Mobile Exergaming in Type 2 Diabetes Mellitus – Innovative Ways to Overcome Physical Inactivity and Increase Exercise Adherence

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List of Abbreviations

6MWT	6 Minute Walk Test
95% CI	95% confidence interval
BMI	body mass index
CVD	cardiovascular disease
DDP-4	dipeptidyl peptidase 4
FFA	free fatty acid
GLUT4	glucose transporter 4
GLP-1	glucagon-like peptide 1
HbA_{1c}	glycated hemoglobin
HDL	high-density lipoprotein
HR	heart rate
IL-6	interleukin 6
IMI	Intrinsic Motivation Inventory
LDL	low-density lipoprotein
NO	nitric oxide
OGTT	oral glucose tolerance test
QoL	quality of life
SD	standard deviation
SGLT2	sodium-glucose cotransporter 2
STS	Sit-to-Stand Test
TNF-α	tumor necrosis factor α
TZD	thiazolidinedione
$\dot{V}O_2$	oxygen uptake
WC	waist circumference
WHR	waist-to-hip ratio

Summary

Background

Type 2 diabetes has developed into a worldwide pandemic in recent years that is associated with vast comorbidity and mortality and has created an enormous financial strain on health care systems all around the globe. Physical inactivity is known to be one of the most important risk factors for the development of type 2 diabetes and responsible for much of the diabetes-related comorbidity. An increase in regular physical activity is therefore an essential component of a successful type 2 diabetes treatment. However, despite the proven benefits of regular physical activity, the vast majority of patients with type 2 diabetes remain inactive – often due to low motivation and lack of physical activity enjoyment. A recent and promising approach to motivate sedentary individuals to be more physically active and sustainably adhere to regular physical activity is exergames. These games integrate physical activity and personal health information into a game or game-like setting and thereby promote physical activity through playful and enjoyable challenges.

Aims

The aims of this Ph.D. project were: (1) to systematically review the current evidence for the effectiveness of exergaming in overweight and type 2 diabetes and (2) to evaluate the suitability of the Wii Fit Plus exergame to improve cardiorespiratory fitness in individuals with type 2 diabetes. The aim was further (3) to develop a behavior change technique-based smartphone game that delivers individualized exercise and physical activity promotion with the intention to motivate inactive type 2 diabetes patients to become sustainably physically active and to plan a 24-week randomized controlled trial evaluating the game's effectiveness. In addition, it was aimed (4) to assess the accuracy of a commercial activity wristband and of iOS and Android smartphones to measure steps during various walking conditions as those devices were intended to be used to measure the primary outcome (steps per day) in the 24-week randomized controlled trial. Finally, the aims were (5) to examine the effectiveness of the smartphone game to increase daily physical activity and improve glycemic control and aerobic capacity as well as (6) to evaluate the game's suitability to increase the intrinsic physical activity motivation and elicit sustained improvements in physical activity adherence in inactive individuals with type 2 diabetes over a 24-week period.

Methods

In this Ph.D. project, one systematic review and three studies were conducted. In the systematic review, electronic bibliographic databases (PubMed, Embase, Web of Science, OpenGrey, and the Cochrane Central Register of Controlled Trials) were searched up to March 2015. Randomized controlled trials and cross-sectional studies published in English in peer-reviewed journals were included. Included studies were required to have analyzed the effects of exergames on objectively measured intensity parameters of physical activity (oxygen uptake, energy expenditure, and heart rate) in overweight adults with and without type 2 diabetes.

In study 1, data collected from a study conducted by Prof. Schmidt-Trucksäss before the start of my Ph.D. was analyzed to evaluate the cardiorespiratory exertion (maximum and mean oxygen uptake) of 12 elderly individuals with type 2 diabetes during 10-minute bouts of different Wii Fit Plus exercises. Oxygen uptake values were compared to the maximally reached values during a previously conducted cardiopulmonary exercise test on a treadmill. Correlations between oxygen uptake values reached during exergame activity and those reached during the all-out exercise test were analyzed using Spearman's rank correlation coefficient.

Following this preparatory work and considering its results, I collaborated with an international team consisting of sports scientists, gamification researchers, professional game developers, and clinical professionals in developing an innovative smartphone game with the aim to encourage a healthier, more active lifestyle through gamified physical activity in inactive type 2 diabetes patients. To evaluate the effectiveness of the game to sustainably increase physical activity in the target group, I planned a 24-week randomized controlled trial with daily physical activity (steps per day) as the primary outcome.

To verify the validity of the devices used to measure the primary outcome (steps per day) in the 24-week intervention study, I conducted a validation study in an additional investigation of this Ph.D. project. In the study, 20 participants were equipped with 3 iPhone SE smartphones (placed in pants pocket, shoulder bag, and backpack), 1 Samsung Galaxy S6 Edge (pants pocket), 1 Garmin Vivofit 2 wristband, and 2 ActiGraph wGTX+ devices (worn at wrist and hip) and instructed to walk for five minutes at four predefined walking speeds (1.6, 3.2, 4.8, and 6.0 km/h) and to complete an outdoor walking course. Video observation was used as gold standard. Validity was evaluated by comparing each device with the gold standard using mean absolute percentage errors.

In the main study (ClinicalTrials.gov identifier NCT02657018) of this Ph.D. project, 36 inactive, overweight type 2 diabetes patients between 45 and 70 years of age were randomly assigned to either the intervention group or the control group. Participants in the intervention group received the self-developed smartphone game, and participants in the control group were instructed to implement the recommendations from the baseline lifestyle counseling autonomously during the

24-week intervention period. Before and after the intervention period, steps per day were objectively measured during six consecutive days. In addition, glycemic control (HbA_{1c}) was measured by analysis of venous blood, and aerobic capacity (oxygen uptake at the first ventilatory threshold) was assessed during an all-out exercise test on a bike ergometer. Intrinsic physical activity motivation was assessed with an abridged 12-item version of the Intrinsic Motivation Inventory (IMI). In the intervention group, adherence to the game-proposed physical activity recommendations during the intervention period was additionally assessed via the phone-recorded game usage data. Analyses of covariance with adjustment for the respective pre-intervention values were used to compare changes in outcome parameters (steps per day, HbA_{1c}, oxygen uptake at the first ventilatory threshold, and IMI score) between the two groups. Correlations between game use (min) and change in steps per day as well as change in workload (W) at the first ventilatory threshold were analyzed using Spearman's rank correlation coefficient, and a linear regression model was used to assess the relationship between total in-game training (min) and change in IMI total score.

