0 (1.4)	7.4 (1.7)	<0.0001
Not recorded	0	0	
SBP (mmHg) (sd)	138.5 (17.6)	138.4 (18.8)	0.321
Not recorded	3762	483	
DBP(mmHg) (sd)	80.8 (10.0)	80.8 (10.4)	0.801
Not recorded	4014	489	
LDL (mmol/mol) (sd)	2.9 (1.0)	3.2 (1.1)	0.954
Not recorded	1910	663	
HDL (mmol/mol) (sd)	1.23 (0.4)	1.16 (0.35)	<0.001
Not recorded	1536	638	
Total cholesterol (mmol/mol) (sd)	5.0 (1.1)	5.3 (1.3)	<0.001
Not recorded	1500	628	
Triglycerides (mmol/l) (sd)	2.0 (1.2)	2.2 (1.4)	<0.001
Not recorded	1809	659	
ACR (mg/mmol) (sd)	2.7 (9.9)	2.3 (9.8)	0.002
Not recorded	2717	812	
eGFR (ml/min/1.73 m^2)	80.1 (21.6)	77.7 (24.0)	0.005
Not recorded	9620	454	
Heart failure†		-	-
Yes	437 (6.6)		
No	6153 (93.4)		
Not recorded	3941		
CVD in family†			0.018
Yes	2718 (37.9)	810 (24.3)	
No	4457 (62.1)	2521 (75.7)	
Not recorded	3355	6	

*Values are numbers (percentages) unless stated otherwise. Percentages have been rounded and might not total 100. †Percentages are out of total with recorded values

SBP = systolic blood pressure; DBP = diastolic blood pressure; ACR = albumin-to-creatinine ratio; CVD = cardiovascular disease

Latent growth mixture modeling

The model with the strongest fit in the development cohort was the 3-trajectory LGMM (Supplemental Table S2). The largest (76.5%) and most stable trajectory showed a pattern of good glycaemic control (HbA1c ≤7% (53 mmol/mol)) over time (figure 1). This trajectory was named *stable, adequate glycaemic control*. The middle trajectory, including 21.3% of the population, was named *improved glycaemic control*, because patients in this trajectory adequately responded to glycaemic treatment and subsequently remained stable at a HbA1c level just above 7% (53 mmol/mol). The smallest trajectory (2.2%) showed very high HbA1c at diagnosis of diabetes, but adequately responded to treatment. However, two years past diagnosis, HbA1c started to increase again to levels >7% (53 mmol/mol). This trajectory was named *deteriorated glycaemic control*. The mean intercepts and slopes for each class are presented in Supplemental Table S3. All intercepts and slope growth parameters were statistically significant. The observed individual trajectories and estimated mean trajectory of the 3-trajectory model are shown in eFigure 1 in the supplement.

In the validation cohort, also a 3-trajectory model was identified based on model fit (Supplemental Table S4) and population trajectory distribution (figure 1). This model was similar in shape and population distribution to the 3-trajectory model of the development cohort. All intercepts and slope growth parameters were statistically significant (Supplemental Table S3).

Supplemental Figures S1 to S5 show all fitted trajectory models in the development and validation cohorts with linear and quadratic slopes, in accordance with the GRoLTS guidelines.[24]

There were significant differences between trajectories at all time points in the percentages of patients with oral glucose lowering drugs and insulin prescriptions ($p<0.0001$). Supplemental Figures S6 and S7 show that more oral glucose lowering drugs and insulin were prescribed to patients in the deteriorated- and improved glycaemic control trajectories compared to the stable, adequate glycaemic control trajectory. Prescription of oral glucose lowering drugs increased over time in all trajectories.

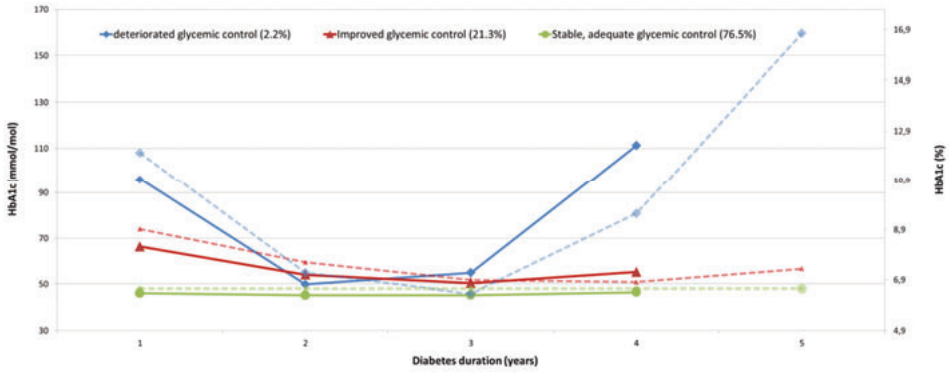

Figure 1. Latent class growth trajectories of the best-fitting models of the development – and validation cohorts identified by LGMM. Solid lines = derivation cohort; dashed lines = validation cohort

Classification into glycaemic control trajectories

In both cohorts, patients in the deteriorated glycaemic control trajectory were more frequently male, current smokers and younger. Their baseline HbA1c, triglycerides and total cholesterol levels were higher compared to the other trajectories (table 2).

After excluding significant correlations between patient characteristics (Supplemental Table S5), 13 baseline characteristics were retained in the analyses as potential predictors: age, gender, race, HbA1c, SBP, LDL, triglycerides, ACR, BMI, smoking, alcohol, CVD, and CVD in family members. The five-fold cross validation in the development cohort showed that the K-nearest neighbour (KNN) machine learning classifier had the highest accuracy (92.3%) (Supplemental Table S6). Using this classifier, the 13-patient feature prediction model had good to excellent diagnostic and prognostic properties with sensitivities between 78.4 and 98.3%, specificities between 81.2 and 99.4%, PPVs between 78.0 and 94.7% and NPVs between 93.7 and 99.5% (Supplemental Table S7). Baseline BMI, HbA1c and triglycerides were the most salient characteristics for predicting trajectory membership according to their weight (table 3). The 13-patient feature prediction model had a ROC-AUC of 0.96 (Figure 2). The external validity of the model with the three most salient patient characteristics (3-patient feature prediction model) was determined in the validation cohort. The linear discriminant classifier (LDC) had the highest accuracy (92.0%) (Supplemental Table S8). Sensitivities were between 67.9 and 99.1%, specificities between 85.3 and 98.6%, PPVs between 45.8 and 96.1% and NPVs between 91.9 and 99.4% (eTable 9 in the supplement). The ROC-AUC was 0.95 (Figure 2). The calibration plot in the validation cohort, showed a good fit for all three trajectories (Supplemental Figure S8). The developed tool can be found on the webpage http://www.patientprofiles.nl which provides the opportunity to fill in different BMI-, HbA1c-, and triglycerides values, and view the related trajectory.

Table 2. Baseline characteristics of the development cohort and the validation cohort according to the different trajectories of HbA1c

	Latent trajectories development cohort*				Latent trajectories validation cohort*			
	Stable, adequate glycaemic control	*Improved glycaemic control*	*Deteriorated glycaemic control*	p-value	*Stable, adequate glycaemic control*	*Improved glycaemic control*	*Deteriorated glycaemic control*	p-value
N	8,049 (76.5)	2,246 (21.3)	233 (2.2)		2,516 (75.4)	702 (21.0)	119 (3.6)	
Age (years) (sd)	63.8 (12.3)	60.3 (13.6)	59.3 (12.6)	<0.001	64.9 (11.6)	60.3 (13.5)	59.7 (12.2)	<0.001
Male sex (%)	4,026 (50.0)	1,261 (56.1)	146 (62.7)	<0.001	1,249 (49.6)	417 (59.4)	78 (65.5)	<0.001
Ethnic group†				0.013				0.797
Caucasian	5,116 (95.7)	1415 (94.0)	138 (93.2)		2,185 (95.4)	623 (96)	105 (95.5)	
Non-caucasian	230 (4.3)	90 (6.0)	10 (6.8)		106 (4.6)	26 (4.0)	5 (4.5)	
Smoking status†				<0.001				<0.001
Non-smoker	6,008 (80.9)	1595 (77.8)	145 (71.8)		1,585 (76.9)	415 (69.5)	65 (64.4)	
Current smoker	1,416 (19.1)	455 (22.2)	57 (28.2)		477 (23.1)	182 (30.5)	36 (35.6)	
BMI (kg/m^2) (sd)	30.3 (5.3)	30.8 (6.1)	29.2 (4.8)	0.103	30.4 (6.1)	31.0 (5.7)	31.1 (6.3)	0.073
Alcohol consumption†				0.553				0.308
<3 glasses/day	4,595 (76.0)	1,301 (76.9)	133 (78.7)		2,375 (94.8)	664 (94.7)	108 (91.5)	
≥3 glasses/day	1,450 (24.0)	390 (23.1)	36 (21.3)		131 (5.2)	37 (5.3)	10 (8.5)	
HbA1c (mmol/mol) (sd)	46.5 (5.7)	70.3 (14.1)	107.2 (15.2)	<0.001	48.4 (5.8)	78.0 (16.9)	112.5 (16.7)	<0.001
HbA1c (%) (sd)	6.4 (0.5)	8.6 (1.3)	11.9 (1.4)	<0.001	6.6 (0.5)	9.3 (1.5)	12.5 (1.5)	<0.001
SBD (mm Hg) (sd)	138.5 (17.3)	138.8 (18.5)	137.2 (17.7)	0.460	138.2 (18.7)	139.8 (19.2)	135.3 (17.4)	0.321
DBP (mm Hg) (sd)	80.5 (9.8)	81.7 (10.6)	82.3 (10.3)	0.003	80.3 (10.5)	82.6 (10.3)	81.7 (9.8)	0.238
LDL (mmol/mol) (sd)	2.9 (1.0)	3.0 (1.0)	3.3 (1.0)	<0.001	3.2 (1.1)	3.3 (1.1)	3.5 (1.2)	0.954
HDL (mmol/mol) (sd)	1.3 (0.4)	1.1 (0.3)	1.2 (0.3)	<0.001	1.2 (0.4)	1.0 (0.3)	1.1 (0.3)	<0.001
Totaal cholesterol (mmol/mol) (sd)	4.9 (1.1)	5.1 (1.3)	5.4 (1.2)	<0.001	5.3 (1.2)	5.4 (1.3)	5.9 (1.7)	0.003

	Latent trajectories development cohort*				Latent trajectories validation cohort*			
	Stable, adequate glycaemic control	*Improved glycaemic control*	*Deteriorated glycaemic control*	p-value	*Stable, adequate glycaemic control*	*Improved glycaemic control*	*Deteriorated glycaemic control*	p-value
Triglycerides (mmol/l) (sd)	1.9 (1.1)	2.2 (1.4)	2.4 (1.8)	<0.001	2.1 (1.2)	2.6 (1.6)	3.6 (2.9)	<0.001
ACR (mg/mmol) (sd)	2.4 (9.2)	3.8 (12.2)	3.4 (8.4)	<0.001	2.2 (10.3)	2.3 (7.1)	3.7 (12.5)	0.002
Heart failure†				0.901	-	-	-	-
Yes	337 (6.7)	92 (6.5)	8 (5.9)					
No	4,697 (93.3)	1,328 (93.5)	128 (94.1)					
CVD in family†				0.534				0.018
Yes	2,072 (37.8)	591 (38.6)	55 (34.2)		603 (24.0)	189 (27.0)	18 (15.3)	
No	3,409 (62.2)	942 (61.4)	106 (65.8)		1,909 (76.0)	512 (73.0)	100 (84.7)	

*Values are numbers (percentages) unless stated otherwise. Percentages have been rounded and might not total 100.
†Percentages are out of total with recorded values

SBD = systolic blood pressure; DBP = diastolic blood pressure; ACR = albumin-to-creatinine ratio; CVD = cardiovascular disease.

Table 3. Patient feature ranking of the 5-fold cross validation as observed in the development cohort

Ranking	Patient baseline characteristics	Patient feature weight
1	BMI	0.3571
2	HbA1c	0.1571
3	Triglyceridess	0.1148
4	LDL	0.0754
5	Age	0.0749
6	SBP	0.0737
7	ACR	0.0618
8	Sex	0.0142
9	Alcohol consumption	0.0142
10	Smoking	0.0142
11	CVD in family	0.0142
12	Heart failure	0.0142
13	Race	0.0142

SBP = systolic blood pressure; ACR = albumin-to-creatinine ratio; CVD= cardiovascular disease.

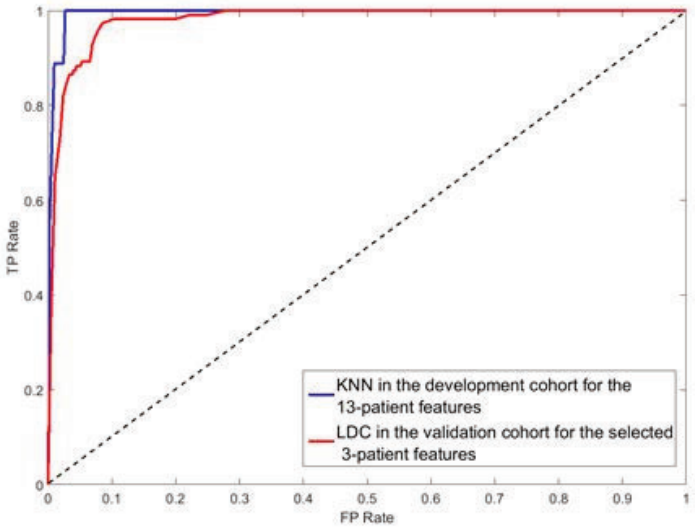

Figure 2. Receiver operating characteristic (ROC) curve of the 13-patient feature prediction model and the 3-patient feature prediction model.
TP = true positive; FP = false positive; KNN = K-nearest neighbor; LDC = Linear discriminant classifier

Discussion

In this retrospective cohort study of patients with newly diagnosed type 2 diabetes treated in primary care, three distinct glycaemic trajectories were identified during the first 5 years after diagnosis: 1) stable, adequate glycaemic control; 2) improved glycaemic control, and 3) deteriorated glycaemic control. Our most important finding was that trajectory membership can be predicted with good to excellent accuracy using no more than three patient characteristics (baseline BMI, HbA1c, and triglycerides). The generalization ability of the model, obtained by training the model on the development cohort and testing it on the validation cohort, was also excellent.

To our knowledge, only two previous studies have examined latent glycaemic trajectories in patients with type 2 diabetes [31, 32]. Both studies identified four glycaemic trajectories, which shared notable similarities with the trajectory patterns we observed in the current study. The similarities between the previous and current studies were most notable for the *stable, adequate glycaemic control* trajectory. In both previous studies, this trajectory was identified and included 83% of their patients, slightly higher than the 72% we found. These results indicate that current practice enables a majority of patients to reach and maintain recommended glycaemic control levels. Our study shows that this group of patients can be identified at diagnosis by applying a model that has a high PPV and NPV.

These findings have important implications for more precision medicine in type 2 diabetes. The main goal of precision medicine is to develop models that can predict disease development or disease outcomes in order to tailor treatment [3]. Our model uses three

relative simple clinical characteristics, BMI, HbA1c and triglycerides to divide patients into three groups, each with different future glycaemic trajectories. Predicting patients' future glycaemic control enables care professionals to provide tailored diabetes management. For patients classified in the stable, adequate glycaemic control group, for example, less intensive monitoring might suffice, whereas patients classified in the deteriorated glycaemic control group could benefit more from frequent monitoring. Previous research suggests that less frequent monitoring of patients with stable, adequate glycaemic control – that is, biannually instead of quarterly check-ups by a GP – is possible without negative effects on health, allowing for considerable cost reductions [33]. More in general, our model enables tailoring of a range of diabetes care components to patients' care needs, including pharmacotherapy, lifestyle advice, and self-management support.

This study is subject to a number of strengths and limitations. In the current study we applied a unique approach by combining LGMM with machine learning techniques. There were three follow-up HbA1c measurements in the development cohort and four in the validation cohort, allowing for the identification of heterogeneity in future glycaemic response. Prescription of glucose lowering drugs and insulin may have influenced the patterns of the trajectories. HbA1c levels in in the stable, adequate- and improved glycaemic control trajectories remained stable or improved, possibly due to an increase in oral- and insulin prescriptions over time. In the deteriorated glycaemic control trajectory, however, HbA1c increased, despite an increase in glucose lowering drugs and insulin prescriptions. Disease progression or difficulties adhering to drug treatment and healthy lifestyle could be explanations for this [34, 35].

The external validation is an important strength of our study, considering that many research findings are based solely on the basis of a single study [36]. A limitation was that both cohorts consisted of a predominantly white population. When compared to whites, other races tend to have higher HbA1c values [37], and their inclusion might have resulted in glycaemic control trajectories that differ in size and shape. One of the previous studies that examined latent glycaemic control trajectories [31], included a mixed-race population, with approximately 50% non-whites. However, as stated before, the identified trajectories in this study are similar to the trajectories in the current study.

So far, predictive models and tools based on machine learning techniques have not been widely used in clinical decision support systems [38]. One of the reasons could be that data obtained from EHRs are considered a byproduct of health care delivery, rather than a resource to improve its performance [39]. Besides, most machine learning models are complex and difficult to interpret, since they heavily depend on aspects related to feature distribution, data availability, and data representation [40]. In the current study we built and validated a simple and interpretable algorithm with excellent accuracy. Despite the high PPV and NPV in the stable, adequate glycaemic control trajectory, the PPV in the deteriorated glycaemic control trajectory was only 45.8% in the validation cohort. This implies that more than half the patients classified in this trajectory do not belong there (false positives), which is a point for

further refinement. The counterpart is that the NPV is high, implicating that membership of this trajectory can be ruled out with high certainty.

In conclusion, only three patient characteristics (BMI, HbA1c and triglycerides) are needed to accurately predict glycaemic response of patients with newly diagnosed type 2 diabetes. The model can be used in practice as a quick, easy and accurate tool to determine patients' care needs and provide tailored diabetes treatment.

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Supplementary Material:

Detailed description analysis

Latent growth mixture modeling

Latent growth mixture modeling (LGMM) was used to systematically identify latent trajectories of glycemic control. This method allows for the clustering of patients into an optimal number of growth trajectories. [1] Most of the missing data is assumed to be unrelated to the outcome variable HbA1c (missing at random (MAR)). [2] Consequently, full information maximum likelihood (FIML) was used as a missing data estimation approach. [3] FIML requires the missing values to be MAR. A protocol, recommended by others, [4, 5] was followed to identify the best LGMM model. First, a series of latent class growth analysis (LCGA) models were estimated. LCGA assumes no within class variance, whereas LGMM freely estimates the within class variance. [4] The growth parameter variances across each trajectory in the LCGA models were therefore fixed to zero. Second, LGMM models that allowed for variation in growth parameters were estimated. In both the LCGA and LGMM models the residual variances and the variance-covariance matrix were fixed across classes. Models were rerun with different starting values to ensure that the final class model solution had been converged to the maximum of the maximum likelihood distribution. The best model was determined by comparing the model fits of a progressive number of trajectories. Fit indices included the Akaike Information Criterion (AIC), [6] Bayesian Information Criterion (BIC) [7] and the Lo-Mendel-Rubin-likelihood ratio test (LMR-LRT). [8] Lower values of the AIC and BIC, and/or a significant result on the LMR-LRT indicate a better model fit in terms of the number of trajectories. To determine model classification performance, entropy was used. Higher entropy values indicate a clearer trajectory membership classification. [9] The usefulness and clinical interpretation of each newly added trajectory were also taken into account.

Machine learning classification methods

To develop the prediction model, a 5-fold cross validation was performed in the development cohort. Several machine learning classification methods were used, because there is no consensus on the best performing classifier. [10] Furthermore, a sparse autoencoder (SAE) algorithm [11] was added on top of the row features to determine if this lead to an improved representation of the included features. SAE is a technique which aims to minimize the reconstruction error between the input and the output in an unsupervised way. It is useful at estimating the underlying data distribution. By placing constraints on the network, such as sparsity, the algorithm can learn an interesting structure of the data. One important parameter of the SAE algorithm is the number of considered hidden units (H), which represents the dimensionality of the new feature set. Experiments were performed with several values of the H parameter. Only results with the best H parameter are reported. To examine the generalizability of the developed prediction model, an external validation

was computed in the development cohort. Receiver operating characteristic (ROC) curves were generated to show the discrimination of the models. To examine the agreement between predicted and observed trajectory membership, calibration slopes were produced. Prognostic values (sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV), were also calculated.

Table S1. Average time between diagnosis of type 2 diabetes and HbA1c measurement per follow-up year and the number of patients per follow-up year

	development cohort		Validation cohort	
Year	Average time between diagnosis and HbA1c measurement (years) (sd)	Number of patients (%)	Average time between diagnosis and HbA1c measurement (years) (sd)	Number of patients (%)
1	0.06 (0.1)	10 528	0.06 (0.07)	3777
2	1.02 (0.13)	4600 (44.8)	0.92 (0.14)	2428 (72.8)
3	2.01 (0.14)	3244 (30.8)	1.91 (0.11)	1935 (51.2)
4	3.01 (0.14)	2245 (21.3)	2.90 (0.11)	1490 (39.4)
5	-	-	3.90 (0.11)	1023 (27.1)

Table S2. Development cohort fit indices using latent class growth analyses (LCGA) and latent growth mixture modeling (LGMM) with intercept and slope growth parameters estimated (n=10.258)

	Loglikelihood	AIC	BIC	Entropy	LMR	Cases per class (%)
LCGA						
1-class	-79 382	158 778	158 829	-	-	100
2-class	-76 810	153 643	153 723	0.955	<0.0001	90/10
3-class	-75 879	151 789	151 898	0.870	<0.0001	82/10/8
4-class	-75 321	150 680	150 818	0.862	<0.0001	77/13/7/3
5-class	-74 872	149 790	149 957	0.754	0.0256	61/25/7/4/3
6-class	-74 673	149 401	149 597	0.771	0.1936	60/26/7/3/3/1
LGMM						
1-class	-77 787	155 600	155 694	-	-	100
RI = c1						
RLS = c1						
2-class	-74 685	149 409	149 547	0.866	0.0003	85/15
RI = c1 & c2						
RIS = c1 & c2						
RQS = c2						
3-class	-73 355	146 758	146 933	0.758	<0.0001	72/25/3
RI = c1, c2 & c3						
RLS = c1 & c2						
RQS = c2						
4-class	-73 159	146 381	146 606	0.771	0.1215	68/25/7/1
RI = c1, c2, c3 & c4						
RLS = c1, c2 & c4						
RQS = c2 & c4						

Unless specified, all other growth parameter variances were fixed at zero. LCGA: latent class growth analyses; LGMM: latent growth mixture modeling; c1 = class 1; c2 = class 2; c3 = class 3; c4 = class 4; RI: random intercept; RLS: random linear slope, RQS: random quadratic slope AIC: Akaike's information criteria; BIC: Bayesian information criteria; LMR: Lo-Mendell-Rubin likelihood ratio test.

Table S3. Intercept and slope growth parameters in each latent class in the 3-class models of the development – and validation cohorts

	Development cohort (ZODIAC)				Validation cohort (ZIO)			
			95% CI				95% CI	
	B	**SE**	**Lower**	**Upper**	**B**	**SE**	**Lower**	**Upper**
1. Glycemic deterioration								
Intercept (mean)*	96.0	7.1	82.2	110.0	107.9	7.2	93.8	122.0
Slope (mean) *	-122.9	3.7	-130.2	-115.6	-118.9	8.5	135.5	-102.1
Quadratic term (mean) *	25.6	0.9	23.8	27.4	22.0	2.3	17.5	26.5
2. Insufficient glycemic control								
Intercept (mean) *	66.3	3.3	59.7	72.8	73.9	2.3	69.4	78.4
Slope (mean)*	-25.1	1.6	-28.2	-22.0	-24.6	1.4	-27.3	21.9
Quadratic term (mean) *	4.3	0.3	3.7	4.9	3.4	0.2	3.0	3.8
3. Sufficient glycemic control								
Intercept (mean) *	46.5	0.4	45.7	47.3	48.2	0.3	47.6	48.8
Slope (mean) *	-3.0	0.2	-3.4	-2.6	-2.6	0.2	-3.0	-2.2
Quadratic term (mean) *	0.6	0.04	0.5	0.7	0.3	0.03	0.2	0.4

*significant at the p<0.05 level.