Results

Publication 1: Effects of Exergaming on Physical Activity in Overweight Individuals. **[1]**

The systematic review showed that exergames are able to increase physical activity among overweight individuals. However, the magnitude of this increase as well as the intensity of the exergame-related physical activity and consequently their suitability to offer a guideline-concordant training is greatly dependent on the console and the game mode as well on the duration of play. The majority of the included studies were of poor or moderate methodological quality. No studies exist that objectively assess the effect of exergames on daily physical activity in type 2 diabetes, and the cross-sectional nature of all included studies does not permit judgement on whether exergames are suitable to increase physical activity in the long term. A general lack of adequate individualization of the intensity and difficulty level was noted for all exergames, making most game modes unsuitable for an effective training and potentially unsafe for inactive individuals with chronic diseases and a likely reduced fitness level.

Publication 2: Cardiorespiratory Exertion While Playing Video Game Exercises in Elderly Individuals With Type 2 Diabetes. **[2]**

In elderly type 2 diabetes patients, carefully selected Wii Fit Plus exercises elicit peak values in oxygen uptake that correspond to 60% of the maximally reached values during an all-out treadmill test. Mean values were just above 40% for all exercises and were thus in a range that corresponds to current exercise guidelines. A moderate-to-strong positive correlation between the peak oxygen uptake during exergame play and the maximal value reach during the exercise test was found, indicating that subjects with a higher fitness level were able to exercise at a higher intensity during exergame play than individuals with a lower fitness level.

Publication 3: Mobile Exergaming for Health – Effects of a Serious Game Application for Smartphones on Physical Activity and Exercise Adherence in Type 2 Diabetes Mellitus – Study Protocol for a Randomized Controlled Trial. **[3]**

The self-developed and innovative game takes the proven motivational benefit of exergames into consideration and further extends them by integrating established behavior change techniques into an elaborate storyline. Shortcomings with regard to the suitability and effectiveness of the exercise regimen of current exergames are addressed by offering a fitness level-adjusted training with an individualized rate of intensity progression that is based on the performance in established and in-game-conducted exercise tests.

Publication 4: Validity of Activity Trackers, Smartphones, and Phone Applications to Measure Steps in Various Walking Conditions. **[4]**

The Garmin Vivofit 2 and iPhone SE showed good accuracy for treadmill walking ≥3.2 km/h (<3% deviation from video recordings) and for free walking thus being suitable to measure steps at normal, fast, and even slow walking speeds. The Samsung Galaxy S6 Edge showed good accuracy (<3% deviation from video recordings) for treadmill walking ≥4.8 km/h and for free walking, demonstrating suitability to measure steps during normal and fast walking. The good validity of the iPhone SE was found independently of the phone's position (pants pocket, backpack, shoulder bag), suggesting a broad versatility of the device for physical activity measurement in various settings.

Publication 5: Publication 5 Behavior Change Technique-based Smartphone Game Sustainably Increases Daily Physical Activity in Type 2 Diabetes Patients – A Randomized Controlled Trial. **[5]**

In persistently inactive type 2 diabetes patients, a novel self-developed smartphone game that follows a cognitive/behavioral approach and incorporates individualized exercise regimens and physical activity recommendations elicited significant and clinically meaningful increases in daily physical activity (+4,000 steps per day) over a 24-week period, classifying the participants as sufficiently active post-intervention (average of 9,782 steps per day). The increase in daily physical activity was accompanied by an increase in aerobic capacity with a significantly higher oxygen uptake and workload at the first ventilatory threshold. Total duration of in-game training was positively correlated with the change in steps per day and the change in workload at the first ventilatory threshold. Glycemic control (HbA_{1c}) did not change during the intervention period; however, as indicated by the significant adjusted difference in HbA_{1c} of -0.9 percentage points in favor of the intervention group, there is reason to assume that regular use of the game supports the stabilization of glycemic control in medically well-controlled patients. In the control group, none of the outcome parameters changed significantly during the intervention period.

Publication 5: Effectiveness of a Behavior Change Technique-based Smartphone Game to Improve Intrinsic Motivation and Physical Activity Adherence in Type 2 Diabetes Patients: A Randomized Controlled Trial. **[6]**

The 24-week randomized controlled trial further showed that participants in the intervention group significantly increased their IMI-measured intrinsic physical activity motivation during the intervention period. Participants in the control group did not show any significant changes in their intrinsic physical activity motivation. The analysis of the usage data revealed that participants in the intervention group used the game for an average of 143.1 (SD 59.1) minutes of in-game training per week, which underlines the game's potential in motivating formerly inactive type 2 diabetes patients to meet and sustainably adhere to established physical activity recommendations.

Conclusions

A novel smartphone game that incorporates established motivational elements and personalized physical activity recommendations into an elaborate storyline elicits clinically relevant increases in daily physical activity and aerobic capacity and contributes to a medically well-regulated glycemic control in persistently inactive type 2 diabetes patients. The game is therefore a suitable treatment option to motivate inactive individuals to increase daily physical activity that may be relevant for other inactive target groups with and without chronic diseases. Future research should further refine the game design as well as the motivational and physical activity-related content to make it an even more comprehensive treatment tool for various target groups.

Chapter 1

Background

Chapter 1 Background

In recent years, type 2 diabetes with its considerable comorbidity and mortality, has developed into a pandemic that presents one of the great health care challenges of our time [7,8]. In 2015, an estimated 1.6 million deaths worldwide were directly attributed to diabetes [9] and in many countries, as much as 20% of the total health care expenditure is attributable to diabetes [10]. The development of type 2 diabetes is determined by a variety of modifiable (and non-modifiable) factors whereby an early detection and treatment of these risk factors is crucial for an optimal prognosis [11]. Physical inactivity is known to be one of the most important risk factors for the aggravation of the metabolic state in type 2 diabetes and contributes significantly to the diabetes-related comorbidity and restricted quality of life [12]. An increase in physical activity is, therefore, one of the key components of any type 2 diabetes treatment [13]. Despite the proven benefits of regular physical activity on disease progression and outcome [13,14], most activity-promoting programs targeting patients with type 2 diabetes are seldom successful in the long term due to low adherence rates [15]. A novel approach to motivate sedentary individuals to be more physically active and sustainably adhere to regular physical activity are active video games (exergames) and gamified systems that integrate physical activity and personal health information into a game or game-like setting and thereby promote physical activity through playful and enjoyable challenges [16].

In this Ph.D. project, the effectiveness of exergaming on parameters of physical activity intensity in overweight and type 2 diabetic adults was systematically reviewed (publication 1) and data from a previously conducted proof-of-concept study was analyzed to assess the cardiorespiratory exertion during exergame use in individuals with type 2 diabetes (publication 2). To address the noted shortcomings of current exergames, a smartphone-based game application was developed through an interdisciplinary collaboration with international partners. The game was specifically designed for the needs of middle-aged type 2 diabetes patients to encourage a healthier, more active lifestyle as part of successful diabetes management. In the study protocol (publication 3), a detailed description of the physical activity and game design-related content of the game application is included, and the intended 24-week randomized controlled trial assessing the effectiveness of the game in increasing daily physical activity (primary outcome) is illustrated. In a side project (publication 4), the devices (activity wristbands and smartphones) used for the assessment of the trial's primary outcome (steps per day) were validated. Finally, a 24-week intervention study was completed assessing the effectiveness of the smartphone application regarding increases in daily physical activity, aerobic capacity and glycemic control (publication 5) as well as regarding intrinsic physical activity motivation and physical activity adherence (publication 6).

1.1 Type 2 Diabetes Mellitus – A Global Health Burden

Type 2 diabetes, previously referred to as non-insulin-dependent diabetes or adult-onset diabetes, is a metabolic disorder that accounts for approximately 90-95% of all diabetes cases and is characterized by insulin resistance and a relative insulin deficiency [17]. The expression of the disease varies from patient to patient and may change as the disease progresses, ranging from a predominant insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance [17]. In the early stages of the disease, insulin resistance (i.e., the decreased sensitivity or responsiveness of the metabolic action of insulin) is compensated for by an increased secretion of insulin; the disease often remains asymptomatic and undiagnosed. With the progression of the disease, insulin resistance intensifies, and insulin secretion becomes increasingly defective and consequently progressively insufficient to compensate for the insulin resistance. An impaired glucose tolerance (prediabetes) develops that eventually, if no adequate therapy measures are undertaken, leads to the development of a pathological and symptomatic glucose intolerance and a manifest type 2 diabetes [17–19]. For the diagnosis of type 2 diabetes, the American Diabetes Association [17] proposes the following four criteria: (1) HbA_{1c} ≥6.5%, (2) fasting plasma glucose ≥126 mg/dl (7.0 mmol/l), (3) two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT), and (4) random plasma glucose ≥200 mg/dl (11.1 mmol/l). Because many cases of prediabetes, as well as type 2 diabetes, remain undiagnosed for several years, early and adequate testing of at-risk patients by health care professionals is imperative to prevent and manage this increasingly common disease [9,11,17].

Prevalence

In the recent decades, type 2 diabetes has grown into an emerging pandemic that is a key determinant of morbidity and mortality in both developed and developing countries worldwide and therefore one of the most challenging health problems of the 21st century [7,8]. In 2014, an estimated 422 million adults worldwide (8.5%) were diagnosed with diabetes, with the global diabetes prevalence having nearly doubled since 1980 (4.7%) [11]. In the U.S., 30.2 million adults (12.2%) had diabetes in 2015, with 1.5 million new cases (6.7 per 1000 persons) during that year [20]. In Switzerland, the overall prevalence of diabetes in the adult population was 4.9% in 2011 [21]. While the 25% increase in Switzerland since 2006 underlines the globally increasing prevalence of the disease, the much lower diabetes prevalence compared to the U.S. illustrates how the prevalence varies between countries. Overall, the percentage of adults with diabetes increases with age, reaching a high of 25% among those aged 65 years or older [20,22]. At the same time, the average age of the first diabetes diagnosis has shown a decrease in recent years due to the dramatic increase in the prevalence of type 2 diabetes in children and adolescents [23]. Globally, 45.8%, of all diabetes cases in adults are estimated to be undiagnosed, ranging from 24.1% to 75.1% across data regions. An estimated 83.8% of those cases of undiagnosed diabetes are in low- and middle-income countries [24], but even in high-income countries such as the U.S., the numbers are alarmingly high (23.8% undiagnosed cases) [20].

The numbers of undiagnosed prediabetes, the direct precursor stage of type 2 diabetes, are even more alarming considering that only 11.6% of U.S. adults with prediabetes are aware of their condition. It has been indicated that individuals within a prediabetic HbA_{1c} range of 5.5-6.4% have a 1.6- to 2.3-fold elevated relative risk of developing type 2 diabetes [25], underlining the importance of early diagnosis and treatment in order to improve the prognosis of the disease [20]. For the coming years, further increases in the global diabetes prevalence are projected. The diabetes prevalence is estimated to increase from 8.5% to over 13% in the next 20 years (a 55% increase) [26] with an estimated total of nearly 700 million diabetics by 2045 [10]. Although the increase in diabetes prevalence for future years has been projected globally, estimates of prevalence, again, vary widely between countries [8,26] with the greatest estimated increases in low-income countries (108%), followed by lower-middle-income countries (60%), upper-middle-income countries (51%), and finally high-income countries (28%) [26].

Risk Factors

The risk of type 2 diabetes is determined by an interplay of genetic, metabolic, and lifestyle-related factors. A family history of diabetes, ethnicity, overweight and obesity, unhealthy diet, and physical inactivity are the most important risk factors associated with the disease [11].