Table S4. Validation cohort fit indices using latent class growth analyses (LCGA) and latent growth mixture modeling (LGMM) with intercept and slope growth parameters estimated (n=3.337)

	Loglikelihood	AIC	BIC	Entropy	LMR	Cases per class (%)
LCGA						
1-class	-38 874	77 765	77 814	-	-	100
2-class	-37 885	75 794	75 867	0.901	0.0022	90/10
3-class	-37 474	74 981	75 079	0.743	0.0866	71/25/4
4-class	-37 147	74 335	74 457	0.787	0.0267	68/24/5/3
5-class	-36 956	73 960	74 107	0.762	0.3827	57/33/5/4/1
LGMM						
1-class	-37 604	75 230	75 297	-	-	100
RI = c1						
RLS = c1						
RQS =c1						
2-class	-36 122	72 283	72 400	0.815	<0.0001	75/25
RI = c1 & c2						
RLS = c1 & c2						
RQS =c1 & c2						
3-class	-35 963	71 979	72 137	0.827	0.0005	72/24/4
RI = c1, c2 & c3						
RLS = c1 & c2						
RQS =c1 & c2						
4-class	-35 879	71 824	72 026	0.842	0.0009	71/24/4/1
RI = c1, c2, c3 & c4						
RLS = c1,c2 & c4						
RQS =c1, c2 & c4						
5-class	-35 834	71 749	71 993	0.822	0.0414	70/22/4/4/1
RI = c1, c2, c3, c4 & c5						
RLS = c1,c2, c4 & c5						
RQS =c1, c2, c4 & c5						
6-class	-35 812	71 718	72 006	0.811	0.5481	69/20/5/3/2/1
RI = c1, c2, c3, c4, c5 & c6						
RLS = c1,c2, c4, c5 &c6						
RQS =c1, c2, c4, c5 & c6						

Unless specified, all other growth parameter variances were fixed at zero. LCGA: latent class growth analyses; LGMM: latent growth mixture modeling; c1 = class 1; c2 = class 2; c3 = class 3; c4 = class 4; c5 = class 5; c6 = class 6; RI: random intercept; RLS: random linear slope, RQS: random quadratic slope AIC: Akaike's information criteria; BIC: Bayesian information criteria; LMR: Lo-Mendell-Rubin likelihood ratio test.

Table S5. Correlations between SBP, DBP, lipid profile features and CDV features

	SBP	DBP	LDL-c	HDL-c*	Total cholesterol	TG*	Heart failure	CVD in family
SBP	-	**0.504*** **	0.082	0.059	0.104	0.032	-0.049	-0.028
DBP	**0.504*** **	-	0.123	0.136	0.145	0.136	-0.126	0.031
LDL-c	0.082	0.123	-	0.089	**0.902**	0.124	-0.050	-0.039
HDL-c	0.059	0.136	0.089	-	0.194	**-0.426*** **	-0.053	-0.056
Total cholesterol	0.104	0.145	**0.902*** **	0.194	-	0.323	-0.049	-0.032
TG*	0.032	0.136	0.124	**-0.426*** **	0.323	-	0.011	0.054
Heart failure	-0.049	-0.126	-0.050	-0.053	-0.049	0.011	-	0.032
CVD in family	-0.028	0.031	-0.039	-0.056	-0.032	0.054	0.032	-

*Not normally distributed = Spearman correlation coefficient (all other variables are normally distributed = Pearson correlation coefficient)

***significant at the p<0.01 level

SBD = systolic blood pressure; DBP = diastolic blood pressure; LDL-c = LDL cholesterol; HDL-c = HDL cholesterol; TG = triglycerides; CVD = cardiovascular disease.

Table S6. Accuracy of different machine learning classifiers of the prediction of glycemic control trajectories in the development cohort using 13 patient features

	Fisher	KNN	Parzen	QDC	LDC	SVM	SVM (RBF)	Logistic Regression	Stacked SVM
Accuracy (%)	79.73	**92.28**	89.77	90.86	91.66%	75.98	75.98	91.43	81.43

KNN = K-nearest neighbor; QDC = quadratic discriminant classifier; LDC = linear discriminant classifier; SVM= supper vector machine; RBF = radial basis function.

Table S7. Sensitivity, specificity, PPV, NPV of the 13-patient feature model as observed in the development cohort

	Trajectories		
	Stable, adequate glycemic control	**Improved glycemic control**	**Deteriorated glycemic control**
Sensitivity (%)	98.3	78.4	81.3
Specificity (%)	81.2	97.8	99.4
PPV (%)	94.7	78.4	78.0
NPV (%)	93.7	94.2	99.5

PPV = positive predictive value;
NPV = negative predictive value.

Table S8. Accuracy of different machine learning classifiers of the prediction of glycemic control trajectories in the validation cohort using 3 patient features

	Fisher	KNN	Parzen	QDC	LDC	Logistic Regression
Accuracy	81.11%	91.46%	91.86%	90.96%	**92.00%**	**92.00**%

KNN = K-nearest neighbor; QDC = quadratic discriminant classifier; LDC = linear discriminant classifier; SVM= supper vector machine.

Table S9. Sensitivity, specificity, PPV, NPV of the 3-patient feature model as observed in the validation cohort

	Trajectories		
	Stable, adequate glycemic control	**Improved glycemic control**	**Deteriorated glycemic control**
Sensitivity (%)	99.1	67.9	87.4
Specificity (%)	85.3	98.6	95.8
PPV (%)	96.1	92.9	45.8
NPV (%)	96.1	91.9	99.4

PPV = positive predictive value;
NPV = negative predictive value.

Figure S1. Estimated means and the observed individual trajectories per trajectory of the final model of the development cohort
A = stable, adequate glyemic control trajectory; B = improved glycemic control trajectory; C = deteriorated glycemic control trajectory.

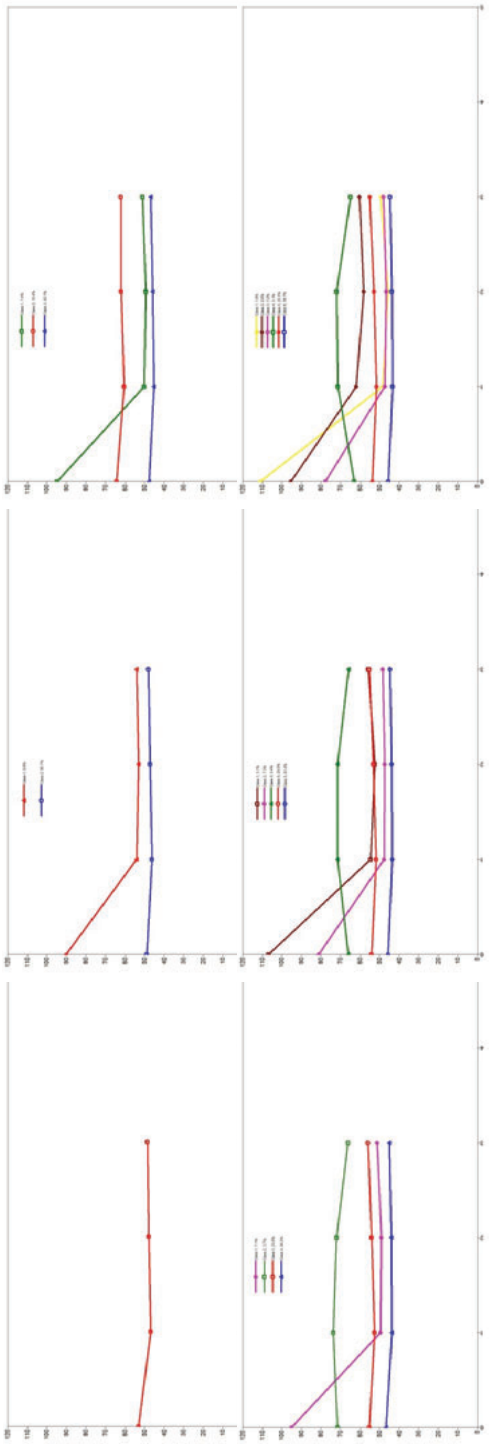

Figure S2. Latent class growth trajectories of the models of the development cohort identified by LCGA using a linear and quadratic term.

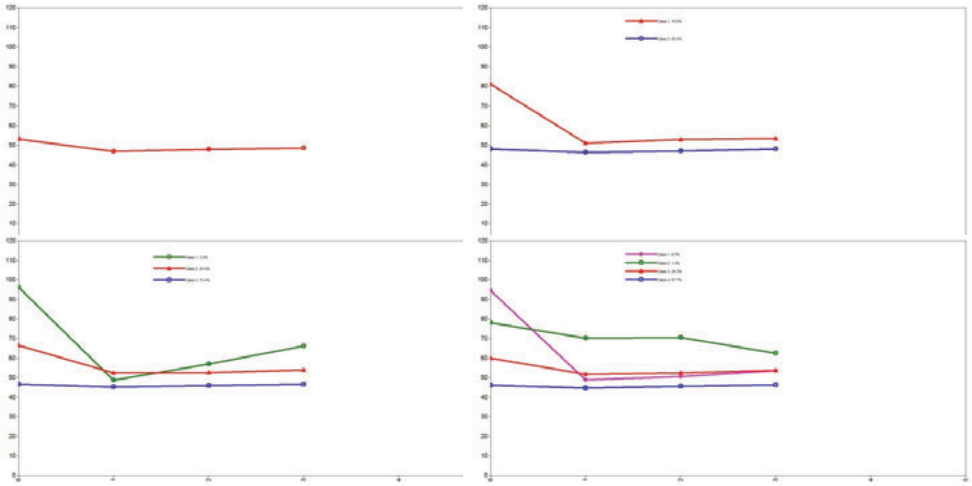

Figure S3. Latent class growth trajectories of the models of the development cohort identified by LGMM.

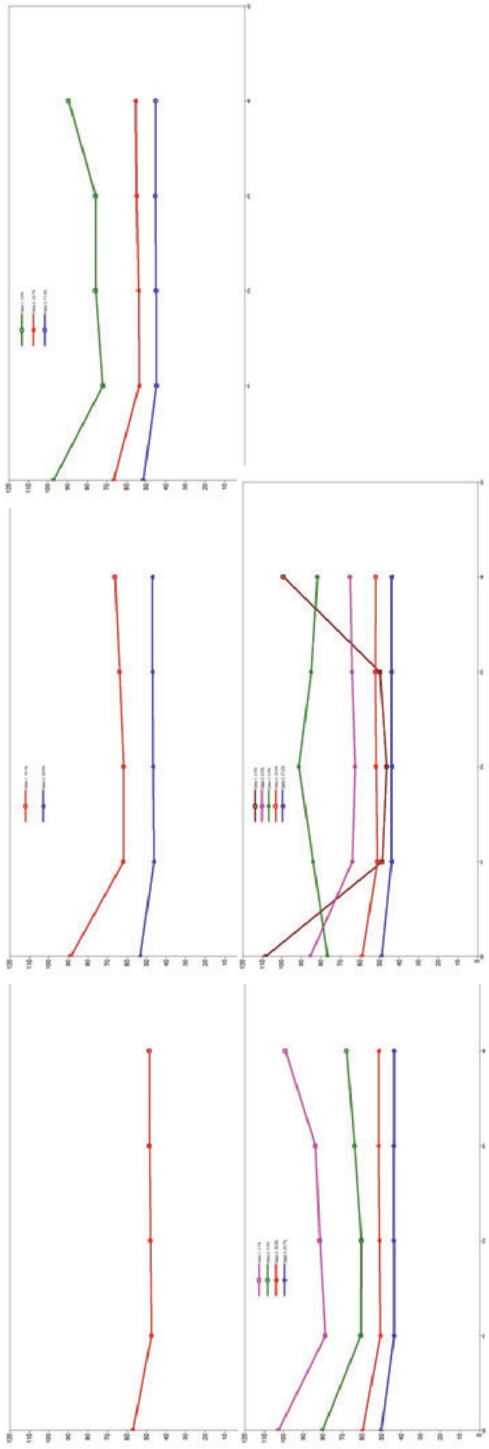

Figure S4. Latent class growth trajectories of the models of the validation cohort identified by LCGA using a linear and quadratic term.

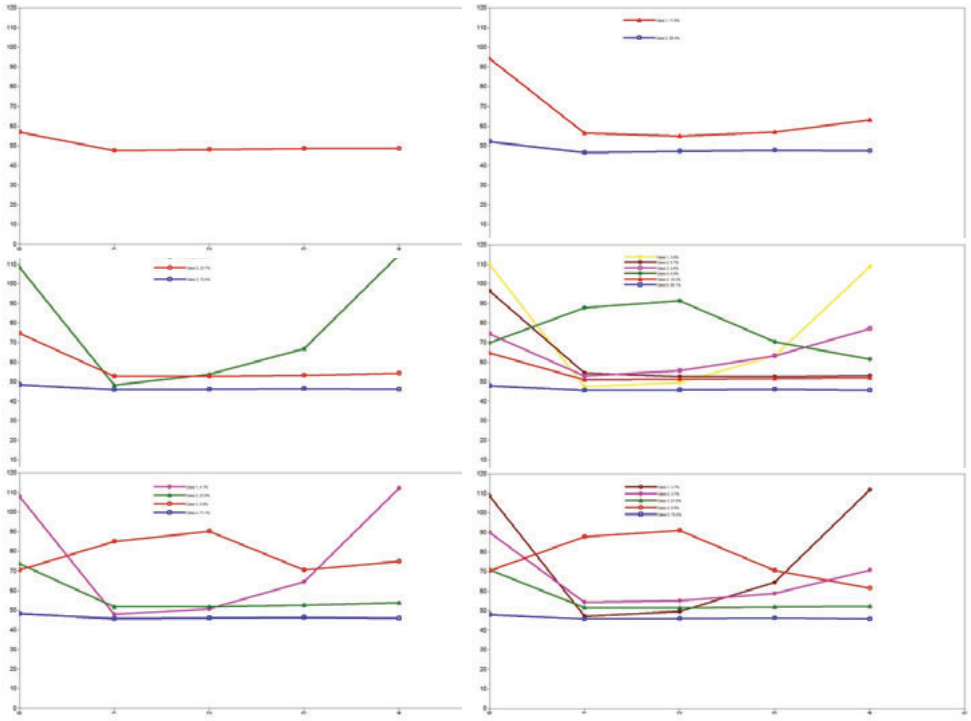

Figure S5. Latent class growth trajectories of the models of the validation cohort identified by LGMM.

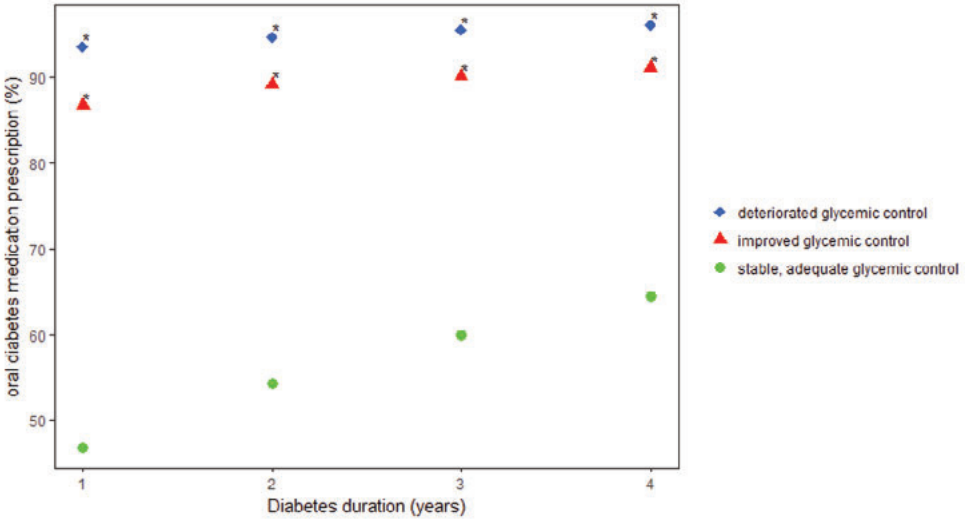

Figure S6. Yearly prescriptions of glucose lowering drugs per trajectory
*significant at the p<0.0001 compared to the stable, adequate glycemic control trajectory.

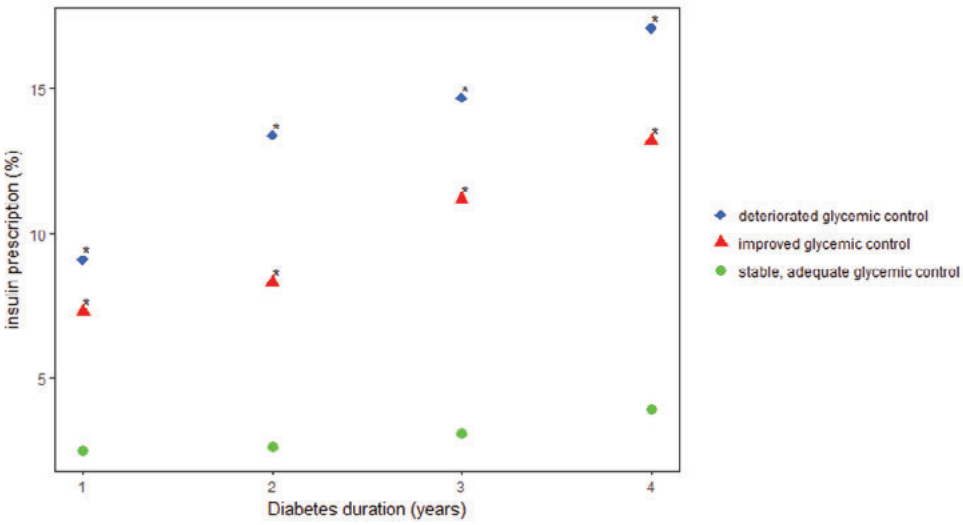

Figure S7. Yearly prescriptions of insulin per trajectory
*significant at the p<0.0001 compared to the stable, adequate glycemic control trajectory .

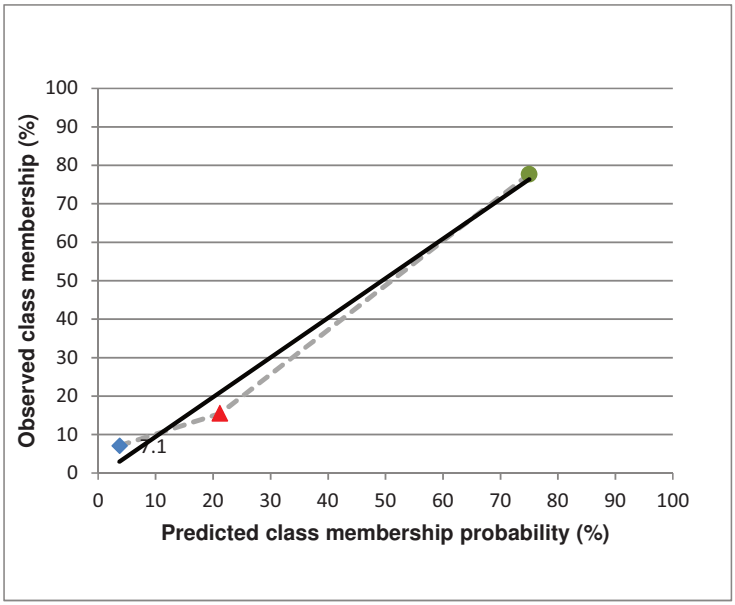

Figure S8. Calibration plot of the 3-patient feature prediction model as observed in the validation cohort ◆ Deteriorated glycemic control trajectory; ▲ improved glycemic control trajectory; ● stable, adequate glycemic control trajectory.

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CHAPTER 6

Relevant patient characteristics for estimating healthcare needs according to healthcare providers and people with type 2 diabetes: a Delphi survey

Under review as:

D.F.L. Hertroijs, M.C.G.J. Brouwers, A.M.J. Elissen, N.C. Schaper & D. Ruwaard. Relevant patient characteristics for estimating healthcare needs according to healthcare providers and people with type 2 diabetes: a Delphi survey.

Abstract

Background: Recently, there has been growing interest in providing more tailored, patient-centered care for the treatment of type 2 T2DM mellitus (T2DM). Yet it remains unclear which patient characteristics should be determined to guide such an approach. Therefore, the opinions of healthcare providers (HCP) and people with T2DM about relevant patient characteristics for estimating healthcare needs of people with T2DM were assessed and compared.

Methods: Two separate online Delphi studies were conducted according to the RAND-UCLA Appropriateness Method: one with HCPs (n=22) from Dutch primary and secondary care and one with people with T2DM treated in Dutch primary care (n=46). The relevance of patient characteristics for estimating healthcare needs, defined as the number of yearly consultations, was assessed on a 5-point Likert scale. Characteristics with a median of 4 or 5 and an interquartile range ≤1.5 were considered relevant with consensus. Participants were also asked to select the top 5 of most relevant patient characteristics. To determine the overall top 5, the mean relative importance score of each characteristic was calculated.

Results: In two Delphi rounds, 28 and 15 patient characteristics were rated by HCPs and people with T2DM, respectively. Both HCPs and people with T2DM found health-related characteristics relevant for estimating healthcare needs of people with T2DM. However, HCPs preferred to estimate healthcare needs using person- and context-related characteristics. They ranked self-efficacy as the most relevant estimator. In contrast, people with T2DM were more in favor of health-related characteristics and ranked HbA1c as the most relevant estimator.

Conclusions: The findings show that there is discrepancy in opinions on relevant patient characteristics for estimating healthcare needs between HCPs and people with T2DM. To achieve more tailored, patient-centered care, it is important that both groups agree on the topics to be discussed during patient consultations.

Background

Type 2 mellitus (T2DM) is one of the most prevalent chronic conditions and a worldwide public health priority [1, 2]. In Europe, an estimated 59.8 million individuals suffer from T2DM. This number is expected to rise to 71.1 million by the year 2040, largely due to the aging of Europe's population [1, 2]. People with T2DM are at high risk for developing complications, such as cardiovascular disease and kidney failure, which in turn lead to increased healthcare costs [2, 3]. Maintaining a good glycemic-, blood pressure-, and lipid control could prevent these complications [4, 5].

A large proportion of T2DM care is based on self-management, which is defined as the active participation of people with T2DM in their treatment [6]. In accordance with evidence-based care protocols for T2DM treatment, people with T2DM regularly visit healthcare providers (HCP) who should assist them in obtaining the knowledge and skills to self-manage their disease with confidence (e.g. day-to-day blood glucose monitoring, medication intake and lifestyle adjustment) [7, 8]. Adhering to these behaviors has been positively correlated with glycemic control [9, 10]. However, the guidelines for T2DM treatment are usually highly standardized, resulting in differential treatment effects [11, 12]. This indicates a need for more patient-centered care, in which patient characteristics are used to predict the healthcare needs of people with T2DM and to adjust care, including self-management education and support, accordingly. Recently, there has been growing interest in providing patient-centered care for the treatment of T2DM [13-15]. Thus far, it is unclear which patient characteristics should be identified to implement such an approach. Several studies have pointed towards psychosocial characteristics, such as self-esteem, self-efficacy and quality of life to tailor care [16, 17], whereas others emphasize the relevance of biomedical characteristics, such as body mass index (BMI) and HbA1c [18, 19].