A family history of diabetes is a strong and independent risk factor for type 2 diabetes, and it has been shown that 40% of first-degree relatives of type 2 diabetes patients develop the disease throughout their lives compared to incident rates of only 6% in the general population [27]. Although the precise factors accounting for the elevated risk are complex and not fully understood, it is likely that both genetic factors, such as defects in β-cell function [28] and shared environmental components among family members mediate this increased risk of developing type 2 diabetes [29]. In addition to family history, ethnicity affects type 2 diabetes risk [30]. Among the U.S. population, ethnic minorities, such as American Indians (15.1%), Blacks (12.7%), and Hispanics (12.1%) show significantly higher prevalence of diagnosed diabetes than Caucasians (7.4%) or Asians (8.0%)[20]. These disparities are influenced by multiple factors including biological (increased insulin resistance in Blacks and Hispanics compared to Caucasians, independent of adiposity [31,32]) and health behavior-related factors (lower levels of physical activity among Blacks and American Indians compared to Caucasians [33]). Further contributors include social and environmental factors (minorities commonly have less access to healthy food sources or places to exercise [31]) and health system-related factors, such as a common lack of health insurance among minorities and subsequently limited access to preventive health care services [34].

The focus of this dissertation is on the lifestyle-dependent, modifiable risk factors and their treatment, particularly on obesity and physical inactivity. Excess body fat, a summary measure of several aspects of diet and physical activity, is the strongest risk factor for type 2 diabetes, both in terms of the clearest evidence base and largest relative risk [11,35]. The 2017 National Diabetes Statistics Report [20] showed that 87.5% of all U.S. adults diagnosed with type 2 diabetes are either overweight or obese. At the same time, a prospective cohort study of women found that

61% of the acquired cases of type 2 diabetes were attributed to overweight and obesity [36], underlining the importance of excess weight as a major risk factor for type 2 diabetes. Overweight and obesity, together with physical inactivity, have further been estimated to cause a large proportion of the global diabetes burden [37], which makes the fact that the obesity prevalence has tripled in the past four decades and continues to be on the rise all the more alarming [38]. While some studies found central obesity, measured via waist circumference (WC), to be most predictive with regard to an elevated type 2 diabetes risk [39,40], others suggest similar predictive values of general obesity indicators (i.e., body mass index (BMI)) and central obesity indicators (i.e., WC [41–43] and waist-hip ratio (WHR) [43]) regarding incident diabetes. This is likely explained by the fact that general obesity is usually accompanied by increased visceral fat mass [42].

The strong association between obesity and type 2 diabetes is likely mediated through an adipose tissue dysfunction that has a direct impact on the lipid and glucose homeostasis and is likely to result in insulin resistance. Adipose tissue dysfunctions, such as hypersecretion of adipokines (i.e., tumor necrosis factor-α (TNF-α) and interleukin (IL)-6), impairments in triglyceride storage and increases in lipolysis, contribute to higher levels of circulating free fatty acids (FFAs) as well as to an excess of FFAs in the skeletal muscle and the liver. The vast quantities of FFAs, TNF-α, and IL-6 in the skeletal muscle, in turn, reduce the responsiveness of the insulin receptors in the musculature and thereby attenuate the insulin signaling cascade [44–46].

In addition to overweight and obesity, physical inactivity is one of the most important modifiable risk factors for type 2 diabetes and has been reported to contribute independently of and especially in combination with obesity to the development and further progression of type 2 diabetes [17,27,47]. The role of physical inactivity in the development and progression of type 2 diabetes is discussed in further detail in chapter 1.1.1. Further risk factors contributing to the development of type 2 diabetes are smoking [48,49], psychosocial problems such as depression [50,51], anxiety [52], emotional stress [53,54] work stress [55,56], and impaired sleep [57] as well as a low level of education [20,58].

Complications and Comorbidities

Type 2 diabetes is associated with numerous comorbidities and complications such as hypertension, dyslipidemia, cardiovascular disease (CVD), and microvascular disease that affect the vast majority of all patients throughout the course of the disease, especially when no adequate treatment is pursued. As shown by the National Health and Nutrition Examination Survey (NHANES), only 14% of patients with type 2 diabetes are not affected by any other medical condition [59], often due to lack of treatment. Adequate therapy, on the other hand, has been reported to lead to persistent risk reductions in any diabetes-related end point, myocardial infarction, and death from any cause [60]. Because many diabetes-related complications, like type 2 diabetes itself, develop insidiously and unnoticed, they often remain undiagnosed and untreated

for several years [11,17]. NHANES showed that 67% of individuals with type 2 diabetes either have uncontrolled hypertension or are being treated for elevated blood pressure [61]. Both diseases share common pathways such as oxidative stress, adipokines, and insulin resistance, which interact and influence each other in development and progression [62]. Hypertension is one of the most important risk factors for CVD and is the leading cause of premature mortality in diabetic patients [63]. The combination of hypertension and diabetes has been reported to further magnify the diabetes-related morbidity and mortality risk, while tight blood pressure control is associated with long-term relative risk reductions for any diabetes-related end point (24%), diabetes-related death (32%), microvascular disease (37%), and stroke (44%) [64].

Like Hypertension, dyslipidemia is highly prevalent and one of the key risk factors for CVD among patients with type 2 diabetes [65]. It has been found that 46% of all patients with type 2 diabetes show elevated blood lipid values, underlining the need for improved identification and control of lipid abnormalities [59]. The multifactorial features of dyslipidemia in type 2 diabetes are characteristically a high concentration of plasma triglycerides, a reduced concentration of high-density lipoprotein (HDL) cholesterol, and an increased concentration of low-density lipoprotein (LDL) cholesterol (atherogenic triad). These changes are caused by insulin resistance with an attendant increase in FFA circulation and aggravated by increased inflammatory adipokines [65]. LDL cholesterol lowering by 39 mg/dl has been associated with a 9% relative risk reduction in all-cause mortality in patients with type 2 diabetes [66]. In addition, the U.K. Prospective Diabetes Study (UKPDS) found an estimated hazard ratio for the upper third relative to the lower third, of 2.26 for LDL cholesterol and of 1.82 for systolic blood pressure, when evaluating the impact of the baseline risk factors hypertension and dyslipidemia for coronary artery disease in patients with newly diagnosed type 2 diabetes and without evidence of vascular disease [67]. These findings underline the role of hypertension and dyslipidemia (especially LDL cholesterol), as major contributors to the increased risk of CVD in patients with type 2 diabetes.

Ischemic heart disease and stroke account for almost 65% of all diabetes-related deaths [20,65], and CVD death rates are 1.7 higher among adults with diabetes than those without diabetes [68]. The relative risk to develop CVD is four to six times higher in diabetic women and two to three times higher in diabetic men compared to those without diabetes [35,69]. In addition to macrovascular complications, microvascular comorbidities such as diabetic nephropathy, neuropathy, and retinopathy are highly prevalent among individuals with type 2 diabetes [11]. Diabetic hyperglycemia induces pathognomonic alterations in the microvasculature, specifically a thickening of the capillary basement membrane and of the arterioles in the glomeruli, retina, myocardium, skin, and muscle that lead to the development of diabetic microangiopathy [70,71].

The most common microvascular complication of diabetes is diabetic retinopathy [71] which affects approximately 35% of all individuals with diabetes [72] and has caused 1.9% of moderate or severe visual impairment globally and 2.6% of blindness in 2010 [73]. In the initial stages of the

disease (non-proliferative diabetic retinopathy), patients are generally asymptomatic, but in more advanced stages (proliferative diabetic retinopathy), symptoms such as floaters, distortion, and/or blurred vision and finally blindness may occur [74]. Patients with advanced diabetic retinopathy have further been shown to have a 2-fold increased risk of incident CVD [75].

Diabetic nephropathy is the leading cause of renal failure in the U.S and is defined by increases in urinary albumin excretion (UAE), with UAE >20 µg/min and ≤199 µg/min being categorized as microalbuminuria and UAE ≥200 µg/min as macroalbuminuria [76]. Over 80% of cases of end-stage renal disease in the U.S. are attributed to diabetes, hypertension or a combination of the two [77]. The incidence of end-stage renal disease is increased up to 10-fold in adults with diabetes [11], and the importance to reduce the risk of renal complications is underlined by the fact that patients with advanced chronic kidney disease have an approximately 15-fold increased mortality risk compared to those without renal complications [78]. Diabetic nephropathy is further associated with diabetic retinopathy as well as with macrovascular complications [71].

Diabetic neuropathy involves both peripheral and autonomous nerve dysfunctions and is, like other microvascular complications, proportional to both the magnitude and duration of the hyperglycemic condition [70,71]. Peripheral neuropathies can emerge as sensory, focal/multifocal or autonomic neuropathies and have been shown to dramatically increase the risk of lower extremity amputation following infected, non-healing foot ulcers [79]. Rates of amputation in populations with diagnosed diabetes are typically increased 10- to 20-fold compared to non-diabetic populations [79]. Because diabetic neuropathy, like other microvascular complications, is associated with considerable morbidity and mortality, early prevention and treatment are crucial [71].

In addition to the aforementioned metabolic and vascular complications, comorbidities relating to mental health, such as depression [80–82], anxiety [81,82], and fatigue [83,84] are highly prevalent among patients with type 2 diabetes. One in four patients with type 2 diabetes suffers from a clinically significant form of depression with a 5-fold increased prevalence compared to the general population and a 3-fold increased mortality risk as a result of the comorbid depression [85]. Fatigue, a condition characterized by disabling tiredness, is a frequent and persistent symptom in people with type 2 diabetes that hinders the ability to perform daily activities and consequently has a significant impact on quality of life (QoL) [83,84]. Although the etiology of fatigue in diabetes is not fully understood, it is likely that the interplay of physiological (i.e., hyperglycemia [86], chronic pain [83], and sleep disturbances [87]), psychological (i.e., depression and emotional stress [84]), and lifestyle-related (i.e., overweight and physical inactivity [83,84]) factors contribute to the common, concomitant symptom [83,84]. It is further likely that fatigue is both a result and a cause of poor diabetes management and thus directly increases the risk for the aforementioned acute and chronic complications associated with diabetes [84].

All of the described complications contribute to an increased mortality risk among patients with type 2 diabetes [78,88,89]. While adherence to glycemic targets in combination with adequate treatment of cardiovascular risk factors such as hypertension and dyslipidemia have been shown to decrease the risk for cardiovascular and all-cause mortality [90], overall, mortality in diabetes remains elevated [78]. In 2015, an estimated 1.6 million deaths worldwide were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose [9]. The magnitude of the excess mortality risk among type 2 diabetes patients varies greatly between studies (hazard ratio of 1.15 [78] to 2.3 [88]), and while there is agreement that mortality in diabetes is mainly attributable to cardiovascular causes [65,68,78,88,89], more research is needed to determine and fully understand the factors that are still missing in diabetes management and that are necessary to further reduce the excess mortality in this population.

Economic Burden

The direct annual cost of diabetes in the world has been estimated at $825 billion in 2014 [91] and accounts for up to 20% of total health care expenditure in many countries [10]. In the U.S., the total diabetes-related cost in 2012 was $245 billion with 72% of the total cost attributable to direct medical costs and 28% to productivity-related costs such as loss in productivity from work-related absenteeism, diminished productivity at work, unemployment from chronic disability, and premature mortality [92]. Average medical expenditures for people with diagnosed diabetes were about $13,700 per year with approximately 60% of this amount being attributed to diabetes [92]. In Switzerland, diabetes patients accrued total health care costs of 8,424 € per patient per year in 2011 while extrapolated costs were highest for those patients aged over 59 years. Overall, the costs attributable to diabetes, that is the difference in mean costs between persons with versus without diabetes, increased significantly from 5,036 € in 2006 to 5,331 € in 2011 [21]. Overall, people diagnosed with diabetes create 2.3 times higher average medical expenditures than people without diabetes [92] with most medical costs being caused by diabetes-related complications and comorbidities [93]. Compared to a white male who has had diabetes fewer than 15 years, is treated with oral medication and has no comorbidities, the following comorbidities lead to drastic increases in medical costs: hypertension (+140%), dyslipidemia +(130%), cardiovascular disease (+220%), neuropathy (+150%), proliferative retinopathy (+210%), and end-stage renal disease (+225%, with dialysis +630%) [93]. Overall, diabetic complications account for 48%–64% of the lifetime medical cost with 57% of those expenses being attributed to treatment of CVD [94]. The financial strain of diabetes-related medical expenditures is especially burdensome for low-income and middle-income countries who bear almost 60% of the global cost [91,95]. Because substantial parts of treatment costs in these countries have to be paid out-of-pocket, the large financial burden affects patients and their families directly and has an immediate effect on treatment utilization and adherence [91]. The projected increase in the global diabetes prevalence (55% globally and over 100% in low-income countries) in the next 25 years [10,26] will lead to concurrent dramatic increases in the diabetes-related medical costs with an estimated 3-fold

increase in the U.S. during that period [96], which will further intensify the global economic burden of type 2 diabetes.