As a first step towards more patient-centered care for people with T2DM, the Dutch PROFILe (PROFiling people with type 2 diabetes healthcare needs to support Integrated, person-centered models for Long-term disease management) project started in 2014. PROFILe aims to develop, validate and test so-called 'patient profiles' as an instrument for tailored T2DM management in practice [20]. Based on the assessment of patient characteristics, people with T2DM with similar healthcare needs, preferences and abilities can be stratified into the appropriate profile, for which optimal combinations of professional-led care and self-management support can be developed. To identify relevant patient- and disease individual characteristics a systematic literature review was conducted [21] and the associations of 38 of such characteristics with HbA1c were analyzed using cross-sectional data of people with T2DM [17]. Furthermore, the electronic health records of people with T2DM were used to identify latent glycemic control trajectories, which are unobserved trajectories that capture the glycemic control of individuals, and to build a model that predicts these trajectories using patient- and disease individual characteristics [22]. Another, more qualitative approach is to gain insight into the opinions of HCPs and people with T2DM regarding this subject. To achieve true translational research, it is important to include the voices of HCPs and people with T2DM

in research due to their experiential knowledge [23]. Therefore and within the context of the PROFILe project, the objective of this study was to assess and compare the opinions of HCPs and people with T2DM about relevant patient characteristics for estimating healthcare needs in primary care.

Methods

Participants

Two separate Delphi studies were conducted: one with HCPs and one with people with T2DM.

The first Delphi study was conducted from September through October 2016 and included a purposive and representative sample of HCPs (general practitioners, practice nurses [who support the general practitioner in primary care], specially trained diabetes nurses, dieticians, internists, psychologists and pharmacists) recommended in the care protocols to be part of the multidisciplinary care team for the treatment of T2DM. The authors composed a list of HCPs (n=20) from their own network who treat or used to treat people with T2DM in the Dutch healthcare system and/or have extensive knowledge on the organization of T2DM care in the Netherlands. These HCPs were asked to participate and to recommend colleagues (n=6) who might be willing to participate as well. Furthermore, the Dutch Professional Association of T2DM Care Providers (EADV) and the Dutch Dietician Nutrition Organization (DNO) were contacted for recommendations on HCPs interested in participation (n=8). In total, 34 HCPs were invited to participate.

The second Delphi study focused on people with T2DM with a diagnosis of T2DM and took place between June and August 2017. For the recruitment of people with T2DM, we contacted one general practitioner with a practice in the north of the Netherlands in which 109 people with T2DM were treated. People with T2DM who also had a diagnosis of dementia were excluded from participation, all other people with T2DM were asked if they were willing to participate.

Procedure

Both Delphi studies were conducted according to the RAND/UCLA appropriateness method and consisted of two rounds [24].

First round

In the first round, participants (i.e. both HCPs and people with T2DM) received a survey which consisted of questions rating the relevance of patient characteristics for estimating the healthcare needs of people with T2DM on a Likert scale ranging from 1 (totally irrelevant) to 5 (extremely relevant). Healthcare needs was defined as the number of yearly consultations needed with a general practitioner and/or practice nurse. Besides rating each characteristic, participants were asked for their opinion on why they considered certain patient characteristics to be more or less relevant for estimating healthcare needs. They were also asked to select the top 5 of most relevant patient characteristics for estimating healthcare

needs and to report other characteristics that they found relevant, but were not included in the survey. A questionnaire on demographic characteristics of the participants was also included.

Second round

In the second round, participants received a summary of the results of all partaking individuals in the first round. This allowed them to re-assess their original opinion about the level of relevance of characteristics on which no consensus was reached between participants.

Next, participants were asked to rate the importance of the characteristics with no consensus and, if any, of the characteristics that were added by the participants in the first round. They were again asked to report the top 5 of most important characteristics for estimating healthcare needs.

Characteristics

Healthcare provider survey

The healthcare provider survey of the first round was composed of 18 characteristics that were found to be associated with or able to predict glycemic control in previously conducted empirical research [17, 21, 22]. To structure these characteristics, they were divided into the three categories of the Anderson and Newman model assumed to be predictors of health services use: person-, context- and health-related patient characteristics[25]. In the person-related category, age, sex and self-efficacy were included. Two context-related characteristics were analyzed: income and educational level. Characteristics included in the health-related category were: HbA1c, systolic blood pressure, LDL-cholesterol, triglycerides, BMI, cardiovascular disease, nephropathy, retinopathy, neuropathy, T2DM duration, T2DM medication, diabetes-related distress and quality of life. The HCP survey of the second round included characteristics of which no consensus was reached in the first round and characteristics that were added by the HCPs in the first round, if any.

Patient survey

To improve understandability we included similar, but fewer characteristics in the patient survey of the first round compared to the healthcare provider survey. Except for HbA1c and BMI (which was named ‘weight’ in the patient survey), all other health-related characteristics were excluded from the survey, because we felt that not all people with T2DM would be able to understand the meaning of these characteristics. The T2DM-related complications nephropathy, retinopathy, neuropathy and cardiovascular disease were simplified by summarizing them in one characteristic called ‘having other diseases’. In addition, we added the top 5 of most relevant characteristics for estimating healthcare needs as rated by HCPs to the patient survey, but only if we felt people with T2DM would understand the meaning of these characteristics. In total, the patient survey in the first round consisted of 13 characteristics. The patient survey of the second round included characteristics of which no

consensus was reached in the first round and characteristics that were added by the people with T2DM in the first round, if any.

Statistical analyses

Descriptive analyses were conducted to assess the demographic characteristics of the participants. The relevance of the person-, context-, and health-related characteristics for the questions with a 5-point Likert scale was classified into three categories based on median scores: not relevant (median 1-2), uncertain (median 3) and relevant (median 4-5). To determine the level of consensus between participants, the interquartile range (IQR) was calculated for each characteristic. An IQR≤1.5 was considered as consensus, meaning that at least 50% of all ratings are situated within 1.5 points around the median rating of the participants [26]. Characteristics with a median of 3 and/or an IQR >1.5 in the first round were considered not relevant and presented again in the second round.

To determine the overall top 5 of most relevant characteristics for estimating healthcare needs of both Delphi studies, each characteristic was awarded points based on the top 5 placement of each individual. A characteristic that was considered as most relevant by an individual received 5 points, the second most relevant characteristic 4 points, etc. The mean relative importance score of each characteristic was assessed by dividing the total awarded points for each characteristic by the total number of participants included in each Delphi study.

All analyses were performed using R Studio version 1.0.153.

Results

First, the results of the Delphi study with HCPs are given, followed by the results of the Delphi study with people with T2DM and finally the outcomes of both Delphi studies are compared.

Healthcare providers

Demographic characteristics HCPs

In total, 23 of the 34 (67.6%) invited HCPs agreed to participate. One healthcare provider did not complete the first survey round and was therefore excluded; twenty-two HCPs completed all Delphi rounds. Demographic characteristics of the HCPs are shown in Table 1. Mean age was 51.4 years (SD 9.5), 14 HCPs (63.6%) were female and the median period of professional experience was 15 years (range 1-35).

Table 1. Characteristics of healthcare providers who responded to the survey (n=22)

Characteristic	N
Sex n (%)	
Female	14 (63.6)
Male	8 (36.3)
Age, mean (sd)	51.4 (9.5)
Profession n (%)	
General practitioner	4 (18.1)
Practice nurse	4 (18.1)
Diabetes nurse	3 (13.6)
Dietician	6 (27.3)
Internist	3 (13.6)
Psychologist	1 (4.5)
Pharmacist	1 (4.5)
Professional experience in diabetes care, median number of years (range)	15 (1 – 35)
Work setting n (%)	
Primary care	14 (63.6)
Hospital	5 (22.7)
Primary care and hospital	1 (4.5)
Other	2 (9.1)

Delphi rounds 1 and 2 healthcare providers

The results of round 1 in the HCPs are shown in Table 2, 18 characteristics were rated as relevant. Of these, 15 characteristics were considered relevant with consensus (median ≥4, IQR ≤1.5) for estimating healthcare needs. The highest ratings of relevance were observed for self-efficacy and nephropathy. Consensus between participants was not reached for the three characteristics: sex, income and triglycerides. Therefore, these characteristics were presented again in the second Delphi round. There were no characteristics considered irrelevant with consensus. HCPs added the characteristics social support (n=7) (e.g. family relations and living situation) , comorbidities (n=4), cultural background (n=3), lifestyle (n=2), profession (n=2), language barrier (n=2), 'taking responsibility for disease' (e.g. taking medications and following a healthy diet) (n=2), financial situation (n=1), psychological characteristics (n=1) and emotional characteristics (n=1). These were included in the HCP survey of the second round.

In the second round characteristics with no consensus in the first round (n=3) were re-assessed and the characteristics added by HCPs were rated for the first time (Table 2). HCPs reached consensus on the characteristics sex and triglycerides, which they found irrelevant for estimating healthcare needs. Consensus was also reached for income, which they found not relevant for estimating healthcare needs. All characteristics that were added by HCPs were considered relevant with consensus, except for the characteristic profession for which the relevance was found uncertain. Both rounds combined, HCPs rated a total of 28 characteristics.

The top 5 of most relevant patient characteristics according to HCPs consisted of: lifestyle, 'taking responsibility of disease' and social support (context-related characteristics) as well as self-efficacy and health-related characteristic quality of life (person-related characteristics).

Table 2. Results of Delphi round 1 and round 2 for healthcare providers

	Round 1		Round 2	
	Median	**IQR**	**Median**	**IQR**
Person-related characteristics				
Age	4	0		
Sex	3	1	2	1
Self-efficacy	5	1		
Lifestyle			5	1
Taking responsibility for disease			5	1
Context-related characteristics				
Educational level	4	1		
Income	3	1		
Social support			4	1
Cultural background			4	1
Profession			3	1
Financial situation			4	1
Language barrier			4	0
Health-related characteristics				
Quality of life	4	1		
HbA1c	4	0		
Systolic blood pressure	4	0		
LDL-cholesterol	4	1		
Triglycerides	3	1.75	2	1
Body mass index	4	1		
Cardiovascular disease	4	1		
Nephropathy	5	1		
Retinopathy	4	1		
Neuropathy	4	1		
Diabetes duration	4	1		
Diabetes medication	4	0		
Diabetes related distress	4	0		
Co-morbidity			4	1
Psychological characteristics			4	0
Emotional characteristics			4	0

Relevance of characteristics: median 1-2 = not relevant, median 3 = uncertain and median 4-5 = relevant. IQR≤1.5 = consensus, IQR>1.5 = no consensus.
Characteristics with a median of 3 and/or IQR>1.5 in the first round, were presented again in the Delphi survey second round. Characteristics that were added by HCPs in the first round were presented in the Delphi survey in the second round.

People with T2DM

Demographic characteristics people with T2DM

A hundred people with T2DM were invited to participate in the study, of whom 48 agreed (48%). People with T2DM who did not agree to participate had a significantly shorter average T2DM duration compared with people with T2DM who did agree to participate (7.9 vs. 11.7 years, 95%CI: -7.04 - -0.44, p-value = 0.027). Other characteristics did not differ. The first Delphi round was completed by 46 people with T2DM and the second round by 41 people with T2DM. Mean age was 68.8 years (SD 9.9), 25 (54.3%) people with T2DM were female (Table 3).

Table 3. Characteristics of people with T2DM who responded to the survey (n=46)

Characteristic	
Sex n (%)	
Female	25 (54.3)
Male	21 (45.7)
Age, mean (sd)	68.8 (9.9)
Country of birth n (%)	
Netherlands	45 (97.8)
Other	1 (2.2)
Educational level n (%)*	
Higher professional education	9 (20.5)
Middle professional education	7 (15.9)
High School	21 (47.7)
Elementary school/no education	7 (15.9)
Not recorded	2
Diabetes duration, mean years (sd)	11.7 (9.6)
Diabetes medication n (%)	
None	11 (23.9)
Glucose-lowering drugs only	26 (56.2)
Insulin only	2 (4.3)
Glucose-lowering drugs and insulin	7 (15.2)

*percentages are out of total with recorded values

Delphi rounds 1 and 2 people with T2DM

As previously described, similar, but fewer characteristics were included in the patient survey compared with the healthcare provider survey. In addition, we added the top 5 of most relevant characteristics for estimating healthcare needs as rated by HCPs to the patient survey, except for lifestyle and 'taking responsibility for disease', because we felt people with T2DM would confuse these with weight and self-efficacy, respectively. In total, people with T2DM rated 13 characteristics in the first Delphi round (Table 4). Eight characteristics were considered relevant with consensus. Consensus between people with T2DM was not reached about the relevance of age, sex, income and social support. Therefore, these characteristics were presented again in the second Delphi round. Educational level was considered irrelevant with consensus for estimating healthcare needs. People with T2DM added the characteristics genetics and insecurity/fear to the final Delphi round.

People with T2DM rated six characteristics in the second Delphi round. Sex was considered irrelevant with consensus. No consensus was reached on the remaining five characteristics (Table 4). Both rounds combined, people with T2DM rated a total of 15 characteristics.

The top 5 of most relevant patient characteristics according to people with T2DM consisted of: HbA1c, T2DM medication, quality of life and co-morbidities (health-related characteristics) as well as self-efficacy (person-related characteristic).

Table 4. Results of Delphi rounds 1 and 2 for people with T2DM

	Round 1		Round 2	
	Median	**IQR**	**Median**	**IQR**
Person-related characteristics				
Age	2	2	3	2
Sex	2	1.75	2	1
Self-efficacy	4	1		
Context-related characteristics				
Educational level	2	1		
Income	2	2	2	2
Social support	3	2	3	2
Health-related characteristics				
Quality of life	4	1		
HbA1c	4	0		
Weight	4	0.75		
Diabetes duration	4	1		
Diabetes medication	4	1		
Diabetes related distress	4	1		
Comorbidity	4	1		
Genetics			4	2
Insecurity/fear			3	2

Relevance of characteristics: median 1-2 = not relevant, median 3 = uncertain and median 4-5 = relevant. IQR≤1.5 = consensus, IQR>1.5 = no consensus.

Characteristics with a median of 3 and/or IQR>1.5 in the first round, were presented again in the Delphi survey second round. Characteristics that were added by HCPs in the first round were presented in the Delphi survey in the second round.

Comparison between HCPs and people with T2DM

Of the total set (n=30) of unique characteristics included across the two surveys, 28 were rated by HCPs and 15 by people with T2DM. Out of all these characteristics, 13 were rated by both the HCP and the people with T2DM. In both groups, eight of these characteristics achieved consensus for relevance, including all health-related characteristics. Both groups agreed that sex was irrelevant for estimating healthcare needs. There were also some discrepancies between HCPs and people with T2DM on person- and context-related characteristics. HCPs found age, educational level and social support relevant with consensus, but people with T2DM found educational level irrelevant with consensus and were uncertain about the usage of age and social support to estimate healthcare needs.

Figure 1 shows the mean relative importance scores of the five most relevant characteristics for estimating healthcare needs according to HCPs (A) and people with T2DM (B). The top 5 according to HCPs mainly consisted of person- and context-related characteristics, whereas for people with T2DM the top 5 mainly consisted of health-related characteristics. HCPs rated self-efficacy as the most relevant patient characteristic with a mean relative importance score of 3.09, whereas people with T2DM rated HbA1c as the most relevant characteristic with a relative mean importance score of 2.11.

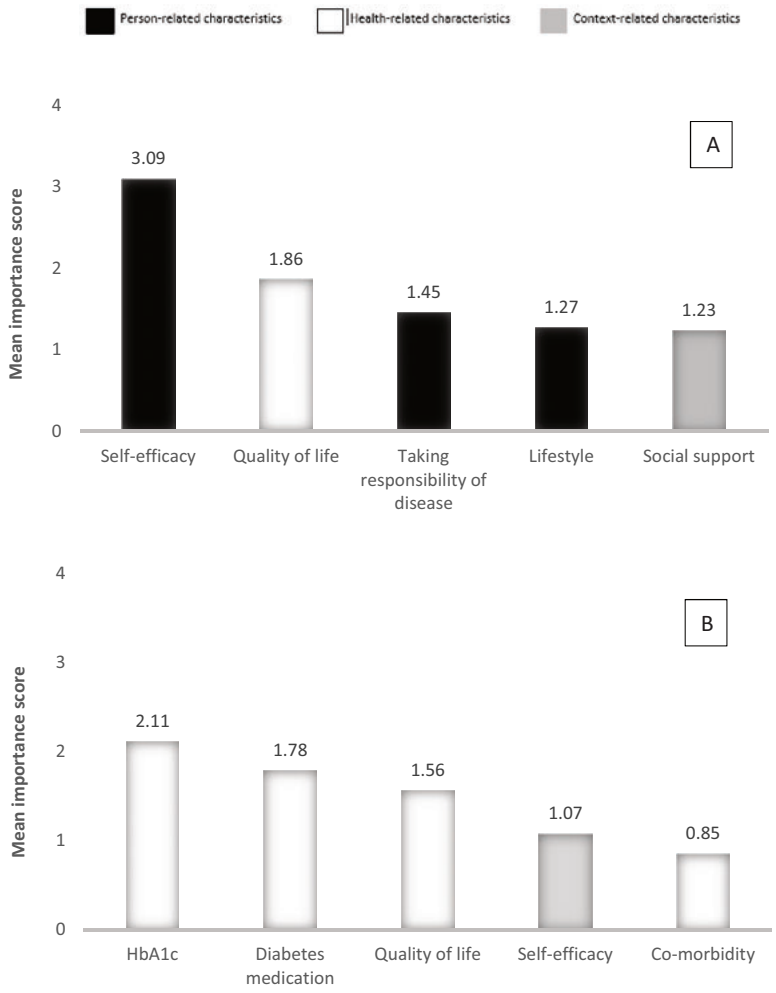

Figure 1. Most relevant 5 characteristics for estimating healthcare needs according to HCPs (A) and people with type 2 diabetes (B).

Discussion

Principal findings

In the present study, HCPs and people with T2DM were asked to give their opinion about the relevance of patient characteristics for estimating healthcare needs of people with T2DM. In two Delphi rounds, 28 and 15 patient characteristics were rated by HCPs and people with T2DM, respectively. Except for triglycerides, genetics and insecurity/fear, all health-related characteristics were found to be relevant with consensus for estimating healthcare needs by both HCPs and people with T2DM.

Discrepancies in opinions between HCPs and people with T2DM were observed for person- and context-related characteristics. HCPs found 75% of these characteristics relevant for estimating healthcare needs, whereas people with T2DM only found 17% relevant. A striking discrepancy was also seen in the top 5 of most relevant patient characteristics for estimating healthcare needs between HCPs and people with T2DM. The top 5 of HCPs mostly consisted of person- and context-related characteristics and they thought that self-efficacy was most relevant for estimating healthcare needs. In contrast, the top 5 of people with T2DM mostly consisted of health-related characteristics and they ranked HbA1c as the most relevant estimator.

Comparison with other studies

Previous research has suggested that more emphasis should be placed on person- and context-related characteristics in the treatment of T2DM [27, 28]. Self-efficacy for example, which was rated as the most relevant characteristic for estimating healthcare needs by HCPs in the current study and defined as an individual's confidence in being able to carry out a behavior, has been associated with lower HbA1c levels and T2DM management- and problem solving behavior [29, 30]. A healthcare provider's knowledge on the self-efficacy of people with T2DM and other person- and context-related characteristics could enhance self-management education –and support and the development of mutually accepted treatment goals, referred to as shared decision making (SDM) [28, 31-34]. Similar to the outcome of the current study, most HCPs agree on such a broad, whole person approach to the treatment of T2DM [35, 36]. However, from the current study it remains unclear whether HCPs practice such an approach. Previous research has shown that HCPs often lack the time, skills and resources to provide self-management education –and support and SDM is not yet embedded in clinical practice [37]. Instead, patient consultations with a healthcare provider seem to focus on clinically orientated issues, such as optimal blood glucose levels [31]. Past qualitative research has shown that people with T2DM were unable to describe the role of the practice nurse beyond clinical checks [38]. They also were not sure what else they could expect from their practice nurse. On the other hand, it could be that HCPs do discuss person- and context-related characteristics during patient consultations, but people with T2DM might be unaware of this or not open to it. These arguments might explain why people with T2DM considered HbA1c as the most relevant characteristic for estimating the healthcare needs of people with T2DM in the current study.

Strengths and limitations

A strength of this study was the unique inclusion of HCPs as well as people with T2DM. A Delphi panel is often referred to as an 'expert panel' and assumed to include professionally and scientifically qualified participants [39]. People with T2DM do not fall under this category. We did, however, decide to include them, because of their relevant knowledge and experience on the topic and because knowing the opinions of both groups can improve the development of patient-centered care. On the other hand, the Delphi method is context free, which could

explain the differences in opinion between HCPs and people with T2DM. We do not know for example, if people with T2DM were trying to see things from the HCPs' perspective, despite the provided instructions that asked them to make their own judgement. In that case, a true qualitative method would have been better to elicit people with T2DM' views.

Given the scale of this study, we decided to only select patients from one primary care practice. This does mean that the included patients all live in the same region and are treated by the same HCPs, which makes it difficult to generalize the results to people with T2DM in other countries and other regions Dutch regions. However, since Dutch general practitioners and especially practice nurses (who treat more patients with diabetes than the GP) strictly adhere to the guidelines for T2DM treatment [40], it is likely that the included patients received T2DM care similar to the care of patients from other primary care practices. Moreover, as patients within the practice differ in terms of which HCP they most frequently see for their T2DM – there is one GP and three practice nurses providing T2DM care – we expect the influence of provider attitude and interpersonal style on patients' opinions to be limited. The included HCPs formed a multidisciplinary Delphi panel. In the Netherlands multidisciplinary cooperation within T2DM teams – comprising not only general practitioners and practice nurses, but also T2DM nurses, dieticians, psychologists and, to a limited extent, internists – forms an important part of T2DM care [41]. They refer people with T2DM to each other and mutually discuss treatment plans. The diversity of our panelists represented the range of HCPs that are involved in the treatment of people with T2DM and their opinions. Only Dutch HCPs were included. We tried to arrange face-to-face meetings with the participants, to allow for more in-depth discussion about the ratings and investigate areas of disagreement. Due to time-constraints of the participants, the decision was made to conduct an online Delphi survey instead. To gain more understanding of the ratings, we did include open questions. Finally, the patient characteristics that were included in the Delphi surveys were derived from studies that were previously conducted as part of the PROFILe project, which included an in-depth systematic literature search [21]. It is, however, possible that we missed relevant patient characteristics for estimating healthcare needs of people with T2DM. Research has, for example, suggested that environmental factors, such as social stratification and political context, have an impact on people's health [28, 42]. These factors are, however, difficult for HCPs and people with T2DM to influence, and were therefore not included in the surveys. Furthermore, participants were given the chance to provide a list of patient characteristics that they found relevant for estimating healthcare needs of people with T2DM and were not included in the survey of the first round.

Clinical implications and future research

The findings of this study complement the results derived from previous empirical research on relevant patient characteristics for estimating healthcare needs. They are important for both HCPs involved in the treatment of people with T2DM and researchers focusing on the development of patient-centered care. The findings suggest that there is discrepancy in opinions on relevant patient characteristics for estimating healthcare needs between HCPs

and people with T2DM. To improve SDM and encourage patient-centered care, it is important that both groups agree on what topics should be discussed during patient consultations. People with T2DM have previously reported that they would like their healthcare provider to show more interest in their life and provide more explanation and involvement in T2DM management, such as providing lifestyle advice and discussing treatment options [31, 38]. Indeed, a recent study on the implementation of a structured T2DM consultation model with a focus on person- and context-related patient characteristics, led to an increase in patient involvement and a substantial number of satisfied people with T2DM [43]. In the current study, HCPs and people with T2DM agreed that self-efficacy and quality of life are relevant patient characteristics for estimating healthcare needs. The measurement of these characteristics should therefore to be included in routine care, for example as part of the intake of people with newly diagnosed T2DM. To save time, people with T2DM could fill in questionnaires that measure these characteristics before their visit with a HCP. Identifying self-efficacy and quality of life in diabetes management allows HCPs to know which aspects of the lives of people with T2DM are most important and which activities they are facing most difficulties with [44]. This has important implications on targeting person-centered education interventions.

Future research should focus on improving the skills and tools HCPs need to take into account patient's person- and context-related patient characteristics and gaining more understanding on the preferences of people with T2DM regarding diabetes care. In the next step of the PROFILe project, a discrete choice experiment will be conducted to elicit preferences of people with T2DM for each of the identified latent glycemic control trajectories [20]. In combination with a consultation model, where person- and context-related characteristics will be discussed, this will enable HCPs to provide patient-centered care by taking into account people with T2DM' care preferences, abilities, - and needs.

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CHAPTER 7

Preferences of people with type 2 diabetes for diabetes care: a discrete choice experiment

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Abstract

Aim: Limited knowledge exists on the preferences of people with type 2 diabetes towards diabetes care. Consequently, these care preferences cannot yet be considered in the development of tailored diabetes care approaches. Therefore, this study aimed to assess care preferences and their determinants in people with type 2 diabetes.

Methods: A discrete choice experiment was conducted to elicit people's preferences. People with type 2 diabetes, treated in 30 Dutch primary care practices, were asked to choose repeatedly between two hypothetical diabetes care packages, which differed in six attributes: role division in daily diabetes care planning, lifestyle education method, type of medication management support, consultation frequency, emotional support, and time spend on self-management. A mixed-logit model was used to estimate the relative importance of the included attributes. Preference heterogeneity among people with different person- and disease-related characteristics was investigated.

Results: In total, 288 participants completed the experiment. They preferred to plan their daily diabetes care together with a healthcare provider, to receive individual lifestyle education, medication- and emotional support from a healthcare provider, one consultation visit every three months, and to spend less time on self-management. Participants did not prefer to receive emotional support from a psychologist. Heterogeneity in preferences could partly be explained by differences in sex, education level and glucose-lowering drug use.

Conclusion: People with type 2 diabetes have a preference for traditional care models. Emotional support was identified as the most important attribute to the participants. It is therefore important to adequately guide them when changes in diabetes care organisation are implemented.

Introduction

In the Netherlands, around one million people (6%) currently live with diabetes of whom approximately 94% have type 2 diabetes [1]. The majority (85%) of them are treated in primary care by a team consisting of a general practitioner and a practice nurse [1-4]. In general, primary care providers strictly adhere to the guidelines from the Dutch college of General Practitioners on type 2 diabetes and the Dutch Diabetes Federation Health Care Standard for type 2 diabetes [3, 5, 6]. These care protocols recommend primary healthcare providers to monitor people with type 2 diabetes two to four times per year, including an annual check-up by the general practitioner.

Internationally, Dutch diabetes care is considered to be of very high quality, mainly due its multidisciplinary approach [5], but it also has its drawbacks. Barring some exceptions for older people, the diabetes guidelines are highly standardised [3]. This is in contrast to the NICE guidelines and the latest consensus report by the American Diabetes Association and the European Association for the Study of Diabetes on the management of type 2 diabetes, which are more lenient towards the type of glucose-lowering drugs that are prescribed [7, 8]. Not all people seem to benefit from this 'one-size-fits-all' approach, leading to differential treatment effects [9]. Furthermore, current type 2 diabetes care places a heavy financial burden on society, health systems, individuals and employees [10]. Thus, ways need to be found to provide the right care, to the right person, at the right time, creating more sustainable diabetes care.

There is increasing consensus that patient-centred care, defined as "care that is respectful of and responsive to individual patient care preferences, needs, and values and ensuring that patient values guide all clinical decisions" [11], could prevent the over-, under-, and misuse of diabetes care and improve the management of type 2 diabetes [12]. Patient preferences, defined as what patients want from their healthcare [13], can help healthcare providers and their patients develop mutually accepted treatment goals leading to improved health outcomes [13]. The number of studies on care preferences of people with type 2 diabetes has increased substantially in the past decade [14]. However, most of these studies assessed pharmaceutical care preferences, such as dosing schedule and risk of side effects [15]. Limited knowledge exists on the preferences of people with type 2 diabetes-related to more general treatment attributes, such as the frequency of consultations or emotional support. Consequently, these care preferences cannot yet be considered in the development of tailored diabetes care approaches. Therefore, the first aim of the present study was to assess preferences of people with type 2 diabetes towards the non-pharmaceutical aspects of diabetes care using a discrete choice experiment. Because people often have diverse preferences for health care interventions and preferences tend to change through the course of an illness [16], the second aim was to examine whether these preferences are characterised by heterogeneity, and if so, to what extent this heterogeneity could be explained by relevant characteristics of people with type 2 diabetes.

Participants and methods

Population and study design

Eighty-four primary care practices in Maastricht and surrounding areas, in the south of the Netherlands, received an email asking for permission to invite their patients with type 2 diabetes to participate in the study. Thirty practices were willing to participate. The practices were also asked to provide data from their electronic health register on patients' biomedical characteristics (body mass index, HbA1c, triglycerides, and prescriptions of glucose-lowering drugs) and date of diabetes diagnosis. Subsequently, patients received an invitation via regular mail including a letter containing information about the study, an informed consent document, a discrete choice experiment survey to elicit their preferences, a questionnaire on their background characteristics and a return envelope. One month after the first mailing, a reminder was sent via regular mail to those who had not returned the informed consent document and/or the questionnaires. Data collection took place from October to December 2017. Approval of the study was obtained from the Medical Ethical Committee of the Maastricht University Medical Center (METC 17-04-104).

Discrete choice experiment

A discrete choice experiment is an increasingly used method to elicit participants' preferences in health care [17]. In a discrete choice experiment, participants have to answer a series of choice tasks. Each choice task consists of at least two scenarios with several attributes (e.g. frequency of consultations and emotional support approach) that vary along different levels (e.g. one consultation every six months or yearly consultations). Participants are asked to choose the preferred scenario in each choice task.

Identification of attributes and levels

In this study, a 3-step process was followed to identify the attributes. First, a list of diabetes care attributes was compiled by conducting a literature review on preferences of people towards diabetes care regarding non-pharmaceutical treatment attributes. Second, to complement the attribute list, five telephone interviews with healthcare providers were held. Attributes were identified by asking healthcare providers to describe the steps they take during consultations with people with type 2 diabetes. Third, three focus groups, with four to six participants with type 2 diabetes each, were organized to determine the most important attributes of diabetes care. During the focus groups, the list of previously identified attributes (based on steps 1 and 2) was presented. In addition, participants were asked to name attributes of diabetes care that were not included on the list. The final list consisted of >10 potential attributes for inclusion. However, to ensure that participants were able to consider all attributes listed when making their choice, most discrete choice experiments contain fewer than 10 attributes [18]. To scale back the attribute list, the nominal group technique was used: participants in the focus groups were asked to individually select a top 5 of attributes from the final list [19]. These attributes were awarded points: from 5 points for the most important

attribute to 1 point for the least important attribute. Per attribute, the mean importance score was then calculated by dividing the total awarded points per attribute by the total number of participants in all focus groups. This process led to the inclusion of six attributes (role division in daily diabetes care planning, lifestyle education method, type of medication management support, consultation frequency, emotional support, and time spend on self-management) with three to four levels each (Table 1). The levels were discussed and determined by the researchers (DH, AE and MB), taking into account their clinical plausibility. In a face-to-face pilot study including eight participants with type 2 diabetes, the participants' understanding of the attributes and levels was tested, as well as the task complexity and length of the discrete choice experiment questionnaire. Minor adjustments to some levels of the attributes were made accordingly.

Table 1. Attributes and levels used in the discrete choice experiment

Attribute	Levels
Role division in diabetes care planning	- Person with type 2 diabetes and healthcare provider - Person with type 2 diabetes - healthcare provider only
Lifestyle education method	- Individual education - Group education - Digital education (app or website)
Type of medication management support	- Via healthcare provider - Via aid (app, website, medicine box) - No help
Consultation frequency	- One visit every two months with practice nurse - One visit every three months with practice nurse - One visit every six months with general practitioner - Yearly visit with general practitioner
Emotional support approach	- general practitioner or practice nurse - Psychologist - No emotional support
Time spend on self-management	- 30 minutes - 1 hour - 2 hours

Experimental design

The attributes and levels were combined to construct choice tasks. Ngene was used to create a Bayesian efficient design to maximize the D-efficiency (a summary measure of the variance covariance matrix) of the chosen choice tasks. By incorporating prior information about the preferences of the attribute levels (positive or negative sign) the precision of the estimated parameters for a given number of choice tasks was maximized, thus increasing the statistical efficiency of the design. The prior information was derived from the pilot results. The D-score of our design was 0.16.

Instrumental design

The design contained 30 choice tasks and was blocked into three 10-choice task survey versions. Participants were randomly assigned to one of the three survey versions. In each choice task, participants had to choose between two care plans (A and B). The fourth choice task was repeated at the end of the discrete choice experiment survey to assess the test-retest

reliability of participants' choices. Thus, each participant received a total of 11 choice tasks. Participants who answered less than 50% of the choice tasks were excluded from the analysis. See Fig 1. for an example of a choice task.

Attributes	Care package A	Care package B
Who makes plans for my daily diabetes care?	The patient and HCP	The HCP only
How is lifestyle information provided to me?	Individual education	Group education
How do I receive help to take my medication according to plan?	Via HCP	Via aid (app, website, medicine box)
How often do I go to consultation for my disease?	1 visit per 2 months with PN	Yearly visit with GP
How do I receive emotional support?	Psychologist	No emotional support
How much time do I invest in my disease per day (e.g. physical activity, nutrition, medication)	30 minutes	2 hours
I choose:		
	☐ Care package A	☐ Care package B

Figure 1. Example of a discrete choice experiment choice task. HCP: healthcare provider, PN: practice nurse, GP: general practitioner

Statistical analyses

Participants' characteristics are presented as means (SDs) for continuous variables and counts and percentages for dichotomous variables. Descriptive statistics were performed in R Studio version 1.0.153.

For the discrete choice experiment, a panel mixed-logit model was estimated, allowing for the determination of the mean preferences of the sample. The level of each attribute that was most similar to current guideline-informed diabetes care in the Netherlands was used as the reference attribute parameter. A positive regression coefficient (beta) suggests that participants prefer more of that level within an attribute, whereas a negative coefficient suggests that participants prefer less of that level within an attribute. To determine the relevant importance of each attribute, the relative importance score was calculated based on the difference between the highest and lowest coefficients of each attribute divided by the total amount of these differences. A significant ($p<0.05$) standard deviation (SD) of the attribute levels indicates preference heterogeneity.

In subgroup analyses, preliminary joint models were estimated using interaction terms to investigate potential preference heterogeneity among people with different person and disease-related characteristics. Person-related characteristics included age (<65 years and ≥65 years), sex, and education level (low/medium and high). Disease-related characteristics

included glucose-lowering drugs (diet with or without oral glucose-lowering drugs and insulin with or without oral glucose-lowering drugs), type 2 diabetes duration (recently diagnosed [≤ 5 years] and longstanding [>5 years]), and predicted glycaemic control trajectory (stable, adequate glycaemic control-, improved glycaemic control-, and deteriorated glycaemic control trajectory). Participants' glycaemic control trajectories were predicted using a risk score (including BMI, HbA1c and plasma triglycerides measured +/- 3 months from diagnosis) that was previously developed to stratify people with recently diagnosed diabetes into one of the three glycaemic control trajectories [20]. Due to the low number of participants in the deteriorated glycaemic control trajectory (n=6), this group was not included in the subgroup analysis. Parameters estimated for the interaction terms that are statistically different from zero (5% level) indicate a difference in preference between subgroups. The discrete choice experiment analyses were performed in NLOGIT version 5. For further details regarding the analysis, see the online supplementary file.

Results

Thirty (35.7%) care practices gave permission to invite a total of 929 people with type 2 diabetes. Of these, 24 people had an incorrect address and four lived in Belgium. Thus, 901 people received an invitation (Fig. 2). Of these, 288 participants answered ≥ 50% of the choice tasks. In total, 80% of participants passed the test-retest task. Their preferences did not differ from those who did not pass the test. Therefore, all 288 participants were included in the analyses. The average age of the participants was 67.4 (SD 10.7) years, 65% were men, and more than two thirds (72%) had a low or medium education level. Further characteristics of the population are presented in Table 2.

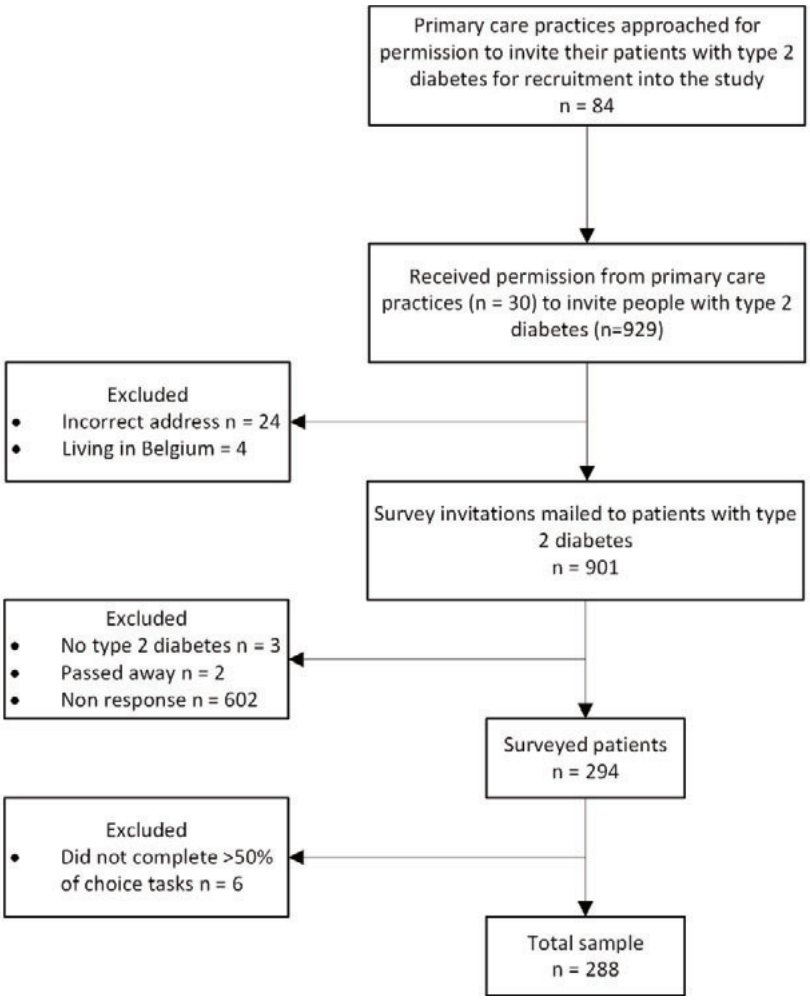

Figure 2. Study flow chart.

Table 2. Demographic and clinical characteristics of the study population

Characteristic	Participants (n=288)
Age, mean (SD)	67.4 (10.7)
Age, n (%)	
≥65 years	168 (58.9)
Missing, n	3
Men, n (%)	187 (64.9)
Missing, n	0
Country of birth, n (%)	
The Netherlands	240 (90.6)
Other	25 (9.4)
Missing, n	23
Education	
Low/medium	188 (72.0)
High	73 (28.0)
Missing, n	27
BMI, kg/m^2, mean (SD)	30.4 (5.0)
Missing, n	0
HbA1c, mmol/mol, mean (SD)	52.0 (10.0)
HbA1c, %	6.8 (3.0)
Missing, n	0
Triglycerides, mmol/L, mean (SD)	2.1 (1.2)
Not recorded, n	1
Diabetes duration, n (%)	
Recently diagnosed type 2 diabetes (≤ 5 years)	174 (60.4)
Longstanding type 2 diabetes (>5 years)	114 (39.6)
Missing, n	0
Diabetes medication, n (%)	
Diet and/or oral glucose-lowering drugs	206 (84.8)
Oral glucose-lowering drugs and insulin	37 (15.2)
Missing, n	45
Glycaemic control trajectory, n (%)	
Stable, adequate glycaemic control	75 (77.3)
Improved glycaemic control	16 (6.0)
Deteriorated glycaemic control	6 (6.2)
Missing, n	191

SD: standard deviation, low/medium education: elementary, preparatory secondary vocational, senior general secondary education or senior secondary vocational education, high education: pre-university , higher professional or academic education, BMI: body mass index.

Diabetes care preferences in the overall population

The results from the panel mixed-logit model are presented in Table 3. Participants showed a preference for planning their daily diabetes care together with a healthcare provider and did not prefer to plan their daily diabetes care by themselves. They preferred individual-based lifestyle education provided by a healthcare provider over group-based lifestyle education. Participants preferred medication management support from a healthcare provider, but not by an aid (i.e. an app, website or medicine box). Of the different possibilities in consultation frequency, participants preferred one visit every three months with a practice nurse. They did

not prefer yearly consultation visits or one consultation every six months with a general practitioner. They preferred receiving emotional support from a general practitioner or practice nurse, but they clearly indicated wanting to avoid emotional support delivered by a psychologist. This attribute had the highest negative beta (-0.68). When deciding on their diabetes care preferences, participants were mostly driven by emotional support (mean relative importance: 25.4%) and frequency of consultations (mean relative importance: 24.2%). The statistically significant standard deviation for all but three attribute levels (digital education, one visit every 2 months with practice nurse, and no emotional support), indicated that there was significant preference heterogeneity within the population.

Subgroup analysis

The subgroup analyses indicated that the observed heterogeneity in the discrete choice experiment was (at least in part) explained by age, sex, education level, and type of glucose-lowering drugs (Supplementary Table 1-6).

Men least preferred planning their daily diabetes care by themselves (β men -0.54 vs β women -0.19; p = 0.016). Preference for having their daily diabetes care planned by a healthcare provider, was also stronger and statistically significant for men compared to women (β men 0.16 vs β women - 0.14; p = 0.012)Participants treated with glucose-lowering drugs had a preference to let their general practitioner plan their daily diabetes care. This preference was stronger for participants treated with insulin (β treated with oral glucose lowering drugs 0.02 vs β treated with insulin 0.23; p = 0.032). Participants treated with insulin also significantly did not prefer to plan their daily diabetes care by themselves to the same degree as participants using oral glucose-lowering drugs (β treated with oral glucose lowering drugs -0.33 vs β treated with insulin -0.85; p = 0.007). In terms of medication management support, participants treated with insulin preferred less not receiving any support, whereas participants treated with oral glucose-lowering drugs were indecisive about their preference for medication management support (β treated with oral glucose lowering drugs 0.02 vs β treated with insulin -0.38; p = 0.021). Participants with a high education level preferred to receive digital lifestyle education, in contrast to participants with low- and medium education levels who least preferred receiving digital lifestyle education (β high education 0.17 vs β low/medium education -0.05; p = 0.030).

No significant differences in preference estimates were found according to age (<65, ≥65), diabetes duration (recently diagnosed, longstanding) and predicted glycaemic control trajectories (stable adequate, improved).

Table 3. Results from the panel mixed logit model

Attribute		Preference estimates		Mean relative importance (%)
		Coefficient	95% CI	
Role division in diabetes care planning				16.3
Person with type 2 diabetes and Healthcare provider (reference)	Mean	0.37	0.13 to 0.61	
	SD	-	-	
Person with type 2 diabetes	Mean	-0.41	-0.54 to -0.28	
	SD	0.55	0.40 to 0.70	
Healthcare provider	Mean	0.04	-0.07 to 0.15	
	SD	0.22	-0.02 to 0.46	
Lifestyle education method				18.1
Individual education (reference)	Mean	0.43	0.23 to 0.63	
	SD	-	-	
Group education	Mean	-0.44	-0.54 to -0.33	
	SD	0.22	0.03 to 0.41	
Digital education	Mean	0.01	-0.09 to 0.10	
	SD	0.11	-0.13 to 0.35	
Type of medication management support				8.5
Via healthcare provider (reference)	Mean	0.22	0.00 – 0.44	
	SD	-	-	
Via aid (app, website, medicine box)	Mean	-0.19	-0.30 to -0.08	
	SD	0.23	0.01 to 0.45	
No help	Mean	-0.03	-0.14 to 0.08	
	SD	0.35	0.17 to 0.52	
Consultation frequency				24.2
One visit every three months with practice nurse (reference)	Mean	0.55	0.13 to 0.97	
	SD	-	-	
One visit every two months with practice nurse	Mean	0.20	0.07 to 0.33	
	SD	0.08	-0.21 to 0.38	
One visit every six months with general practitioner	Mean	-0.15	-0.27 to -0.02	
	SD	0.37	0.15 to 0.58	
Yearly visit with general practitioner	Mean	-0.61	-0.77 to -0.44	
	SD	0.69	0.50 to 0.88	
Emotional support				25.4
General practitioner or practice nurse (reference)	Mean	0.54	0.26 to 0.81	
	SD	-	-	
Psychologist	Mean	-0.68	-0.81 to -0.54	
	SD	0.37	0.20 to 0.54	
No emotional support	Mean	0.14	-0.00 to 0.28	
	SD	0.09	-0.57 to 0.75	
Time spend on self-management*	Mean	-0.004	-0.006 to -0.002	7.5
	SD	0.01	0.009 to 0.01	

CI, confidence interval.* The time spend on self-management attribute was coded as a continuous variable in the choice model. Nevertheless, in the choice tasks it was presented at three possible levels: 30 minutes, 1 hour and 2 hours.

Discussion

In the present study, preferences of people with type 2 diabetes towards diabetes care were investigated using a discrete choice experiment. Our outcomes can be helpful to provide person-centred type 2 diabetes care.

Previous research has shown that people's preferences regarding health care are influenced by their experience of care [21]. In the Netherlands, people seem to be satisfied with the primary health care they receive, with more than 85% of people claiming to have confidence in their general practitioner [22]. It is therefore not surprising that our participants preferred to receive current care, such as one consultation visit per three months. Another reason for the preference towards current care could be that people who receive care do not know what they want beyond what they already know. In past qualitative research, people were unable to describe the role of the practice nurse beyond clinical checks and they indicated not knowing what else they could expect from their practice nurse [23]. Nevertheless, healthcare needs to adapt to the growing number of people with chronic disease by moving from a standardised to a more personalised approach [11, 24]. Previous research has shown that most people with type 2 diabetes are able to maintain adequate glycaemic control when consultations with healthcare providers are reduced [25]. Such changes in diabetes care organisation are needed to keep healthcare sustainable. Taking into consideration that people with type 2 diabetes prefer current care, it is important to discuss these changes with them when implemented.

In the current study, emotional support was identified as the most important attribute. Strikingly, our participants clearly indicated that they did not prefer to receive emotional support from a psychologist, even though mental health problems and type 2 diabetes frequently co-occur [26]. It is possible that the prevalence of mental health problems in the current study was low, because of the relatively low average HbA1c values in this study (i.e. 52 mmol/mol (7%). Hyperglycaemia and mental health disorders are positively correlated [27]. Moreover, care from a general practitioner / practice nurse is viewed as more accessible, more comprehensive, since it manages both physical and mental problems, and less stigmatizing compared to care from a psychologist [28], which might also explain why participants showed a preference for receiving emotional support from a general practitioner or practice nurse.

Participants in this study preferred individual- over group lifestyle education. The few non-pharmaceutical preference studies that have previously been conducted, found the same result [29, 30] . However, literature is indecisive when it comes to the best education method for people with type 2 diabetes [31]. Both individual as well as group education methods have been shown to improve glycaemic control. In this respect, it would be preferable to give patients the option of whether they want to learn individually or in a group.