1.1.1 Physical Inactivity

Physical inactivity is one of the most prevalent and most important independent risk factors associated with type 2 diabetes [12]. Forty percent of adults with type 2 diabetes show high levels of physical inactivity, which is defined as getting less than 10 minutes a week of moderate or vigorous activity in each of the physical activity categories of work, leisure time, and transportation [20]. Physical inactivity is the fourth leading cause of death worldwide [97] and has been estimated to be responsible for 6-10% of all deaths from non-communicable diseases and for up to 30% of deaths from ischemic heart disease [98]. It has further been estimated that an inactive lifestyle has a 2-fold increased relative risk of diabetes [99] and a 1.6-fold increased risk of all-cause mortality [100]. This makes the impact of physical inactivity comparable to that of smoking [97,100], an established risk factor for all-cause mortality. Particularly TV viewing [101–105], sitting at work [106], and total sitting time [107] have been shown to be associated with an increased mortality risk. Eliminating physical inactivity globally would lead to an increased life expectancy of the world's population of 0.68 years [98]. As much as 2.32 million cases of type 2 diabetes in the U.S. in 2012 could have theoretically been prevented, independent of BMI, if all patients met physical activity guidelines [108]. Adults with type 2 diabetes are 30% less likely to engage in physical activity than those without diabetes [15], and when compared with other significant predictors of physical inactivity, such as lower level of education, higher HbA_{1c}, peripheral pain, higher BMI [109], and depressive symptoms [110], previous physical inactivity is the strongest (odds ratio 3.27) predictor for continuing inactivity in type 2 diabetes [109], underlining how pervasive and distinctly difficult to treat physical inactivity is in this population.

It has been hypothesized that obesity, highly prevalent among individuals with type 2 diabetes, lowers voluntary physical activity through a leptin-dependent dopamine dysregulation with a subsequent suppression of the dopamine-related rewarding effect of physical activity [111,112]. Leptin is predominantly produced by adipose cells and is mainly responsible for regulating energy balance by inhibiting hunger. Similar to insulin resistance in type 2 diabetes, in obese individuals, a decreased sensitivity of leptin occurs over time, resulting in an inability to detect satiety despite high energy stores [113]. In addition to leptin’s role of inhibiting hunger, it has been shown to suppress dopamine activity leading to significant reductions in voluntary wheel running in mice [112]. The high levels of circulating leptin with the associated lack of dopamine-induced reward for physical activity are therefore thought to play an important role in the prevalence of physical inactivity among individuals with obesity and type 2 diabetes.

Patients with diabetes have a 3-fold increased risk of sarcopenia with a prevalence of over 15% in this population [114]. Severe decreases in muscle mass in older adults with type 2 diabetes have been found in several studies [115,116,114], demonstrating the negative effects of the disease on

body composition. The decrease in muscle mass is independent of body weight change over time and has been found to be most pronounced in the lower limb [115]. Although men are usually more prone to age-related losses of muscle mass, it has been shown that women with type 2 diabetes show 2-fold rapid declines in thigh muscle mass that are equal to those of non-diabetic men, suggesting that type 2 diabetes causes women to lose the beneficial effect of female sex on preserving lean muscle mass [115]. The loss of muscle mass is accompanied by a 1.5-fold rapid decline in muscle quality (i.e., strength) compared to non-diabetics, illustrating the disease's impairing effect on muscular function [117].

While insulin resistance has been suggested to be a decisive factor in the accelerated sarcopenia in type 2 diabetes [118], physical inactivity also has a strong influence on the development and progression of muscle wasting in diabetes and obesity [119,120] and it seems that these two factors are mutually dependent. Inactivity-related sarcopenia and concurrent excess fat in obese individuals lead to shifted proportions of myocyte and adipocyte insulin receptors with the consequence of a decreased efficiency of insulin-induced glucose uptake. Insulin acting on adipocyte receptors induces about 50% less glucose uptake than a comparable interaction with myocyte receptors. As a result, in individuals with a disproportionate muscle/fat composition, any given glucose load requires an excessive amount of pancreatic insulin secretion for adequate glucose uptake. The subsequent hyperinsulinemia causes insulin-sensitive tissues to become desensitized ultimately resulting in insulin resistance and type 2 diabetes [121]. Thus, sarcopenia combined with obesity encourages insulin resistance, which in turn amplifies sarcopenia leading to an even more unfavorable body composition with an aggravated insulin resistance.

In addition, type 2 diabetes, especially when not adequately controlled, is commonly associated with a reduced aerobic exercise capacity [122], and a low cardiorespiratory fitness has been shown to be one of the earliest indicators of the disease [123]. Conversely, a high cardiorespiratory fitness is associated with a low HbA_{1c} and overall diabetes incidence [124] that is independent of the genetic predisposition [125]. This is likely explained by the fact that regular aerobic exercise improves insulin sensitivity via an increased expression of glucose transporter 4 (GLUT4) in the skeletal muscle and a stimulation of its translocation to the cell membrane [126]. In addition to being physical inactivity-related, the reduced aerobic capacity in type 2 diabetes is caused by a disease-related impairment to recruit skeletal muscle capillaries [122] and by an impaired bioenergetics capacity of skeletal muscle mitochondria [127].