Participants also preferred one visit every two or three months over one visit every six months. However, it is frequently presumed that due to the digital revolution, face-to-face interactions with Healthcare providers will become less common and exchanges will

increasingly be mediated by electronic devices [32]. Although innovations in e-health technology have the potential to improve access to many types of healthcare services, it needs to be taken into account that connectivity and comfort levels with e-health applications differs between people [33]. Indeed, subgroup analyses in this study revealed that participants with lower education levels had a tendency towards wanting to avoid digital lifestyle education.

Other explanations for the observed preference heterogeneity were sex and type of glucose-lowering drugs. Men and participants treated with insulin had a stronger aversion to planning their daily diabetes care by themselves than women and participants treated with oral glucose-lowering drugs, respectively. For participants treated with insulin, this seems self-evident as insulin use requires more knowledge and skills [34]. A possible explanation for the difference found between men and women could be that more men than women with type 2 diabetes live alone (considering the facts that there are more men than women with type 2 diabetes and that more men than women live alone) [35]. Socially isolated individuals are more prone to have newly diagnosed and prevalent type 2 diabetes [36].

This study has several strengths and limitations. One of the major strengths of our study is the use of a discrete choice experiment to elicit people's preferences. This method takes trade-offs into account, which are difficult to measure in other methods, such as simple rating scale exercises [17]. It has, however, been criticized for being too difficult to understand [37]. This can lead to inaccurate choices that do not reflect true preferences and, as a recent meta-analysis revealed, affect response rates [38], which might have led to selective non-response. Deciding about health-related services is different and more complex than other, more every day decisions, such as where to buy a bike or what to order for lunch. To improve the comprehension of the discrete choice experiment and the precision of the parameter estimates in this study, a face-to-face pilot study was conducted and an explanation on how to complete the choice tasks was provided, as well as an example choice task. In total, 80% of participants passed the test-retest task, which provides an indication that the true preferences of the participants are reflected in this discrete choice experiment. Another strength of our study is the participation of multiple primary care practices. These practices were located in different neighbourhoods, thereby representing patients with various socio-economic backgrounds. However, our study only included participants from the south of the Netherlands. Compared to other parts of the Netherlands, the south has a predominantly Caucasian population. It is therefore unclear to what extent the preferences of the participants in our study represent the preferences of the general population with type 2 diabetes of the Netherlands or elsewhere.

Conclusion

Emotional support was identified as the most important attributes to the participants in this study, followed by frequency of consultations. In future research, it would therefore be interesting to compare diabetes care preferences between people with and without mental health problems. Furthermore, this discrete choice experiment revealed that people with type

2 diabetes prefer to receive the care they currently receive. Therefore, it is important to adequately guide people when changes in diabetes care are implemented to keep healthcare sustainable. Heterogeneity in preferences was detected and could be explained by differences in sex, education level and type of glucose-lowering drugs. This information can be used to tailor type 2 diabetes care by identifying subgroups of people with varying preferences towards type 2 diabetes care. For example, digital lifestyle education could replace some of the consultation visits for people with high education levels, whereas people with lower education levels might benefit more from frequent individual lifestyle education with a healthcare provider. This could potentially lead to more person-centred care.

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Supplementary material

Detailed description analysis

Participant characteristics are presented as means (SDs) for continuous variables and counts and percentages for dichotomous variables. Descriptive statistics were performed in R Studio version 1.0.153.

For the DCE, a panel mixed-logit model was estimated, allowing for the determination of the mean preferences of the sample. A panel mixed-logit model adjusts for within-subject correlation and accounts for unobserved preference heterogeneity by attaching a random component to the model attributes, which allows the model parameters to vary between individuals [1]. A significant ($p<0.05$) standard deviation (SD) of the attribute levels indicates preference heterogeneity. The attribute 'time spend on self-management' was analyzed as a continuous variable, because a linear relationship exists between its levels. All other attributes were included as effects-coded categorical variables assumed to be normally distributed. Effects coding was used to account for nonlinearities [2]. Compared to dummy coding, effects coding codes the reference category -1, so the mean of the attributes is normalized to zero [3]. The level of each attribute that was most similar to current guideline-informed diabetes care in the Netherlands was used as the reference attribute parameter. A positive regression coefficient (beta) suggests that participants prefer more of that level within an attribute, whereas a negative coefficient suggests that participants prefer less of that level within an attribute. To determine the relevant importance of each attribute, the relative importance score was calculated based on the difference between the highest and lowest coefficients of each attribute divided by the total amount of these differences.

In subgroup analyses, preliminary joint models were estimated using interaction terms to investigate potential preference heterogeneity among people with different person-related- and disease-related characteristics. Person-related characteristics included age (<65 years and ≥65 years), sex, and education level (low/medium and high). Disease-related characteristics included glucose-lowering drugs (diet with or without oral glucose-lowering drugs and insulin with or without oral glucose-lowering drugs), type 2 diabetes duration (recently diagnosed [≤ 5 years] and longstanding [>5 years]), and predicted glycaemic control trajectory (stable, adequate glycaemic control-, improved glycaemic control-, and deteriorated glycaemic control trajectory). Participants' glycaemic control trajectories were predicted using a risk score, including BMI, HbA1c and plasma triglycerides measured +/- 3 months from diagnosis (this was previously developed as part of the PROFILe project to stratify people with type 2 diabetes with recently diagnosed diabetes into one of the three glycaemic control trajectories [4]). Due to the low number of participants in the deteriorated glycaemic control trajectory (n=6), this group was not included in the subgroup analysis. Parameters estimated for the interaction terms that are statistically different from zero (5% level) indicate a difference in preference between subgroups. The DCE analyses were performed in NLOGIT version 5 [5].

Supplementary Table 1. Results from the panel mixed logit model stratified on age

Attributes	<65 years (n=117)		≥65 years (n=168)		P-value of the interaction test
	Coefficient	95% CI	Coefficient	95% CI	
Constant	-0.29		-0.25		-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.48	-	0.27	-	-
Person with type 2 diabetes	-0.51	-0.71 - -0.30	-0.34	-0.50 - -0.18	0.147
HCP	0.03	-0.16 - -0.21	0.07	-0.06 -0.21	0.887
Lifestyle education method					
Individual education (ref)	0.40	-	0.47	-	-
Group education	-0.50	-0.68 - -0.31	-0.41	-0.54 - -0.28	0.775
Digital education (app or website)	0.10	-0.06 - 0.26	-0.06	-0.17 - 0.06	0.151
Type of medication management support					
Via HCP (ref)	0.04	-	0.31	-	-
Via aid (app, website, medicine box)	-0.08	-0.25 - 0.09	-0.29	-0.43 - -0.14	0.133
No help	-0.04	-0.21 - 0.13	-0.02	-0.16 - 0.12	0.998
Consultation frequency					
3-monthly visit with PN (ref)	0.63	-	0.51	-	-
2-monthly visit with PN	0.15	-0.06 - 0.35	0.24	0.07 - 0.40	0.306
6-monthly visit with GP	-0.07	-0.25 - 0.12	-0.19	-0.35 - -0.02	0.186
Yearly visit with GP	-0.71	-0.98 - -0.45	-0.56	-0.76 - -0.35	0.427
Emotional support approach					
GP or PN (ref)	0.50	-	0.57	-	-
Psychologist	-0.62	-0.83 - -0.40	-0.73	-0.90 - -0.55	0.232
No emotional support	0.12	-0.11 - 0.35	0.16	-0.02 - 0.34	0.546
Time spend on self-management	-0.004	-0.01 - 0.0001	-0.005	-0.007 - -0.002	0.121

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

Supplementary Table 2. Results from the panel mixed logit model stratified on sex

Attributes	Female (n=101)		Male (n=187)		P-value of the interaction test
	Coefficient	95% CI	Coefficient	95% CI	
Constant	-0.17	-	-0.34	-	-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.33	-	0.38	-	-
Person with type 2 diabetes	-0.19	-0.39 - 0.002	-0.54	-0.70 - -0.37	0.016
HCP	-0.14	-0.31 - 0.036	0.16	0.01 - 0.31	0.012
Lifestyle education method					
Individual education (ref)	0.43	-	0.44	-	-
Group education	-0.37	-0.54 - -0.20	-0.49	-0.63 - -0.35	0.607
Digital education (app or website)	-0.06	-0.21 - -0.09	0.05	-0.07 - 0.17	0.219
Type of medication management support					
Via HCP (ref)	0.18	-	0.25	-	-
Via aid (app, website, medicine box)	-0.23	-0.41 - -0.04	-0.19	-0.33 - -0.04	0.596
No help	0.05	-0.12 - -0.20	-0.06 (0.07)	-0.21 - 0.09	0.427
Consultation frequency					
3-monthly visit with PN (ref)	0.50	-	0.61	-	-
2-monthly visit with PN	0.23	0.02 - 0.44	0.17	0.007 - 0.34	0.494
6-monthly visit with GP	-0.23	-0.43 - -0.04	-0.08	-0.25 - 0.08	0.373
Yearly visit with GP	-0.50	-0.74 - -0.24	-0.70	-0.90 - -0.46	0.928
Emotional support approach					
GP or PN (ref)	0.51	-	0.56	-	-
Psychologist	-0.64	-0.84 - -0.44	-0.71	-0.89 - -0.52	0.567
No emotional support	0.13	-0.08 - 0.36	0.15	-0.04 - 0.34	0.874
Time spend on self-management	-0.005	-0.008 - -0.002	-0.004	-0.006 - -0.001	0.188

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

Supplementary Table 3. Results from the panel mixed logit model stratified on education level

Attributes	High (n=73)		Low/medium (n=188)		P-value of the interaction test
	Coefficient	95% CI	Coefficient	95% CI	
Constant	-0.19	-	-0.29	-	-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.47	-	0.32	-	-
Person with type 2 diabetes	-0.44	-0.66 - -0.21	-0.39	-0.53 - -0.24	0.951
HCP	-0.03	-0.23 - 0.16	0.07	-0.05 - 0.20	0.999
Lifestyle education method					
Individual education (ref)	0.42	-	0.45	-	-
Group education	-0.59	-0.79 - -0.39	-0.40	-0.53 - -0.28	0.217
Digital education (app or website)	0.17	0.005 - 0.34	-0.05	-0.16 - 0.08	0.030
Type of medication management support					
Via HCP (ref)	0.08	-	0.30	-	-
Via aid (app, website, medicine box)	-0.06	-0.25 - 0.12	-0.26	-0.39 - -0.13	0.085
No help	-0.02	-0.21 - 0.17	-0.04	-0.17 - 0.08	0.999
Consultation frequency					
3-monthly visit with PN (ref)	0.44	-	0.61	-	-
2-monthly visit with PN	0.14	-0.08 - 0.37	0.25	0.10 - 0.40	0.409
6-monthly visit with GP	-0.03	-0.24 - 0.19	-0.22	-0.36 - -0.08	0.063
Yearly visit with GP	-0.55	-0.83 - -0.27	-0.64	-0.83 - -0.44	0.473
Emotional support approach					
GP or PN (ref)	0.39	-	0.62	-	-
Psychologist	-0.50	-0.71 - -0.29	-0.74	-0.90 - -0.58	0.242
No emotional support	0.11	-0.14 - 0.36	0.12	-0.05 - 0.28	0.439
Time spend on self-management	-0.007	-0.01 - -0.003	-0.004	-0.006 - -0.001	0.153

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

Supplementary Table 4. Results from the panel mixed logit model stratified on diabetes medication

Attributes	Diet and/or glucose lowering drugs (n=206)		Insulin with or without glucose lowering drugs (n=37)		P-value of the interaction test
	Coefficient	95% CI	Coefficient	95% CI	
Constant	-0.32**	-	-0.23*	-	-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.31	-	0.62	-	-
Person with type 2 diabetes	-0.33	-0.46 - -0.2	-0.85	-1.19 - - 0.50	0.007
HCP	0.02	-0.09 - 0.13	0.23	-0.02 - 0.48	0.032
Lifestyle education method					
Individual education (ref)	0.44	-	0.37	-	-
Group education	-0.43	-0.54 - -0.32	-0.54	-0.80 - -0.29	0.914
Digital education (app or website)	-0.01	-0.11 - 0.08	0.17	-0.04 - 0.38	0.177
Type of medication management support					
Via HCP (ref)	0.18	-	0.52	-	-
Via aid (app, website, medicine box)	-0.20	-0.32 - -0.08	-0.14	-0.38 - 0.11	0.314
No help	0.02	-0.09 - 0.13	-0.38	-0.63 - -0.12	0.021
Consultation frequency					
3-monthly visit with PN (ref)	0.47	-	0.94	-	-
2-monthly visit with PN	0.20	0.07 - 0.34	0.34	0.05 - 0.63	0.603
6-monthly visit with GP	-0.11	-0.24 - 0.02	-0.43	-0.70 - -0.16	0.121
Yearly visit with GP	-0.56	-0.72 - -0.40	-0.85	-1.25 - -0.46	0.142
Emotional support approach					
GP or PN (ref)	0.49	-	0.74	-	-
Psychologist	-0.67	-0.83 - 0.54	-0.63	-0.93 - -0.33	0.792
No emotional support	0.18	0.03 - 0.33	-0.11	-0.42 - 0.19	0.888
Time spend on self-management	-0.31	-0.006 - -0.011	-0.005	-0.009 - -0.0002	0.259

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

Supplementary Table 5. Results from the panel mixed logit model stratified on diabetes duration

Attributes	Recently diagnosed T2DM (n=174)		Longstanding T2DM (n=114)		P-value of the interaction test
	Coefficient	95% CI	Coefficient	95% CI	
Constant	-0.30	-	-0.25	-	-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.40	-	0.33	-	-
Person with type 2 diabetes	-0.39	-0.56 - -0.22	-0.47	-0.69 - -0.25	0.393
HCP	-0.01	-0.16 - 0.13	0.14	-0.04 - 0.33	0.169
Lifestyle education method					
Individual education (ref)	0.48	-	0.39	-	
Group education	-0.50	-0.65 - -0.35	-0.37	-0.54 - -0.20	0.755
Digital education (app or website)	0.02 (0.06)	-0.10 - 0.15	-0.02	-0.17 - 0.13	0.733
Type of medication management support					
Via HCP (ref)	0.17	-	0.33	-	
Via aid (app, website, medicine box)	-0.19	-0.34 - -0.04	-0.21	-0.40 - -0.03	0.394
No help	0.02	-0.12 - 0.17	-0.12	-0.30 - 0.05	0.270
Consultation frequency					
3-monthly visit with PN (ref)	0.51	-	0.64	-	-
2-monthly visit with PN	0.21	0.04 - 0.38	0.21	0.0001 - 0.43	0.774
6-monthly visit with GP	-0.07	-0.24 - 0.09	-0.27	-0.47 - -0.06	0.241
Yearly visit with GP	-0.65	-0.87 - -0.44	-0.58	-0.86 - -0.30	0.412
Emotional support approach					
GP or PN (ref)	0.52	-	0.61	-	-
Psychologist	-0.64	-0.82 - -0.46	-0.80	-1.02 - -0.58	0.065
No emotional support	0.12	-0.06 - 0.31	0.19	-0.04 - 0.42	0.238
Time spend on self-management	-0.003	-0.006 - -0.000	-0.007	-0.01 - -0.003	0.07

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

Supplementary Table 6. Results from the panel mixed logit model stratified on glycaemic control trajectory

Attributes	Stable, adequate glycaemic control (n=75)		improved glycaemic control (n=16)		P-value of the interaction test
	Coefficient	95% CI	Coeffecient	95% CI	
Constant	-0.44	-	-0.33	-	-
Role division in diabetes care planning					
Person with type 2 diabetes and HCP (ref)	0.53	-	0.45	-	-
Person with type 2 diabetes	-0.41	-0.70 - -0.13	-0.44	-1.14 - 0.25	0.858
HCP	-0.12	-0.37 - 0.12	-0.01	-0.60 - 0.58	0.945
Lifestyle education method					
Individual education (ref)	0.48	-	0.73	-	-
Group education	-0.57	-0.84 - -0.31	-0.90	-1.79 - 0.002	0.572
Digital education (app or website)	0.09	-0.12 - 0.29	0.17	-0.37 - 0.71	0.598
Type of medication management support					
Via HCP (ref)	0.09	-	0.42	-	-
Via aid (app, website, medicine box)	-0.12	-0.37 - 0.13	0.11	-0.52 - 0.75	0.886
No help	0.03	-0.22 - 0.29	-0.43	-1.28 - 0.41	0.619
Consultation frequency					
3-monthly visit with PN (ref)	0.53	-	1.33	-	-
2-monthly visit with PN	0.10	-0.18 -0.38	0.72	-0.22 - 1.65	0.629
6-monthly visit with GP	0.01	-0.28 - 0.30	-0.72	-1.62 - 0.18	0.614
Yearly visit with GP	-0.64	-0.99 - -0.30	-1.33	-2.74 - 0.08	0.888
Emotional support approach					
GP or PN (ref)	0.84		0.08	-	-
Psychologist	-0.88	-1.21 - -0.54	-0.67	-1.60 - 0.25	0.336
No emotional support	0.04	-0.27 -0.35	0.59	-0.26 - 1.44	0.183
Time spend on self-management	-0.004	-0.008 - 0.0003	-0.001	-0.02 - 0.01	0.360

HCP: healthcare provider, PN: practice nurse, GP: general practitioner.

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CHAPTER 8

Tailored health care: Two perspectives on the development and use of patient profiles

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Abstract

Calls for a more tailored approach to the management of cardiometabolic- and musculoskeletal diseases have been increasing. Although tailored care is a centuries old concept, it is still unclear how it should be best practiced. The current paper introduces two phenotype-based Dutch approaches to support tailored care. One approach focuses on patients with type 2 diabetes, the other on patients undergoing total joint replacement. Using the patient profiling approach, both projects propose that care can be tailored by the assessment of biopsychosocial patient characteristics, stratification of patients into subgroups of patients with similar care needs, abilities, and preferences (so-called patient profiles), and tailoring of care in concordance with the common care preferences of these profiles. In this article, the advantages and disadvantages of the method are discussed to enable researchers or clinicians who want to extent the patient profiling approach to other patient populations to carefully evaluate these in relation to their project's focus and available resources.

Introduction

Tailored care was first described 4000 years BC in sacred texts from India known as 'the Vedas' [1]. It was then called 'Ayurvedic medicine' and its aim was to tailor treatment to each person's 'prakiti' (or constitution) in order to maintain a balance between body, mind and spirit. Nowadays, the aim of tailored care is to improve patients' health outcomes and care experience by taking the individual needs and preferences into account in developing a treatment plan. Due to the aging population and associated growing burden of cardiometabolic and musculoskeletal diseases [2], calls for a more tailored approach to the management of diseases have been increasing [3-5]. Although tailored care is millennia old, it is still unclear what the best approach is.

Currently, the majority of patients receives standardized care, based on evidence-based, disease-specific guidelines [6,7]. However, there is a growing body of evidence that shows the inherent limitations of this 'one-size-fits-all' approach. For example, patients differ in the amount and type of information they need and which aspects of care they prioritize [8-10]. While healthcare professionals do tailor communication during medical consultation to some extent, neither care needs nor preferences are routinely accommodated [10,11]. Thus, we need to think of other ways to deliver care. A tailored approach based on the phenotyping of patients may be such an approach. In this approach, patients' biopsychosocial characteristics are used to identify subgroups of patients with similar care needs, abilities, and preferences, for whom tailored solutions can be developed.

In the current paper we introduce two phenotype-based Dutch approaches to support tailored care. One approach focuses on patients with type 2 diabetes, the other on patients who undergo total joint replacement. Both use the term *patient profiles* to represent identified subgroups of patients, which form the basis for the development of tailored care, and are set to deliver final results in 2018-2019. Here, we outline the common steps in patient profiling, with a detailed description of their development, focusing on the differences in the patient characteristics assessed to identify the profiles and the process by which patients were stratified into subgroups.

Patient profiling

The aim of patient profiling is to enable care providers to provide the right care, to the right person, at the right time. It draws on the concept of 'mass customization', where goods and services are delivered to a large number of clients with enough variety and customization that nearly everyone finds exactly what they want [12]. Starbucks, Levi's, and Burger King are prominent examples of companies that have implemented this concept of targeting 'markets of a few' [13]. At Starbucks, for example, customers can customize their coffee by choosing from a variety of sizes, flavors and toppings. In healthcare, mass customization is less well-known, but with many patients with specific diseases that have varying care needs, abilities, and preferences, it could be a solution for delivering more tailored healthcare.

Patient profiling uses the individual's preferences to tailor the content, context and delivery mode of care to improve care experience and health outcomes [14-16], including quality of life, as well as reducing the per capita costs of care. The development of the tailored

care based on profiles consists of four steps: 1) identification of the target population; 2) assessment; 3) stratification, and 4) tailoring (see Figure 1). After defining the population (e.g. patients with type 2 diabetes treated in primary care), care providers assess relevant phenotypic patient characteristics, such as body weight, quality of life and self-efficacy, which are predictive of relevant outcomes, such as glycemic control and patient satisfaction. Subsequently, these characteristics are used to stratify patients into profiles. This approach results in subgroups of patients who are more homogeneous than the population as a whole in terms of care needs, abilities, and preferences, while acknowledging that a certain amount of heterogeneity within these subgroups will remain. In the last step, the patient's care is adapted depending on his or her profile.

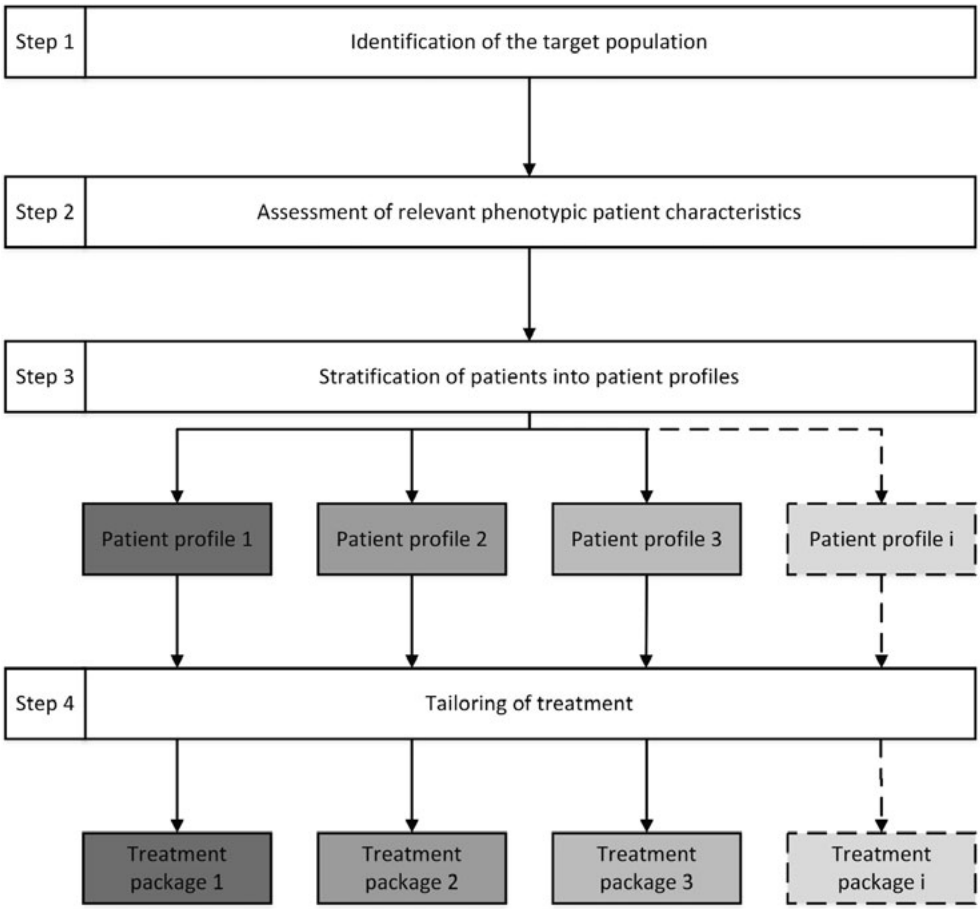

Figure 1. The patient profiling approach. Treatment packages may differ in frequency of consultations, education material, e.g.

Comparison of two patient profiles studies

In the following section, two ongoing research projects that use the modus operandi as described above are explained. Both projects apply different techniques to do so. One uses a quantitative and the other a mixed-method approach. The current conceptual article is based on the two projects and does not directly contain any studies with human participants or animals performed by any of the authors for which ethical approval was required. An overview of both approaches can be found in Table 1.

Patient profiles: a quantitative approach

The Dutch PROFILe (PROFiling patients' healthcare needs to support Integrated, person-centered models for Long-term disease management) project started in 2014 and is a 4-year public-private research collaboration between a university, hospital, pharmaceutical company and two diabetes care networks (DCN). PROFILe aims to develop, validate and test patient profiles as an instrument for tailored diabetes management in primary care [17]. The two DCNs both routinely collect patient data. One DCN was considered the development cohort (n=10.528), and the other the validation cohort (n=3.777).

A quantitative approach was used to develop the patient profiles. In the first step, the longitudinal electronic health records of the development cohort were used to conduct growth mixture modeling [18]. This technique identified three subgroups of patients based on glycemic control trajectories starting from the point of diagnosis: 1) stable, adequate glycaemic control; 2) improved glycaemic control; and 3) deteriorated glycaemic control. Glycaemic control trajectories were chosen as the outcome, because the researchers hypothesized that patients with different glycaemic control trajectories prefer different configurations of diabetes care and support. The identified subgroups were validated in the validation cohort. Second, to explore which phenotypic patient characteristics should be assessed to determine a patient profile and to stratify patients into the right trajectory, machine learning methods were applied. Using the most salient characteristics (baseline body mass index, HbA1c and triglycerides), an algorithm was built to predict the identified glycemic control trajectories, which was subsequently validated in the validation cohort. The project is currently on the third step 'tailoring': the adaption of care per patient profile. A so called 'discrete choice experiment (DCE)' is conducted among 300 patients to provide insight into the patients' preferences for specific configurations of diabetes care and support (e.g. frequency of professional monitoring, involved providers, information provision). These care preferences are paired with the corresponding patient profiles. To diminish heterogeneity within each profile, the influence of psychosocial characteristics, such as self-efficacy and quality of life, on the preferences is also determined.

In the final step of the PROFILe project, a clustered-randomized controlled trial will be performed at primary care practices in the Netherlands to assess the perceived benefits, risks and the feasibility of implementing patient profiles as an instrument to safely and successfully provide tailored type 2 diabetes management.

Table 1. Overview of two approaches to develop and use patient profiles

	Quantitative approach (PROFILe project)	**Mixed-method approach (Tailored Healthcare project)**
Objective	To develop, validate and test patient profiles as an instrument to support more tailored type 2 diabetes management in primary care.	To define and validate patient profiles, and to test the effect of integrating profiles in healthcare services, materials, and systems on total joint replacement patients' satisfaction with care provision.
Patient profile development		
Target population	Adult patients with type 2 diabetes treated in primary care.	Older adults undergoing lower limb joint replacement surgery.
Identification of subgroups	Growth mixture modeling	K-means clustering
Population size	~10,000 (development cohort) ~ 3,000 (validation cohort	~200 (retrospective cohort) ~30 (qualitative interviews)
Prediction of subgroups	Machine learning	Recursive partitioning
Patient profile use in practice		
Assessment: Which patient characteristics are assessed?	Body mass index	Coping style
	Glycated haemoglobin	Anxiety
	Triglycerides	Communication preferences
Stratification: How are patients stratified into subgroups?	Healthcare provider enters patients BMI, HbA1c and triglycerides levels into a tool, which enables him/her to view the related subgroup with a similar glycemic control trajectory.	Healthcare provider enters the patient's scores as determined during the consultation in a decision tree. Alternatively, patients fill out a self-reported questionnaire which is scored according to the decision tree decision rules. A suggestion for the patient's subgroup is provided along with the level of certainty.
Tailoring: How is care tailored?	Daily diabetes care planning, lifestyle information, help taking medication, frequency of consultations and emotional support are tailored according to the preferences per subgroup.	Preoperative education materials and supportive systems for postoperative (tele)rehabilitation are tailored to the preferences per subgroup.

Patient profiles: a mixed-method approach

The *Tailored healthcare through customer profiling* project is a 4-year public-private research collaboration between a hospital, medical device manufacturer, technical university, and the creative industry. Its main aims are to define a validated set of design-oriented patient profiles and to test the effect of integrating these profiles in healthcare services (e.g. educational materials and telerehabilitation systems) on satisfaction with care provision following joint replacement surgery.

A mixed-method approach was used to develop the profiles. As a first step, self-reported communication preferences, experiences with pain and stress, self-efficacy, clinical symptoms, and surgical outcomes of patients who had underwent joint replacement surgery were assessed. To stratify patients in groups with similar preferences and experiences, *k-means* cluster analysis was used. The resulting subgroups were validated by comparing the average subgroup characteristics to patients' actual and ideal hospital experience as expressed in qualitative interviews. To ease classification of future patients to the relevant subgroup by health professionals, recursive partitioning was used to build a decision tree [19]. By asking three questions (which assess active coping skills, experienced helplessness, information needs) either during the consultation or via a self-reported questionnaire, health professionals can quickly stratify future patients to one of the subgroups and deliver care that is better aligned to the patient's preferences, even when time-constrained.

The final 'tailoring' step in this project consists of developing modular variations of existing patient education materials and supportive telerehabilitation systems by design engineers. From their iterative work, it will be determined how preferences should be embedded in tailored design. The envisioned benefit of profile usage (i.e. improved satisfaction) will be examined in a pilot validation of the developed tailored prototypes.

Discussion

The current paper describes two ongoing research projects that develop and use *patient profiles* to tailor healthcare. Both propose that care can be tailored by the assessment of biopsychosocial patient characteristics, stratification of patients into profiles, and tailoring of care in concordance with the common care preferences of these profiles. Patients stratified into a high-risk profile could, for example, receive more intensive disease management, to address their care needs and preferences. Vice versa more emphasizes on self-management could be established for patients of the low-risk profile. It is expected that such tailored approaches will benefit clinical practice by efficiently allocating resources to where they are most needed.

The projects discussed use different methods of profiling, both of which have important advantages and disadvantages. The identification of patient profiles in each approach was carried out in different ways: in the quantitative approach, profiles were identified based on a disease-related health outcome, assuming that patients within a profile share the same preferences for care provision, whereas in the mixed-method approach, profiles were identified based on preferences, assuming patients within a profile show similar disease-related health outcomes. If these assumptions are not met, additional research might be required to identify separate 'sub'profiles based on preferences for care provision

(quantitative approach) or disease-related health outcomes (mixed method approach) within the previously identified profiles.

Thus, future work on patient profiling should carefully specify the intended goal of the patient profiles, as this influences which characteristics should be assessed and consequently, which profiles are identified. The different methods of data collection also affect the time, energy, and monetary investments required for profile development. The mixed-method approach employed in the Tailored Healthcare project requires less patients to be enrolled in the study which curbs the burden. Therefore, we assume that this approach is more suitable for individual clinics that may serve fewer patients. On the other hand, accurate stratification into subgroups tends to be more reliable in data produced by larger samples, like those used in the quantitative approach of the PROFILe project. These methods may be most suitable for large clinics, or multi-centre collaborations. Again, we stress the importance of clarifying the goals and expected results of any patient profiling approach in considering these cost and benefits.

Conclusion

The concept of tailored healthcare has been around for centuries. Still, only recently have modern techniques emerged to transform raw data of electronic health records into usable information for care management [20]. It are techniques like these (e.g. machine learning, natural language processing[20], and neural network analysis [21]) that enable healthcare professionals and researchers alike to explore new approaches such as patient profiling, described in this paper.

It is expected that patient profiling will result in tailored care. As such, it constitutes a promising method for achieving the so called 'Triple Aim' by: 1) improving patient experience, by including patients' care needs and preferences in treatment decisions; 2) improving population health and quality of life, by supporting tailored care; and 3) reducing the per capita cost of care, by reducing the over-, under- and misuse of health care services[22]. Healthcare practitioners who currently provide care to diabetes type 2 or lower limb joint replacement patients can soon use insights from both projects to gain an improved understanding about their patients and to find support in aligning their practice to their patients' needs. Researchers or clinicians who want to extent the profiling approach to other patient populations should carefully evaluate these expected advantages in relation to their focus and available resources.

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CHAPTER 9

General discussion

Introduction

Type 2 diabetes is one of the most prevalent chronic diseases worldwide and can have severe short- and long-term consequences for the patient. In the Netherlands, evidence-based care protocols exist to optimize the management of type 2 diabetes. These protocols, however, are highly standardized [1, 2]. The overall aim of this dissertation was to develop and validate patient profiles as a tool to establish tailored care for patients with type 2 diabetes. This aim has been operationalized according to three themes: 1) determination of relevant health-, person-, and context-related patient characteristics; 2) validation of these patient characteristics; and 3) assessment of the preferences of patients for type 2 diabetes care. This general discussion presents and discusses the main findings of this dissertation, theoretical considerations, several methodical strengths and limitations of the studies, and implications for practice, research, and policy.

Main findings

Development of the patient profiles

With regard to relevant patient characteristics for patient profiling, our systematic literature review revealed that age, glucose-lowering drugs use, diabetes duration and baseline HbA1c influence the Hba1c levels of patients with type 2 diabetes. These are mostly health-related characteristics, which does not necessarily mean that person-related characteristics, such as age and sex, and context-related characteristics, such as self-efficacy and social support, are less important predictors. Most included studies simply did not consider these characteristics when studying possible relationships with glycaemic control. In The Maastricht Study, a cross-sectional epidemiological study, person- and context-related patient characteristics in addition to health-related characteristics were measured in patients with type 2 diabetes. We found that patients with insufficient glycaemic control had a worse biopsychosocial profile (e.g. more diabetes-related distress and complications, higher body mass index, and lower self-efficacy) than patients with sufficient glycaemic control. Zooming in on the group of patients with insufficient glycaemic control, we further identified two health-related quality of life (HRQoL) classes: one with a low probability of HRQoL problems and one with a higher probability in several HRQoL domains. Patients belonging to the low HRQoL class had a worse biopsychosocial profile than those belonging to the high HRQoL class.

Using the electronic health records (EHRs) of a large Dutch diabetes care network, i.e. the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC), we identified three distinct glycaemic control trajectories in patients with newly diagnosed type 2 diabetes: 1) stable, adequate glycaemic control (76.5%); 2) improved glycaemic control (21.3%); and 3) deteriorated glycaemic control (2.2%). Trajectory membership could accurately be predicted with three easily obtainable patient characteristics: baseline BMI, HbA1c and triglycerides. Again, we could not make any inferences on the prediction accuracy of person- and context-related characteristics, as these are not routinely measured in practice.

Validation of relevant patient characteristics

The glycaemic control trajectories and the prediction model with the three patient characteristics were validated using EHR data from another Dutch diabetes care network, i.e. the regional care group ZIO. In this cohort, we identified three glycaemic control trajectories, similar in shape and population distribution to the trajectories identified in the development cohort. The trajectories of both cohorts can be seen in Figure 1. The prediction model, trained in the development cohort and tested in the validation cohort, showed excellent external validity.

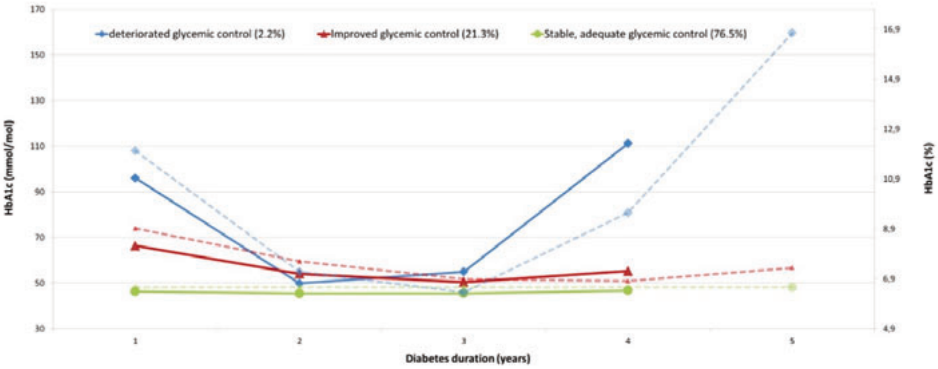

Figure 1. Latent class growth trajectories of the best-fitting models of the development and validation cohorts identified by latent growth mixture modeling. Solid lines = development cohort; dashed lines = validation cohort.

Besides the statistical validation of relevant patient characteristics for patient profiling, we also determined which patient characteristics were most relevant for estimating health care needs according to healthcare providers (HCP) and patients. Both HCPs and patients found health-related characteristics relevant for estimating patients' healthcare needs. However, HCPs preferred to estimate healthcare needs using person- and context-related characteristics. They ranked self-efficacy as the most relevant estimator. In contrast, patients were more in favor of health-related characteristics and ranked HbA1c as the most relevant estimator.

Preferences towards type 2 diabetes care

With regard to the preferences of patients towards type 2 diabetes care, we found that patients preferred to receive usual care: they had a preference towards planning their daily diabetes care together with a HCP, receiving individual lifestyle education, medication and emotional support as well as having three-monthly consultation visits, and spending less time on self-management. Patients strongly did not prefer to receive emotional support from a psychologist. Heterogeneity in preferences could be explained in part by differences in sex, education level and glucose-lowering drug use. We did not find significant preference differences between the three glycaemic control trajectories.

Theoretical considerations

This section reflects on the results of this dissertation. First, a reflection on the patient profiling approach for type 2 diabetes is provided. Second, the quality of diabetes care will be addressed. Finally, patient satisfaction is discussed.

Patient profiling approach for type 2 diabetes

The patient profiling approach, described in more detail in Chapters 2 and 8, is a tailored care approach based on the assessment of health-, person-, and/or context-related patient characteristics and the subsequent stratification of patients into subgroups with similar care needs, preferences and abilities. For each subgroup different configurations of care and support are available. Figure 2 shows the framework of the patient profiling approach.

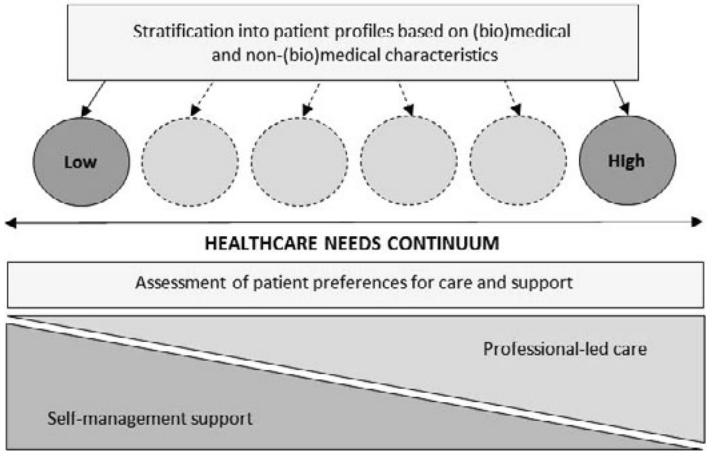

Figure 2. Framework for tailored chronic care management based on patient profiles

In this dissertation, we described the development of patient profiles for the treatment of type 2 diabetes. The first part of our profiles contains the stratification of patients into a glycaemic control trajectory based on BMI, HbA1c, and triglycerides (Chapter 5). The second part is not completely developed yet, but it will contain a consultation model to promote a dialogue between HCPs and patients on relevant biopsychosocial patient characteristics. The exact characteristics that should be discussed and how care should be tailored is yet to be determined. When complete, the patient profiles can serve as a tool to establish more personalization of care.

We started to develop the patient profiles as a response to the current state of type 2 diabetes care in the Netherlands. Although the quality of the care seems to be quite good (described in the section below), it is not a perfect fit for the 21st century. Current type 2 diabetes care is based on a disease management approach, introduced to change care from reactive and episodic to proactive, continuous, and multidisciplinary care [3]. This has led to a

better coordination of care and the introduction of evidence-based protocols [1, 2, 4]. However, disease management is a disease-oriented approach, which tends to neglect, for example, patients' co-morbidities [5, 6]. Therefore, the Chronic Care Model (CMM) was developed to respond to the growing need of the healthcare system to change how it addresses the needs of patients with chronic diseases [5]. The CCM is a framework consisting of various strategies important to present-day healthcare systems, such as self-management support (e.g. patient education) and information systems (e.g. EHRs). These strategies can be tailored to the patients' conditions. However, the CCM is patient rather than person-centered. It tends to neglect the person behind the patient, which is problematic, because in the past decade or so, the landscape of chronic care has further changed, increasing the need for a more person-centered approach [7-9]. Previous studies, including our own cross-sectional study with data from The Maastricht Study, have for example found individuals with low socioeconomic status (SES) (often measured by using several indicators such as income and education) are more likely to develop type 2 diabetes and have a worse disease progression compared to individuals with higher SES [10-14]. Therefore, it is important to discuss context-related patient characteristics in the treatment of type 2 diabetes. The recently introduced framework on integrated, people-centered health services by the World Health Organization (WHO), emphasizes the need for such person-oriented approach [15]. The vision of this framework is to ensure that health services are tailored to patients' needs and preferences and are provided in partnership with them. An important part of our patient profiling approach is the dialogue between HCPs and patients on relevant biopsychosocial patient characteristics. Therefore, the patient profiles we are developing, correspond with this vision of the WHO framework.

It also corresponds with the vision of George Engel, and American physician, who, already forty years ago, stated that there was hardly any room for the social, psychosocial, and behavioral dimensions of illness in health care [16]. He agreed that HCPs should not only know their patients on a biological level, but also on a social and psychosocial level. Indeed, our Delphi panel, described in Chapter 6, revealed that HCPs who treat patients with type 2 diabetes seem to agree on such a broad, whole person approach. Furthermore, the results from our cross-sectional analysis with the data from The Maastricht Study, described in Chapter 4, showed that person- and context-related characteristics might be relevant as well for patient profiling. The success of patients' self-management behavior increases when cultural differences and personal, family, and community resources become part of the treatment [17]. In previous research, patients have reported that they would like their healthcare provider to show more interest in their life and provide more explanation and involvement in diabetes care [18, 19]. Indeed, a recent study showed that when HCPs not only discuss health-related patient characteristics, but also person- and context related characteristics, such as quality of life, self-management skills, and social support, patients seem to appreciate it and their involvement increases [20].

Quality of diabetes care

In the studies described in Chapters 4 and 5 of this dissertation, we found that 65 to 75% of patients with type 2 diabetes had sufficient glycaemic control. Most of the patients included in these studies received care according to a Dutch primary care-based disease management program for type 2 diabetes, which ensures the delivery of multidisciplinary care under a bundled payment system [21]. In other countries where such an approach is implemented, similar percentages of sufficient glycaemic control were observed [22-24]. Based on these results, one could argue that the quality of diabetes-specific management programs is good. For the Netherlands, this is not only shown by the high number of patients with sufficient glycaemic control, but also by its second ranking in the Euro Diabetes Index [4]. At the same time, the care for patients with type 2 diabetes is expensive [25]. In 2016, the direct healthcare costs for type 2 diabetes in the Netherlands were €1.3 billion. A total of €1.1 billion was spend on diabetes-related complications.

Taking into account the good quality and high costs of current type 2 diabetes care, and the need to keep the care sustainable on the long term, it is prudent to focus on improving the efficiency of care. For example, by offering less frequent consultation visits. A previous Dutch study found that patients with sufficient glycaemic control who either preferred or were undecided about receiving six-monthly consultations, maintained their glycaemic control level with six-monthly consultations instead of the usual three-monthly consultations [26]. However, taking away part of their care might be difficult for patients with type 2 diabetes. A described in the section above, Individuals with low SES, are more likely to suffer from or develop type 2 diabetes. Low SES has also been associated with low self-management [27]. In addition, our DCE, described in Chapter 7 of this dissertation, showed that, regardless of glycaemic control status, patients with type 2 diabetes did not prefer less frequent consultation visits. This means that we need to find a common ground in redistributing healthcare resources. Patients with sufficient glycaemic control could, for example, receive less professional-led care and more effective (digital) self-management education- and support. Patients with insufficient control on the other hand, might not only need to receive effective self-management education- and support, but also a higher intensity of professional-led care.

Patient satisfaction

In current diabetes care, patient consultations seem to focus on clinically oriented issues, such as optimal blood glucose levels [19]. Furthermore, past qualitative research has shown that patients are unable to describe the role of the practice nurse beyond clinical checks and were also not sure what they can expect from their practice nurse [18]. Therefore, it is not a surprise that the results of our Delphi panel showed that patients with type 2 diabetes considered health-related patient characteristics to be the most relevant characteristics for estimating healthcare needs (Chapter 6). The results from our DCE (Chapter 7) also showed that patients had a preference for the traditional care model for type 2 diabetes in the Netherlands, including three-monthly consultations and individual group education. From these findings,

we could conclude that patients have a preference for maintaining the current care approach for type 2 diabetes in primary care. However, healthcare is the fastest growing service in the world, which currently faces increasing demands and diminishing resources [28]. Therefore, changes are needed in order to keep health care sustainable, as already briefly discussed in the section above. Several factors necessary for a sustainable healthcare have been mentioned in the literature [29]. One of these factors is the acceptability and support or the public (alias patients) towards health care changes. Although the evidence remains weak, personalization of care seems to increase patient satisfaction [30]. When implementing approaches to personalize care, such as patient profiling, it is important to adequately guide patients when changes in diabetes care organization are implemented to keep healthcare sustainable.

Methodological considerations

This section discusses the methodological strengths and limitations of the studies in this dissertation. The study designs and data sources, group-based methodology, patient involvement, and generalizability of the results are discussed.

Study designs and data sources

The main objective of this dissertation was to develop and validate patient profiles as a way to establish tailored care for patients with type 2 diabetes. To do this, we used several study designs: a systematic literature review (Chapter 3), a cross-sectional study (Chapter 4), retrospective cohort studies (Chapter 5), a Delphi study (Chapter 6), and a DCE (Chapter 7). Using these different study designs to develop patient profiles is unique. Together they provided us with more in-depth information and knowledge, and each of the studies helped us to shed light on the topic from different angles, creating a more complete picture.

The systematic review shed light on the fact that person- and context-related patient characteristics in relation to glycaemic control are rarely taken into account in evaluation studies of integrated diabetes care programs. The cross-sectional study with data from The Maastricht Study enabled us to explore this relationship further. The main advantage of this study is its comprehensive phenotyping approach [31]. In contrast to the retrospective cohort studies, which included real-world data, the Maastricht Study has strict inclusion and exclusion criteria. For example, only participants age 40 to 75 years old were included. Furthermore, part of the participants in The Maastricht Study were diagnosed with type 2 diabetes at the study sight and had not yet received diabetes care. Their HbA1c might have therefore been higher compared to patients who already received type 2 diabetes care. These limitations might have reduced the external validity of the findings [32].

We chose to build the first part of the patient profiles (step 2 and 3 in Figure 3) based on the results of the retrospective cohort studies. In comparison to the Maastricht Study, this design allowed us to follow quite a large number of patients over a longer period and to build and validate a stratification model based on latent growth mixture modeling (LGMM) analysis

and machine learning techniques. Moreover, cohort studies with real-world data have the advantage of recording the actual care that patients receive. This may paint a more realistic picture, as the data was registered without the presence of a researcher or study protocol to influence the data [33]. Furthermore, the generalizability of real-world data studies are generally higher then, for example randomized controlled trials, as they often include data from large patient groups who did not have strict in- or exclusion criteria [34].