It has been estimated that physical inactivity causes 7% of the burden of disease from type 2 diabetes [97] with an estimated $18.3 billion attributable to type 2 diabetes patients not meeting physical activity guidelines and $4.65 billion attributable to physical inactivity in 2012 [108]. Overall, the direct medical expenditures associated with physical inactivity in the U.S. were an estimated $131 billion/year between 2006 and 2011 [128] and thereby, again, comparable to the economic burden caused by smoking ($175 billion in 2013) [129].

1.2 Prevention and Management of Type 2 Diabetes

There is discouraging evidence that because hyperglycemia often develops gradually and is especially in the earlier stages often not severe enough to cause any of the typical diabetes symptoms, many at-risk patients do not receive adequate testing and remain consequently undiagnosed for several years [17]. In this regard, it is important to note that the choice of the diagnostic criterion can heavily influence whether or not diabetes is diagnosed [8]. Estimates of the proportion of undiagnosed diabetes range from 20% based on HbA_{1c} [130], 30% based on fasting plasma glucose [131] to 40-60% based on OGTT [132] when only one criterion is used for diagnosis. On the other hand, the use of the OGTT in addition to fasting plasma glucose has been shown to result in the detection of an extra 30% of previously undiagnosed cases of type 2 diabetes. The use of several diagnostic criteria for at-risk patients is, therefore, strongly advised and indispensable for a timely detection and treatment of the disease [17].

The focus of the prevention and management of patients with type 2 diabetes and those at risk is primarily on glycemic control combined with comprehensive measures to reduce cardiovascular risk factors [133]. Reducing hyperglycemia in type 2 diabetes below the HbA_{1c} goal cut-off point of 7% has been associated with decreased onset and progression of microvascular complications [133,134]. More or less stringent glycemic targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events [17]. In general, treatment approaches should be individualized and should balance the benefits of glycemic control with the potential risks such as the patient's age and health status and adverse effects of blood glucose-lowering medication to ensure a successful and safe disease management [133]. An effective diabetes treatment is dependent on several patient-related and health care provider-related factors, including adherence, knowledge and awareness, financial resources, comorbidities, and social support of the patient, as well as, the health professional's knowledge and compliance with treatment guidelines, the patient-clinician interaction, and the health care system [135]. The vast number of influencing factors illustrate the complexity of successful diabetes care and underline the challenge of achieving an optimal prognosis.

An essential goal of diabetes prevention and management is to induce lifestyle changes in the patient, especially with regard to dietary and physical activity behavior [14], to treat diabetes-related risk factors. Particularly a reduction in body fat mass along with maintenance or even increase in muscle quantity and quality are targeted to improve insulin resistance [136]. It has been shown that lifestyle modifications such as a calorie-restricted diet and exercise to promote body fat loss reduce the risk of developing type 2 diabetes in patients with impaired glucose tolerance by 58% [137], and that these beneficial effects are independent of ethnicity [137–140] and persistent in the long term [141,142]. Several pharmacological interventions have been reported to prevent or delay type 2 diabetes as well; however, it has been found that medical treatment alone is not as effective as changes in diet and physical activity and that the beneficial

effects of blood glucose-lowering medication dissipate after discontinuation [143]. In addition to the proven effectiveness of preventing diabetes, diet and physical activity promotion programs are distinctly more cost-effective [144] and consequently the primary target of any type 2 diabetes treatment. Appropriate medication may be used to augment lifestyle improvements depending on the severity of the disease and presence of comorbidities; however, they should never replace them [11]. While a general reduction of the calorie intake is necessary to achieve losses in body fat, it has been found that the quality of dietary fats and carbohydrates is more crucial concerning a successful diabetes management than the mere quantity of these macronutrients [145]. High quality plant-based fats, particularly omega-6 polyunsaturated fatty acids rather than animal fats [36,146] and diets rich in cereal fiber [147] (i.e., whole grains rather than processed, white grains [148,149]) have demonstrated to lower diabetes risk and improve glycemic control and blood lipids in patients with diabetes [145]. Further, for patients on calorie-restricted diets for weight loss, maintenance or even increases in protein intake may be advised to prevent losses in muscle mass [150], yet there is currently no sufficient evidence [150–152] to justify restrictions of protein intake for adults with type 2 diabetes, even those with diabetic nephropathy. Generally, an appropriate diet for diabetes management is rich in whole grains, fruits, vegetables, legumes, and nuts and mostly avoids refined grains, red/processed meats, sugar-sweetened beverages, and alcohol consumption [145].

In addition to dietary changes, physical activity is a key element in the prevention and management of type 2 diabetes that can help create a caloric deficit to aid fat reduction and improve insulin resistance. Participation in regular physical activity is well known to prevent or delay type 2 diabetes by improving blood glucose control and reduce the risk of typical comorbidities such as dyslipidemia, hypertension, and cardiovascular events [153]. The role of physical activity in the treatment of type 2 diabetes is discussed in further detail in chapter 1.3.

If lifestyle changes are not sufficient to reach glycemic targets or if the severity of hyperglycemia and the presence of comorbidities require an expedited achievement of an adequate glucose control, drug therapy is advised to support the lifestyle modifications [133,154]. In most patients, oral antidiabetic drugs such as metformin are the favored initial drug choice and usually added at, or soon after, diagnosis. Metformin has been shown to have only few contraindications and side effects, to be weight-neutral, and to be potentially beneficial with regard to cardiovascular outcomes [133]. If patients are unlikely to attain their glycemic targets using monotherapy or if HbA_{1c} is ≥9%, a combination of metformin and one or more of the following second-line agents are prescribed: sulfonylurea, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonist, or basal insulin [133]. Because insulin may be effective in providing glycemic control even when oral antidiabetics are insufficient, the addition of insulin to any combination therapy is indicated in cases of severe hyperglycemia and especially when any catabolic features such as weight loss or ketosis are present [27,133]. Any choice of medication should be based on disease-

and drug-specific characteristics, should directly involve the patient in the decision-making process, and should include frequent counseling sessions to ensure the highest possible effectiveness and lowest risk for adverse effects [133,154]. In cases of severe obesity and those patients with an inability to attain glycemic targets despite extensive drug treatment, nonpharmacological interventions such as bariatric surgery may be considered to achieve adequate glycemic control at last [155].