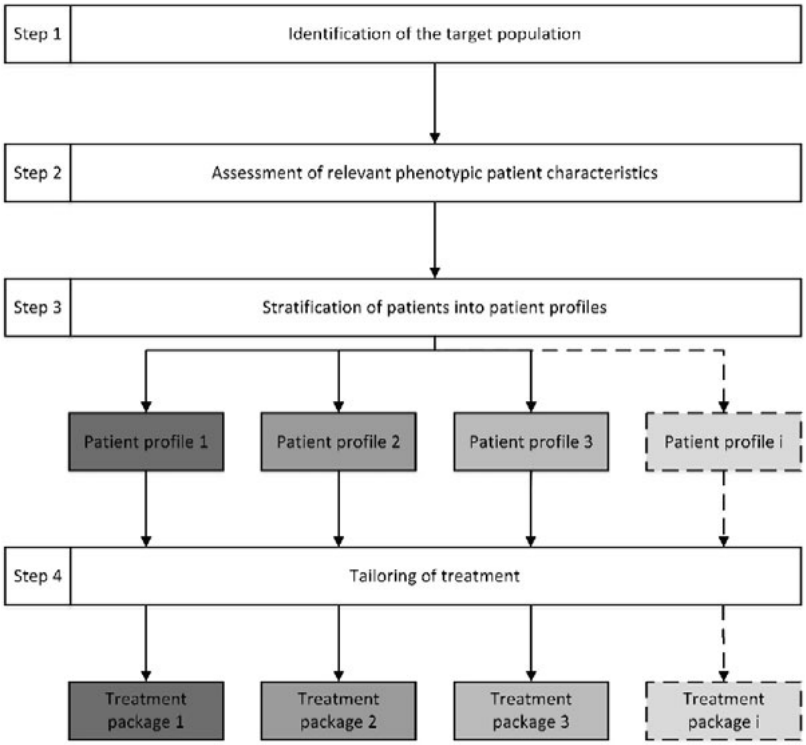

Figure 3. The patient profiling approach. Treatment packages may differ in frequency of consultations, education material, etc.

However, a retrospective study design, especially one with real-world data, also has its limitations. First, there is a lack of quality control surrounding data collection. HCPs from the participating primary care practices collected and recorded the data in the EHRs from the start of diabetes diagnosis, without an accurate check on consistency and appropriateness. This could have led to missing and less rigorous data. Fortunately, HCPs use the information in the EHRs for the treatment and follow-up of their patients and as proof that they provided the care as agreed upon with health insurers for declaration purposes, which might have improved the accuracy of data registration. Furthermore, to guarantee the quality of the data, we conducted range checks, excluded outliers and used full information maximum likelihood (FIML) as a missing data estimation approach [35].

Second, retrospective methods are limited to the data available in the database and cannot be influenced by the researchers. This has three consequences. First, the data becomes less comparable to other data. The variable heart failure for example was collected in the development cohort, but not in the validation cohort. As a result, we could not check whether this variable was a relevant characteristic for predicting glycaemic control trajectories. Second, the diabetes care that patients received may have influenced the patterns of the identified glycaemic control trajectories. For example, the HbA1c levels in the stable, adequate and improved glycaemic control trajectories remained stable or improved, possibly because of an increase in glucose-lowering drug prescriptions.

Third, important patient information in relation to the research question might be unavailable. In both our retrospective cohorts, context-related characteristics were not included in the database, because they are not routinely measured in practice. Earlier studies have shown that these characteristics have an impact on people's health, which suggests that they might be important for patient profiling. To overcome this problem, the original idea was to match the retrospective data from the ZIO cohort with the cross-sectional data from The Maastricht Study [11, 36, 37], creating a longitudinal dataset, containing not only health and person-related patient characteristics, but also context-related patient characteristics. Matching was to take place using patient identification numbers, which are given to all patients who receive diabetes disease management through the bundled payment system in the Netherlands. However, part of the participants in The Maastricht Study were diagnosed with type 2 diabetes at the study sight, did not yet have such a number, and could therefore not be matched. This resulted in a dataset one-fourth the size of the ZIO cohort. We therefore chose not to combine the two datasets, but analyze them separately instead.

To achieve true translational research it is important to include the voices of HCPs and patients as well. Therefore, we conducted a Delphi study (Chapter 6) and DCE (Chapter 7). The studies provided us with useful views on the opinions of patients regarding relevant patient characteristics for estimating healthcare needs and their preferences towards type 2 diabetes care. In both studies, patients had to complete questionnaires and although instructions were provided, this might have been difficult for some patients. Especially since the patient population in both studies included older (the average age was 69 years in the Delphi study and 67 years in the DCE) and mostly lower educated patients. In a DCE, respondents are assumed to use complex decision strategies by considering all attributes and making their choice based on trade-offs [38]. This becomes more difficult for patients who are older, lower educated and less literate and could result in invalid conclusions regarding the attribute level estimates [38]. The lack of context in the Delphi study might have resulted in patients seeing things from the HCPs' perspective. In these respects, a more qualitative approach method, such as face to face interviews, to gain insights into the opinions and preferences of patients towards type 2 diabetes care might have been better. It would have given the researchers a chance to define and explain the characteristics and attributes more thoroughly. However, face to face interviews give patients less time to think and could result in potential interviewer bias [39].

Group-based methodologies

The application of latent class and growth mixture modeling in clinical research has rapidly increased in the past decade [40]. These approaches simplify heterogeneous populations into a number of homogeneous classes based on individual response patterns [41]. As the main theme of this dissertation is about personalizing care, these person-centered approaches seemed appropriate. Instead of variable-centered approaches, such as regression, which focus on describing the relationship among variables, person-centered approaches focus on the relationship among individuals [41]. This is relevant, because the goal of the patient profiling approach is to stratify patients into distinct classes based on individual response patterns, in our case individual glycaemic control patterns, so that patients within a class are more similar than patients between classes and most likely also need and prefer other configurations of care.

In Chapters 4 and 5 of this dissertation, we applied latent class analysis (LCA) and LGMM to identify classes of patients based on quality of life measures (Chapter 4) and glycaemic control over time (Chapter 5), respectively. Instead of LCA and LGMM, we could have chosen other clustering methods, such as *k*-means clustering, mentioned in Chapter 8 of this dissertation or hierarchical clustering [42]. In all three methods, patients with similar characteristics can be stratified into classes. The most important difference between LCA and LGMM and *k*-means- and hierarchical clustering is the procedure of choosing the number of classes. LCA and LGMM use a "model-based" method [42]. This means that a statistical model allows the comparison between different numbers of classes to be statistically tested. In *k*-means- and hierarchical clustering the decision on the number of classes is arbitrary or subjective and thus less robust. We therefore chose to identify classes of patients using LCA and LGMM. This does not mean that the number of classes in a LCA and LGMM should be solely determined by the statistical model. The research question, clinical relevance, and the individual variability within a group should also be taken into account [41, 43]. To obtain further evidence that the classes are real, the results should be replicated in another dataset [44]. As described in Chapter 5, we replicated our LGMM findings from the ZODIAC cohort in the ZIO cohort.

For the LGMM analysis we used HbA1c as the dependent variable, because it is considered an important intermediate outcome in the treatment of type 2 diabetes. In the current Dutch care protocols for type 2 diabetes, HCPs are instructed to monitor HbA1c levels of patients to reduce the risk of diabetic complications. However, trials have failed to show a negative relationship between tight glycaemic targets and macrovascular complications [45, 46]. It has been stated that the optimal glycaemic control target should depend on patients' risk for complications [46]. Therefore, efforts should be taken to adequately report diabetic complications in patients' EHRs, which could then be used as outcomes in type 2 diabetes research.

Patient involvement

Research generally continues to be carried out on patients, but not with patients [47]. However, it is difficult to appropriately inform patient-centered decision making without

patient involvement [48]. For example, researchers might be interested in knowing the decrease in HbA1c in patients with type 2 diabetes after intake of a certain hypoglycaemic drug. Some patients, however, may be more interested in the effect of the drug on their body weight. Without asking, researchers cannot know which questions and outcomes are important to patients. Since patients are gaining a more active role in health care and care is becoming more personalized, the collaboration with patients in health care research in the past decades has increased [47, 49]. Authors who would like to publish in the BMJ, one of the oldest general medicine journals, are now required to report on their partnership with patients during the research project [50]. Although much of the evidence base concerning the impact of patient involvement in research remains weak, it is thought to lead to greater quality and relevance of the research [49].

At the start of the PROFILe project we therefore established a patient panel consisting of six patients with type 2 diabetes. The patient panel met once to twice a year with the researchers of the PROFILe project. During the first meeting, patients were informed on the aims and activities of the PROFILe project. Their roles and expectations and those of the researchers were discussed. During consecutive meetings, patients were informed on the results of the project and asked for advice on the user friendliness and clarity of recruitment materials, patient information and questionnaires. The inclusion of a patient panel helped to assess the appropriateness, wording and timing of the research instruments, and to adapt the information in patient information letters to better suit patients with type 2 diabetes. Therefore, it is likely that the face validity, which refers to the relevance of a test as it appears to the test participants, of the DCE and Delphi panel questionnaires improved. These beneficial impacts of patient involvement in research have also been observed in previous studies [49].

The 'participation ladder' model shows that we could have given the patient panel more decision-making power [51, 52]. This model consist of five levels of patient participation in research, ranging from only informing patients to giving patients complete control in decision making. The patient panel of our research project acted on the second level, called the consultation level, in which patients are asked for advice, but the research team holds decision making power. It has been stated that patient involvement has the most positive impact when patients are involved as partners in a research team (level 4) [49]. We chose a less prominent role for the patient panel, because at the start of our project we were unsure about the contribution patients could bring to the research. We felt that the topics discussed during our research meetings (e.g. data analysis) might be too difficult for patients to understand. We were also unsure about how confidential information provided in meetings would be treated. These and other problems related to the involvement of patients in research have been reported before and are often reason for researchers not to involve patients [49]. However, these problems or challenges may be diminished by providing enough time and money to the researchers to establish a good working relationship with the patients and to appropriately educate and train them. If so, patient involvement in research can be a valuable contribution

providing insights from different perspectives, improving the quality of the research process, and leading to the identification of gaps in research that future studies need to address.

Generalizability

When developing a prediction model, like the one we built to predict the glycaemic control trajectories of newly diagnosed patients with type 2 diabetes, it is not sufficient to show that it successfully predicts the outcome of interest in the initial development cohort [53]. Unfortunately, it is common for studies to perform an internal validation only [54] . In this approach, the dataset is split into two or more parts. The model is developed on the first portion of the dataset, also known as the training set, and its predictive accuracy is tested on the other portion(s) of the dataset. This does not give evidence on how well the model performs in other groups of patients. It tends to give optimistic results, because the datasets are very similar. Indeed, in our study described in Chapter 5, the 5-fold cross-validation of the prediction model in the development cohort performed very well. However, an accurate prediction model is of no benefit if it is not generalizable.

To test the true generalizability of a prediction model, an external validation is necessary on data elsewhere. One of the major strengths of our prediction model is therefore that we added a validation cohort to our study. This enabled us to train the prediction model in the development cohort and test it in the validation cohort. The patients in the validation cohort received care according to the same protocols as the patients in the development cohort, but they lived in another Dutch province. The prediction model performed very well in the validation cohort, which made us to conclude that the model is generalizable to other populations.

However, all patients in the studies included in this dissertation were from the south of Limburg, one of the twelve Dutch provinces, and/or in the north of the Netherlands. In these Dutch regions, there is hardly any ethnic diversity, as the majority of inhabitants is Caucasian. Our results are therefore generalizable to these parts of the Netherlands, but might be less generalizable to the central-western part of the Netherlands, consisting of the four largest Dutch cities. In this region, there is more ethnic diversity. The prevalence of type 2 diabetes is higher in the Dutch non-western immigrant population compared to the Dutch non-immigrant population. They also tend to have higher HbA1c values, less physical activity and a higher use of healthcare services [55]. The inclusion of patients with a non-western immigrant background in our studies might have therefore resulted in glycaemic control trajectories that differed in size and shape and in different patient opinions and preferences towards type 2 diabetes care. Indeed, a previously developed risk score for type 2 diabetes developed for the Caucasian population, turned out to be less efficient among South Asians and Africans [56].

Another issue with the generalizability lies in the fact that only a small percentage (2-4%) of the population with newly diagnosed type 2 diabetes was stratified into the deteriorated glycaemic control trajectory. For the DCE, this meant that we were only able to include six patients into this trajectory. Due to this low number of patients, inferences about their preferences towards type 2 diabetes care are difficult to make. Since the glycaemic control of

the patients belonging to this trajectory is far from sufficient, learning about their preferences in especially important for tailoring their care. Therefore, another recruitment strategy for this population might have been in place. For example, instead of recruiting this patient population via postal mail, having their GPs personally ask them might have maximized participation.

Future directions

Practice

Our patient profiling approach consists of several steps (Figure 3). In step 3, patients are stratified into glycaemic control trajectories, based on three easily obtainable patient characteristics (BMI, HbA1c, and triglycerides). Subsequently, between step 3 and step 4, a dialogue takes place between HCPs and patients on relevant biopsychosocial patient characteristics. This step is not yet portrayed in Figure 3. We decided later on to add this step to the patient profiling approach, based on the results of the cross-sectional study with data from The Maastricht Study (Chapter 4) and our Delphi panel (Chapter 6), which showed us that it might be relevant to also tailor treatment based on psychosocial characteristics.

The patient profiling approach has several implications for clinical practice. First, the prediction tool, predicting patients' glycaemic control trajectories, forms a good starting point for HCPs and patients to discuss further diabetes management. It may also reassure those patients stratified into the adequate glycaemic control trajectory and raise awareness about the importance of good self-management for patients stratified in the deteriorated glycaemic control group. Second, the dialogue that follows after the stratification of patients into the glycaemic control trajectories allows the HCPs to listen to the stories of patients while gaining insights into the needs, preferences, and abilities, but also into their attitudes, and barriers to change, which undoubtedly influence self-management. Third, both steps allow for the active involvement of patients in the decision-making process. Previous studies have found that the majority of patients prefer to be actively involved in decision-making [57]. Shared-decision making (SDM) also seems to improve patient's knowledge of and attitude towards a disease, satisfaction towards the care, and trust in the HCP [20, 58]. Over time this may lead to greater treatment adherence, cost-effectiveness of care and ultimately improved health. However, these relationships remain largely untested in the empirical research [58].

Depending on the outcomes of the prediction tool and the dialogue between HCPs and patients, care can be tailored to match the patients' needs, preferences and abilities. Thus far, we are unsure about the content and the strategy for offering the different treatment packages to patients. Two main approaches to tailored care have been mentioned in the literature: 1) The assistive decision approach, where recommended treatment packages are not provided; and 2) the directive decision approach, which recommends or even prescribes a specific treatment package depending on the glycaemic control trajectory and the outcome of the dialogue between HCPs and patients [59]. Both approaches have their (dis)advantages. The assistive approach leaves more room for intuition of HCPs and patients and is therefore more respectful of the judgement of HCPs and patients. The directive approach on the other

hand may have greater clinical impact. Another possibility might be to offer something in between these two approaches. In that case, each treatment package would consist of different treatment options, varying, for example, from group-based education, and six-monthly consultation visits, to a self-management app. It is up to the HCPs and patients to decide which of the options inside a treatment package to pick.

Policy

In April 2018, a task force, led by the Dutch ministry of Health, Welfare and Sport and consisting of HCPs and healthcare administrators, published a report called 'The right care in the right place' (in Dutch: De juiste zorg op de juiste plek) to contribute to the needed transformation towards a more sustainable healthcare system [60]. The meaning behind 'the right care in the right place' is to prevent (expensive) care, transfer care (closer to home), and replace care (by for example e-health). Patient profiles can form an instrument to achieve part of these goals by tailoring care depending on patients' needs, preferences and abilities. For example, some of the consultation visits for patients with sufficient glycaemic control may be replaced with self-management, supported by e-health applications, thereby transferring and preventing unnecessary care.

However, before the implementation of the profiles in practice, it is important that health insurers play a role in the patient profiling approach. Currently, in the Netherlands, care groups receive a single fee from health insurers for the full 'bundle' of diabetes care. The services that the bundle should contain are codified in the Dutch Diabetes Federation Health Care Standard for type 2 diabetes [2] and are in accordance with diabetes guidelines from the Dutch college of General Practitioners on type 2 diabetes [1]. HCPs in the Netherlands who treat patients with type 2 diabetes strictly adhere to these guidelines [4]. Furthermore, health insurers oblige care groups to reveal their results on performance indicators, such as the number of patients having their HbA1c measured [61]. In the long term, the patient profiling approach could form the basis for a more tailored funding approach for type 2 diabetes care, by establishing a 'bundle' of diabetes care services matching each patient profile. Such a responsible and flexible approach to healthcare funding has been shown to lead to better alignment of resources and more effective cost management [62]. This also entails that adjustments need to be made in the diabetes care protocols. In the current Dutch Diabetes Federation Health Care standard for type 2 diabetes, it is mentioned that HCPs should tailor care by providing personal care plans [2]. However, currently there is no tool available to guide them in providing these care plans. The patient profiling approach could be a solution to this problem.

Whether the patient profiles are implemented in practice or not will depend, for a large part, on the cost-effectiveness of the approach. In a recent study on the implementation of a structured diabetes consultation model with a focus on personal and context-related patient characteristics, incremental diabetes care costs were low [20]. Moreover, the authors assumed that the effectiveness of diabetes care is enhanced if patients' preferences are

structurally taken into account. It is likely that this would also be the case for the patient profiles that we are developing.

As described in Chapter 8 of this dissertation, the patient profiling approach is not restricted to the management of type 2 diabetes. The approach could be applied to the management of many, if not all, diseases, but with varying types of patient characteristics for the stratification of patients into subgroups. Due to the rise in number of people with multiple medical conditions, there is a growing need for approaches that take into account this multi-morbidity instead of focusing on a single-disease [63, 64]. The patient profiling approach might also be suitable for this. Of course, stratifying patients with disease-specific characteristics, such as we did, is not appropriate, but psychosocial characteristics, such as SES and social support, affect the progress of many diseases and could therefore be used for the stratification of patients with multi-morbidity into subgroups.

Research

First, because not all the steps in our patient profiling approach have been completely finished, qualitative approaches should be used to gain a better understanding on relevant person- and context-related characteristics from both the HCP and patient perspective and the preferences of patients from each of the glycaemic control trajectories towards type 2 diabetes care. The insights gained will be used to inform the dialogue between HCPs and patients, as well as the content and approach for offering the treatment packages.

Part of the development of our patient profiling approach consisted of multivariable prediction research. In the literature, three phases in prediction research are distinguished: 1) development of the prediction model; 2) external validation of the model; and 3) studying the impact of the prediction model in clinical practice (e.g. HCPs and patient experience, health outcomes, and cost-effectiveness of care) [65]. While there are plenty of publications on the development of a prediction model, publications on the validation and even more so on the impact of prediction models are scarce [59, 65]. In this dissertation, we described the development and the validation of our prediction model. After completion of the patient profiles, the next step should therefore be the execution of an impact study to determine whether the patient profiling approach leads to achieving the Triple Aim (e.g. improved patient experience, health outcomes, and cost-effectiveness of care) [66]. The ideal design of an impact study is a cluster-randomized controlled study, where primary care practices are the cluster units of randomization [65]. When randomization takes place on the patient level, the same HCP would have to treat half his/her patients using usual care and the other half using the patient profiling approach. This could lead to a learning effect, reducing the contrast between usual care and the patient profiling approach [65]. Randomizing on the HCP level could also lead to contamination, when HCPs exchange experiences and information with each other. Therefore, randomization on the primary care practice level is preferable.

Research on EHRs and data driven research are increasing in popularity [67]. They can provide major opportunities for improving health systems, including facilitating more stratified care by using patient characteristics. However, most data collected in healthcare

organizations only contain health-related patient characteristics. To achieve more effective stratified care it is important to create databases that also include person- and context-related characteristics. Sharing of data from different sources is therefore essential. In the Netherlands for example, EHR data could be matched with government population level epidemiological data, such as those stored and managed by Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek), creating a rich dataset with a broad range of patient characteristics. However, data sharing is not as easy as it sounds, because it is related to issues of trust, data privacy, confidentiality and control of data about individuals once it is shared [67]. Right now, healthcare data is scattered in different healthcare systems, which prevents data sharing and puts the privacy of patients at risk [68]. It would help if healthcare data are owned and controlled by patients themselves. A solution for this are so-called blockchain storage platforms [68]. Blockchain decentralizes data, which is therefore not impacted by the behavior of any one organization and ideal for ensuring data integrity. For example, when an EHR is generated and signed it can be written to a blockchain, providing absolute proof that the EHR cannot be changed. Right now, blockchain use is slow and difficult. However, there is hope, as blockchain services are emerging.

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SUMMARY

In the Netherlands, evidence-based care standards exist to optimize the management of type 2 diabetes. These care standards are highly standardized. Not all patients seem to benefit from this 'one-size-fits-all' approach. Therefore, the Dutch PROFILe project, which stands for *PROFiling people's healthcare needs to support Integrated, person-centered models for Long-term disease management*, started in 2014. The aim of this project was to develop and validate so-called 'patient profiles' as an instrument for tailoring chronic care management to the needs, preferences and abilities of patients. This dissertation describes the development and validation of patient profiles for type 2 diabetes care.

Chapter 1 contains a general introduction to this dissertation. The symptoms, epidemiology, consequences, and quality of care for type 2 diabetes are discussed, as well as the importance of personalizing care. Furthermore, the aims and outlines of this dissertation are specified.

The design of the PROFILe project is presented in **Chapter 2**. The research aims and questions are described, as well as the different phases of the project, its settings, and the methods used for data collection and analysis. A conceptual framework for the patient profiling approach is also provided.

Chapter 3 describes a systematic literature review that was performed to identify which patient-related effect modifiers influence the outcomes of integrated care programs for type 2 diabetes in primary care. A total of 27 studies were included. We found that baseline age, glucose-lowering drugs, diabetes duration and HbA1c were associated with glycaemic control, at either baseline or follow-up. Information on person- and context-related patient characteristics in the included studies was limited.

A cross-sectional epidemiological study using data from The Maastricht Study **(Chapter 4)** was performed to assess the biopsychosocial profile (including person-, context-, and health-related characteristics) of patients with type 2 diabetes. We observed that patients with insufficient glycaemic control had a worse biopsychosocial profile (e.g. more diabetes-related distress and complications, higher body mass index, and lower self-efficacy) than patients with sufficient glycaemic control. Zooming in on the group of patients with insufficient glycaemic control, we identified two health-related quality of life (HRQoL) classes: one with a low probability of HRQoL problems and one with a higher probability in several HRQoL domains. Patients in the former class had a better biopsychosocial profile than those in the latter class. We concluded that insufficient glycaemic control, particularly in combination with low HRQoL, is associated with a generally worse biopsychosocial profile. Further research is needed into the complex and multidimensional causal pathways explored in this study, so as to increase our understanding of the heterogeneous care needs and preferences of persons with type 2 diabetes, and translate this knowledge into tailored care.

Chapter 5 shows the results of a retrospective cohort study using real-world data from a large diabetes care network, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC). In total, 10,528 patients with newly diagnosed type 2 diabetes were included in the analysis. Within this population, three distinct glycaemic control trajectories were identified using a clustering method called 'latent growth mixture modeling' (LGMM): 1) stable,

adequate glycaemic control; 2) improved glycaemic control; and 3) deteriorated glycaemic control. Trajectory memberships could accurately be predicted with three easily obtainable patient characteristics: baseline body mass index, HbA1c, and triglycerides. The trajectories and prediction tool were validated using data from 3,777 patients with type 2 diabetes treated in a different Dutch diabetes care network (i.e. the regional care group ZIO). Again, three glycaemic control trajectories were identified, similar in shape and population distribution to the trajectories identified in the development cohort. The external validity of the prediction model with the three patient characteristics, trained in the development cohort and tested in the validation cohort, was high. The receiver-operating characteristic (ROC) area under the curve was 0.96, indicating excellent accuracy. It can therefore be used in clinical practice as a quick and easy tool to provide tailored diabetes care.

Chapter 6 presents the findings from an online Delphi study among healthcare providers (HCPs) and patients with type 2 diabetes. Aim of this study was to gain insight into the opinions of HCPs and patients regarding relevant patient characteristics for estimating the healthcare needs of people with type 2 diabetes. Both HCPs and patients reported health-related characteristics as relevant for estimating patients' healthcare needs. However, there was also discrepancy in opinions between HCPs and patients. HCPs found context-related and person-related characteristics more relevant to estimate healthcare needs than patients did. They ranked self-efficacy as the most relevant estimator. In contrast, patients found health-related characteristics more relevant and ranked HbA1c as the most relevant estimator. To achieve more tailored, patient-centered diabetes care, it is important that both groups agree on the topics that are important to discuss during patient consultations.

To elicit patients' preferences towards type 2 diabetes care, a discrete choice experiment was conducted among 288 patients **(Chapter 7)**. We found that patients had a preference towards planning their daily diabetes care together with a HCP, receiving individual lifestyle education, medication- and emotional support from a HCP, three-monthly consultation visits, and spending less time on self-management. Patients strongly preferred to not receive emotional support from a psychologist. Heterogeneity in preferences could be explained by differences in sex, education level and glucose-lowering drug use. We did not find preference differences between the three glycaemic control trajectories. This discrete choice experiment revealed that people with type 2 diabetes prefer to receive the care they currently receive. Therefore, it is important to adequately guide people when changes in diabetes care are implemented to keep healthcare sustainable.

In **Chapter 8**, the PROFILe project of the Maastricht University and The Tailored Healthcare project of the Technical University Delft (TU Delft) were compared. The aim of both projects was the development of patient profiles. At Maastricht University, the profiles were developed for the management of type 2 diabetes and at the TU Delft for the management of patients undergoing low limb joint replacement surgery. Both projects are similar in terms of the steps taken in the patient profiling approach, but differ with respect to the methods used for identification of the profiles. Both approaches have their advantages and disadvantages. For example, the mixed-methods approach used by the TU Delft requires less patients to be

enrolled in the study, whereas our approach with a large sample size might lead to a more accurate stratification of patients into the patient profiles. Researchers or clinicians who want to extend the patient profiling approach to other patient populations should carefully evaluate the advantages and disadvantages of each approach in relation to their project's focus and available resources.

Chapter 9 summarizes and discusses the main findings. In addition, the theoretical- and methodological considerations of the studies are presented, as well as implications for future practice, policy and research.

SAMENVATTING

In Nederland wordt gebruik gemaakt van evidence-based zorgstandaarden om de zorg voor patiënten met diabetes mellitus type 2 (hierna diabetes type 2 genoemd) te optimaliseren. Deze zorgstandaarden, zoals het woord al suggereert, zijn erg gestandaardiseerd. Niet alle patiënten ondervinden voordeel van deze 'one-size-fits-all' aanpak. In 2014 is daarom het Nederlandse PROFILe project van start gegaan, wat staat voor *PROFiling people's healthcare needs to support Integrated, person-centered models for Long-term disease management*. Het doel van dit project was om zogenaamde 'patiëntprofielen' te ontwikkelen en valideren, als instrument om de chronische zorg af te stemmen op de behoeften, preferenties en mogelijkheden van patiënten. Dit proefschrift beschrijft de ontwikkeling en validatie van de patiëntprofielen voor diabetes type 2 zorg.

Hoofdstuk 1 bevat een algemene introductie van dit proefschrift. De symptomen, epidemiologie, consequenties en de kwaliteit van zorg voor diabetes type 2 worden bediscussieerd, alsmede het belang van het personaliseren van zorg. De doelen en de inhoud van dit proefschrift worden ook benoemd.

Het design van het PROFILe project is gepresenteerd in **Hoofdstuk 2**. De onderzoeksdoelen en vragen zijn uitgelegd, alsmede de verschillende fases van het project, de setting en de methoden van dataverzameling- en analyses. Een conceptueel raamwerk voor de patiëntprofielen is ook verschaft.

Hoofdstuk 3 beschrijft een systematische literatuur review die is uitgevoerd om te achterhalen welke patiënt-gerelateerde effectmodificatoren invloed hebben op de uitkomsten van geïntegreerde zorgprogramma's voor diabetes type 2 in de eerste lijn. In totaal werden 27 studies geïncludeerd. We vonden dat leeftijd, bloedsuikerverlagende medicatie, diabetesduur en HbA1c op baseline geassocieerd waren met glykemische controle. Informatie over persoons- en context-gerelateerde patiëntkarakteristieken in de geïncludeerde studies was bijna niet beschikbaar.

Een cross-sectionele epidemiologische studie werd uitgevoerd met gebruik van data van De Maastricht Studie **(Hoofdstuk 4)** om het biopsychosociale profiel (bestaande uit persoons-, context- en gezondheids-gerelateerde karakteristieken) van patiënten met diabetes type 2 vast te stellen. We observeerden dat patiënten met ontoereikende glykemische controle een slechter biopsychosociaal profiel hadden (bijvoorbeeld meer diabetes-gerelateerde stress en complicaties, hogere body mass index en een lagere zelfredzaamheid) dan patiënten met een toereikende glykemisch controle. Door verder in te zoomen op de groep patiënten met ontoereikende glykemische controle identificeerden we twee klassen qua gezondheids-gerelateerde kwaliteit van leven (KvL): één met een lage kans op beperkingen in KvL en één met een hogere kans op beperkingen in KvL. Patiënten in die laatste klasse hadden een minder gunstig biopsychosociaal profiel dan patiënten in de eerste klasse. We concludeerden dat ontoereikende glykemische controle, vooral in combinatie met een lage kwaliteit van leven, geassocieerd is met een minder gunstig biopyschosociaal profiel. Meer onderzoek is nodig naar de complexe en multidimensionale oorzaak-gevolg relaties die in deze studie zijn

verkend, om de heterogene zorgbehoeften en preferenties van patiënten met diabetes type 2 beter te kunnen begrijpen en om deze kennis te kunnen vertalen in zorg op maat.

Hoofdstuk 5 laat de resultaten zien van een retrospectieve cohortstudie waarin gebruik is gemaakt van data afkomstig uit een groot diabetes zorgnetwerk, de Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC). In totaal werden er 10,528 patiënten met nieuwe gediagnosticeerde diabetes type 2 geïncludeerd in de analyses. In deze populatie werden, doormiddel van een clustermethode genaamd 'latent growth mixture modeling' (LGMM), drie klassen van glykemische controle over de tijd geïdentificeerd: 1) stabiele, toereikende glykemische controle; 2) verbeterde glykemische controle; en 3) verergerde glykemische controle. Klasse lidmaatschap kon accuraat voorspeld worden met drie simpel te verkrijgen patiëntkarakteristieken: baseline body mass index, HbA1c en plasma triglyceriden. De klassen en het predictiemodel werden gevalideerd met data van 3,777 patiënten met diabetes type 2 die behandeld werden in een ander diabeteszorgnetwerk (de regionale zorggroep ZIO). Ook in deze populatie werden drie klassen geïdentificeerd op basis van glykemische controle over de tijd, vergelijkbaar in beloop en populatiedistributie met de klassen geïdentificeerd in het ontwikkelcohort. De externe validiteit van het predictiemodel met de drie patiëntkarakteristieken, getraind in het ontwikkelcohort en getest in het validatie cohort, was hoog. De receiver-operating characteristic (ROC) area onder de curve was 0.96, wat een excellente accuraatheid weergeeft. Het model kan dus gebruikt worden in de klinische praktijk als een snelle en makkelijke tool om zorg op maat te leveren.

Hoofdstuk 6 presenteert de uitkomsten van een online Delphi studie onder zorgverleners en patiënten met diabetes type 2. Het doel van deze studie was om inzicht te verkrijgen in de mening van zowel zorgverleners als patiënten met betrekking tot relevante patiëntkarakteristieken om de zorgzwaarte van mensen met diabetes type 2 te kunnen bepalen. Zowel zorgverleners als patiënten rapporteerden gezondheids-gerelateerde karakteristieken als relevant om de zorgzwaarte van patiënten te bepalen. Echter waren er ook discrepanties tussen de mening zorgverleners en patiënten. Zorgverleners vonden context- en persoons-gerelateerde karakteristieken meer relevant voor het bepalen van de zorgzwaarte dan patiënten. De zorgverleners beoordeelden zelfredzaamheid als de meest relevante karakteristiek. Patiënten daarentegen vonden gezondheids-gerelateerde karakteristieken relevanter en scoorde HbA1c als de meest relevante karakteristiek. Om meer zorg op maat te bewerkstelligen, is het van belang dat beide groepen het eens zijn over de onderwerpen die belangrijk zijn om te bespreken tijdens een patiëntconsult.

Om de patiëntvoorkeuren van patiënten met diabetes type 2 met betrekking tot de eerstelijnszorg mee te nemen, werd een zogenaamd discrete choice experiment uitgevoerd onder 288 patiënten **(Hoofdstuk 7)**. We vonden dat patiënten een voorkeur hadden voor het plannen van hun dagelijkse diabeteszorg samen met een zorgverlener, het ontvangen van individuele leefstijleducatie, het ontvangen van medicatie- en emotionele steun van een huisarts, één consultatie met een praktijkondersteuner per drie maanden en het besteden van minder tijd aan zelfmanagement. Ze hadden ook een sterke voorkeur om emotionele steun niet van een psycholoog te ontvangen. Heterogeniteit in de voorkeuren van patiënten

kon verklaard worden door verschillen in geslacht, educatieniveau en type glucose verlagende medicatie. We vonden geen verschillen in voorkeur tussen de drie glykemische controle groepen, zoals beschreven in Hoofdstuk 5. Dit discrete choice experiment heeft laten zien dat patiënten met diabetes type 2 de voorkeur geven aan de huidige zorg. Het is daarom belangrijk om patiënten goed te begeleiden als veranderingen in de zorg geïmplementeerd worden om de zorg te verduurzamen.

In **Hoofdstuk 8** werden het PROFILe project van de Universiteit Maastricht en het Tailored Healthcare project van de Technische Universiteit Delft (TU Delft) met elkaar vergeleken. Het doel van beide projecten was het ontwikkelen van patiëntprofielen. De patiëntprofielen van de Maastricht University zijn ontwikkeld voor patiënten met diabetes type 2 en de patiëntprofielen van de TU Delft voor de behandeling van patiënten die een gewricht vervangende operatie van de onderste extremiteiten ondergaan. Beide projecten zijn vergelijkbaar qua stappen die gevolgd zijn in de patiëntprofielenaanpak, maar verschillen op het gebied van de methoden die gebruikt zijn om de profielen te identificeren. Beide aanpakken hebben hun voor- en nadelen. De mixed-methods aanpak die is gebruikt door de TU Delft bijvoorbeeld, vereist de inclusie van minder patiënten, terwijl onze aanpak met een grotere patiëntenpopulatie wellicht tot een accuratere stratificatie van patiënten in profielen leidt. Onderzoekers en zorgverleners die de patiëntprofielenaanpak uit willen breiden naar andere patiëntpopulaties moeten de voor- en nadelen van de twee projecten zorgvuldig evalueren in relatie tot de focus van hun eigen project en de beschikbare middelen.

Hoofdstuk 9 geeft een samenvatting en bediscussieerd de belangrijkste resultaten. Daarnaast zijn de theoretische- en methodologische consideraties van de studies gepresenteerd, alsmede de implicaties voor de praktijk, onderzoek en beleid.

VALORISATIE

Diabetes mellitus type 2, ook wel suikerziekte genoemd, is een ziekte waarbij het lichaam niet meer goed reageert op insuline, een hormoon verantwoordelijk voor de bloedsuikerspiegel. In Nederland hebben ongeveer één miljoen mensen diabetes mellitus type 2 (hierna diabetes type 2 genoemd), vaak veroorzaakt door een ongezonde leefstijl. Wanneer de bloedsuikerspiegel van mensen met diabetes type 2 niet voldoende daalt, kunnen er complicaties en andere ziekten optreden, zoals amputaties, hart -en vaatziekten en nierfalen. Dit betekent dat diabetes type 2 niet alleen een grote impact heeft op de patiënt, maar ook op de zorgkosten. In 2016 heeft de ziekte in Nederland ongeveer 2,9 miljard euro gekost. De verwachting is dat het aantal patiënten met diabetes type 2 en de daarmee gepaarde kosten de komende jaren alleen maar toe zullen nemen. Om de gezondheid en de ervaren kwaliteit van de zorg te waarborgen en de zorgkosten niet verder te laten stijgen, moeten er daarom veranderingen plaatsvinden in de zorg. Op dit moment ontvangen de meeste patiënten met diabetes type 2 eerstelijnszorg bij een praktijkondersteuner en/of huisarts. Deze zorg is gebaseerd op de standaarden van het Nederlands Huisartsen Genootschap (NHG) en de Nederlandse Diabetes Federatie (NDF). In deze standaarden worden adviezen gegeven aan zorgverleners over bijvoorbeeld medicatie, het ondersteunen van een gezonde leefstijl en het aantal consulten per jaar. De adviezen gaan uit van de gemiddelde patiënt met diabetes type 2. Dit betekent dat, enkele uitzonderingen daargelaten, iedere patiënt met diabetes type 2 dezelfde zorg aangeboden krijgt. Deze zorg werkt niet voor alle patiënten even goed. Ongeveer één derde van de patiënten met diabetes 2 heeft bijvoorbeeld een bloedsuikerspiegel die onvoldoende onder controle is. In plaats van gestandaardiseerde zorg aan te bieden, wordt daarom steeds meer geopperd om de zorg persoonsgerichter te maken. Een eerste stap om dit te verwezenlijken is het doen van wetenschappelijk onderzoek. Een tweede belangrijke stap is het kenbaar maken van de onderzoeksresultaten aan belanghebbenden. Onder deze zogenaamde ‘valorisatie’ verstaat de Universiteit van Maastricht “het proces van waarde creatie uit kennis, door kennis geschikt en/of beschikbaar te maken voor maatschappelijk (en/of economische) benutting en geschikt te maken voor vertaling in concurrerende producten, diensten, processen en nieuwe bedrijvigheid”. In dit hoofdstuk wordt daarom een overzicht gegeven van de relevantie van dit proefschrift voor belanghebbenden.

Relevantie voor patiënten en zorgverleners

We kunnen helaas niet voor iedere patiënt de zorg zo aanpassen dat deze perfect aansluit op zijn of haar wensen, behoeften en mogelijkheden. Wel kunnen we proberen om de zorg daar beter op aan te laten sluiten dan nu het geval is. Daarom hebben we in ons onderzoek zogenaamde ‘patiëntprofielen’ ontwikkeld. Het doel van deze profielen is om patiënten op basis van een aantal kenmerken in te delen in subgroepen met vergelijkbare wensen, behoeften en mogelijkheden. Uit ons onderzoek kwam naar voren dat we met een drietal biomedische patiëntkenmerken de toekomstige bloedsuikerspiegel van patiënten kunnen voorspellen en ze zo in kunnen delen in één van drie klinisch relevante subgroepen: 1) een groep met een adequate bloedsuikerspiegel; 2) een groep met een verbeterende bloedsuikerspiegel en 3) een groep met een verslechterende bloedsuikerspiegel. Het voorspellen van de bloedsuikerspiegel kan een goede aanleiding zijn voor patiënten en zorgverleners om de diabetesmedicatie en leefstijl van patiënten te bespreken. Het kan

daarnaast patiënten geruststellen die in de groep met een adequate bloedsuikerspiegel zijn ingedeeld en patiënten in de verslechterende groep het belang doen inzien van een gezonde leefstijl. Het gesprek dat volgt na het indelen van patiënten in subgroepen geeft tevens de mogelijkheid aan zorgverleners om te luisteren naar de verhalen van patiënten en daarmee inzicht te verkrijgen in hun behoeften, voorkeuren en mogelijkheden. Het geeft patiënten de mogelijkheid om actief betrokken te zijn bij het zorgproces. Uit eerder onderzoek is gebleken dat patiënten hier behoefte aan hebben. Een actieve patiëntparticipatie kan na verloop van tijd leiden tot betere medicatietrouw, gezondere patiënten en lagere zorgkosten.

Aan de hand van de indeling van patiënten in één van de drie subgroepen en het gesprek dat daar op volgt, kan de zorg voor patiënten worden aangepast om beter te voldoen aan hun behoeften, voorkeuren en mogelijkheden. Op dit moment wordt nog onderzocht hoe deze zorg er precies uit moet komen te zien.

Relevantie voor beleidsmakers en zorgverzekeraars

Voordat de patiëntprofielen geïmplementeerd kunnen worden is het voor beleidsmakers en zorgverzekeraars van belang om te weten of de patiëntprofielen kosteneffectief zijn. Omdat de ontwikkeling van de patiëntprofielen nog niet volledig is afgerond, kunnen we daar op dit moment nog niks over zeggen. De verwachting is dat de patiëntprofielen de zorg persoonsgerichter maken aan de hand van de behoeften, voorkeuren en mogelijkheden van patiënten. Een aantal consulten voor patiënten in de groep met een adequate bloedsuikerspiegel zouden bijvoorbeeld vervangen kunnen worden door zelfmanagementondersteuning in de vorm van een e-health programma. De zorg wordt daardoor vervangen en onnodige zorg wordt voorkomen. Dit is de essentie van het in 2018 opgestelde rapport ‘de juist zorg op de juiste plek’. Dit rapport, opgesteld door o.a. zorgverleners, wetenschappers en beleidsmakers onder leiding van het Ministerie van Volksgezondheid, Welzijn en Sport, heeft als doel een bijdrage te leveren aan het stapsgewijs verbeteren van het Nederlandse zorgstelsel.

Mocht de patiëntprofielenaanpak kosteneffectief blijken, dan dient het integrale bekostigingssysteem van de diabeteszorg aangepast te worden. Op dit moment wordt de diabeteszorg bekostigd op basis van keten-DBC contracten tussen zorgverzekeraars en zorggroepen. Een zorggroep bestaat uit een groep zorgverleners, bijvoorbeeld huisartsen, praktijkondersteuners en diëtisten, die samen de zorg voor diabetes op zich nemen. Voor iedere patiënt met diabetes type 2 krijgt een zorggroep per jaar een bepaald budget van de zorgverzekeraars om de complete diabetesbehandeling in de eerste lijn te bekostigen. Die behandeling is gebaseerd op wat er in de richtlijnen staat. De patiëntprofielenaanpak kan in de toekomst de basis vormen voor een flexibeler bekostigingssysteem, waarbij het budget en de behandeling passen bij het profiel van de patiënt. Zo’n flexibele aanpak kan leiden tot een betere besteding van middelen, afgestemd op de zorgbehoefte van patiënten.

Relevantie voor onderzoekers

De studies die beschreven zijn in dit proefschrift zijn relevant voor onderzoekers, die onderzoek doen naar persoonsgerichte zorg. De aanpak voor het ontwikkelen van patiëntprofielen zoals wij die hebben voorgesteld bestaat uit vier stappen: 1) identificatie van de patiëntpopulatie; 2) beoordelen van relevante patiëntkarakteristieken; 3) stratificatie van

patiënten in patiëntprofielen en 4) aanpassen van de zorg. Deze aanpak is niet exclusief bedoeld voor het persoonsgerichter maken van de diabeteszorg, maar kan ook gebruikt worden door onderzoekers voor de ontwikkeling van persoonsgerichtere behandeling van andere ziekten en multimorbiditeit.

Bij de ontwikkeling van patiëntprofielen is het belangrijk om de voorkeuren van patiënten mee te nemen. Zoals beschreven in Hoofdstuk 7 van dit proefschrift hebben wij de voorkeuren van patiënten met betrekking tot de diabeteszorg achterhaald doormiddel van een discrete choice experiment (DCE). Deze methode wordt steeds vaker gebruikt in de gezondheidszorg. Hoewel een DCE een goede manier is om voorkeuren te achterhalen, zijn er ook nadelen. Eén van de belangrijkste nadelen is dat een DCE niet voor iedereen even makkelijk te begrijpen is. Dit kan tot selectieve non-respons leiden. Onderzoekers doen er daarom goed aan om na te denken over het inzetten van andere methoden om patiëntvoorkeuren te achterhalen. Voor sommige patiëntgroepen zijn kwalitatieve methoden wellicht betrouwbaarder.

Uit dit proefschrift blijkt dat niet alleen gezondheids-gerelateerde kenmerken belangrijk zijn voor het persoonsgerichter maken van de zorg, maar ook persoons- en context-gerelateerde kenmerken. De meeste databanken bevatten voornamelijk gezondheids-gerelateerde kenmerken van patiënten. Het is daarom belangrijk om databanken te creëren die ook de persoons- en context-gerelateerde kenmerken van patiënten bevatten en de mogelijkheden van koppeling op persoonsniveau te verkennen.

Verspreiding van de resultaten

Vanaf de start van ons onderzoek in 2014, hebben verschillende activiteiten plaatsgevonden om de resultaten te verspreiden. Allereerst heeft tijdens de uitvoering van de onderzoeken overleg plaatsgevonden met patiënten, zorgverleners, wetenschappers, beleidsmakers en zorgverzekeraars om de resultaten te bespreken. Daarnaast zijn in totaal zes van de zeven hoofdstukken uit dit proefschrift gepubliceerd in wetenschappelijke tijdschriften. Deze publicaties zijn vrij beschikbaar voor iedereen die daar interesse in heeft. Naast deze publicaties zijn de resultaten uit dit proefschrift gepresenteerd op verschillende congressen in binnen- en buitenland. De komende periode zal aandacht besteed worden aan het afronden van de ontwikkeling van de patiëntprofielen en het implementeren van de profielen in de praktijk.

DANKWOORD

In de zomer van 2014 verhuisde ik van New York, Manhattan naar Maastricht voor een vierjarig promotietraject. Chocolate chip cookies van Levain Bakery ruilde ik in voor Limburgse vlaai, de metro voor de fiets en een klein kamertje voor een appartement met terras. Ik liet veel goede vrienden achter en ging in het stille, kleine en voor mij onbekende Maastricht een nieuw leven opbouwen. Ik had er een hard hoofd in, maar dankzij een hele fijne werkplek, een nieuwe vriendenkring, mijn familie, improvisatietheater, vastelaovend, de zaote hermenie en de wekelijkse vlaai, voelde ik mij in no time helemaal thuis. Aan het onderzoek en de totstandkoming van dit proefschrift hebben velen bijgedragen. Een aantal mensen die ik de afgelopen jaren heb ontmoet wil ik op deze plek graag hiervoor bedanken.

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ABOUT THE AUTHOR

Dorijn Hertroijs was born on the 8th of October 1985 in Kampen, the Netherlands. After finishing secondary education at Almere College in Dronten and Seneca High School in Louisville, Kentucky, she studied Nutrition and Dietetics at The Hague University of Applied Sciences, obtaining her bachelor's degree in 2008. She continued her studies at the VU University in Amsterdam, where she obtained her research master's degree in Lifestyle and Chronic Disorders with the distinction cum laude. As part of the master program she conducted research at the Dutch Malnutrition Steering Group at the VU University Medical Center in Amsterdam and at the Obesity Research Clinic at Columbia University in New York City. After employment as a project coordinator at the Youth Alcohol Clinic at the Reinier de Graaf Hospital in Delft, she returned to New York City where she worked as a teaching assistant and obtained a master's degree in Nutrition at New York University. She returned to the Netherlands to start a PhD at the department of Health Services Research at Maastricht University. She finished this PhD in 2019 and is currently working as a post-doctoral researcher at the same department.

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