In addition to seeking improvements in glycemic control, consistent and comprehensive treatment of risk factors and type 2 diabetes-related complications is eminently important with regard to cardiovascular events and mortality risk. Adequate antihypertensive therapy [156], blood lipid management [65], and smoking cessation [49] have been shown to be particularly beneficial in lowering the risk for macro- and microvascular complications and in improving survival in patients with type 2 diabetes.

1.3 Physical Activity and Type 2 Diabetes

Physical activity is a central component in the prevention and treatment of type 2 diabetes, and the beneficial health effects with regard to the disease and its comorbidities are well documented [153]. Effects of physical activity include increased insulin-independent and insulin-dependent glucose uptake into the active muscles during exercise and a subsequently improved glycemic control that lasts from 2 to 72 hours post-exercise, depending on intensity and duration [153,157]. Chronically, the exercise-induced molecular adaptions improve systemic insulin action and overall metabolic health and thereby augment the disease outcome [126].

1.3.1 Molecular Adaptions of Glucose Uptake Through Physical Activity

During physical activity, energy supply shifts from a predominant utilization of FFAs to a mix of fat, muscle glycogen, and glucose. Particularly higher exercise intensities elicit an increased metabolization of carbohydrates [153,158], and a long exercise duration with increasingly depleted glycogen stores leads to an up-regulation of blood glucose uptake and utilization along with an increased release of FFAs from adipose tissue [153]. Despite an impaired insulin action, the exercise-induced increases in carbohydrate oxidation are somewhat preserved in type 2 diabetes and contribute along with the exercise-induced increases in fat oxidation to an augmented glycemic control and a reduction of adipose tissue [157]. During exercise, muscular contractions trigger GLUT4 translocation to the cell membrane through 5’-AMP-activated kinase and thereby increase glucose uptake into skeletal muscles, which can persist for several hours post-exercise [153,157]. Since muscle activity-related GLUT4 translocation involves a distinct and insulin-independent pathway, it is not impaired by insulin resistance [159,160]. In individuals with type 2 diabetes, the increased uptake and utilization of blood glucose during exercise is usually not matched by an equal increase in hepatic glucose production and thus leads to a favorable decline in blood glucose levels [161].

As plasma insulin levels likewise decrease during exercise, the risk of hypoglycemia in those not using exogenous insulin is very small [153]. In addition to the insulin-independent increase in glucose uptake and subject to the severity of insulin resistance, insulin action is also acutely enhanced by physical activity [159,160]. The enhancement in systemic insulin action is believed to be caused by adaptations in muscle insulin signaling, GLUT4 expression and action, and an associated improvement in insulin-stimulated glucose uptake [162] that persists even longer post-exercise than that of the insulin-independent pathway [160]. Over time, the physical activity-induced, steady increase of GLUT4 expression, along with an enhanced responsiveness of skeletal muscles to insulin, leads to an improved glucose control [162]. The improved insulin-stimulated glucose disposal seems to be mediated through an exercise-induced restoration of mitochondrial function of skeletal muscles, specifically an enhanced oxidation of intramyocellular lipids, and an associated improved metabolic flexibility [126,127,163,164]. Regularity of physical activity is key to maintaining the beneficial effects of exercise because the effects of a single exercise bout wane within a few days [153].

Beyond the beneficial effects on the glucose and lipid metabolism, physical activity is beneficial with regard to diabetes-related comorbidities such as hypertension. In general, the exercise-induced mechanical stress on the arterial walls acutely encourages the release of vasodilating substances (i.e., nitric oxide (NO) and bradykinin), improves baroreflex sensitivity, and decreases sympathetic nervous activity that together promote post-exercise hypotension [165]. Admittedly, endothelial function is often impaired in type 2 diabetes, resulting in a reduced release of NO and a subsequently diminished antihypertensive effect of physical activity. However, especially high-intensity exercise has been shown to increase the bioavailability of NO in type 2 diabetes and consequently, albeit attenuated, to be vasoprotective and antihypertensive despite the general endothelial dysfunction [157,166].

1.3.2 Effects of Increased Daily Physical Activity

Reductions of sedentary behavior combined with increases in unstructured physical activity, applicable to patients' daily life and home environment, can be initial measures and potential stepping-stones towards more structured exercise in inactive individuals with type 2 diabetes who are unable or unwilling to participate in regular physical activity [13]. Interrupting prolonged sitting by brief bouts (2-5 minutes) of standing [167] or light- to moderate-intensity walking every 20-30 minutes [167–169] has been shown to lead to improvements in glycemic control in inactive individuals with an impaired glucose regulation that are persistent for up to 22 hours [170]. Alternating 30-minute bouts of standing and sitting [171], as well as standing during desk-based office work [172], have further been shown to attenuate the postprandial glucose response related to uninterrupted sitting during a typical workday, thus being particularly beneficial after meals.

Other non-exercise activities such as strolling, household tasks, dog walking, or light gardening are additional opportunities to reduce the total daily sedentary time and improve glycemic control in type 2 diabetes [173,174]. Activities of daily life have further been associated with a lower mortality risk in a population with chronic kidney disease [175], suggesting a potentially beneficial effect on disease outcome. Although the longer-term health benefits of briefly interrupting sedentary time remain to be conclusively determined, non-exercise activity with its reported benefits of (acutely) improving glycemic control should be encouraged among unmotivated, inactive individuals with type 2 diabetes due to their low-threshold character and easy implementation into the daily routine [13,176]. Future studies are needed to examine the clinical benefit of such non-exercise activities in the long term and evaluate if this approach, in fact, improves adherence rates.

Walking as a typical form of daily physical activity is the most popular and most preferred form of exercise among patients with type 2 diabetes [173]. Because no additional equipment or a gym membership is necessary to walk, implementation of regular walking into the daily routine may have a lower threshold than many other forms of physical activity. Promoting walking such as habitual active transport may be a promising approach to increase daily physical activity among those who are unmotivated to participate in structured exercise. Prospective data of a population with otherwise high levels of sedentary behavior (>8 hours of sitting time per day) and consequently an expected increased mortality risk, suggest that high volumes of daily walking (>40 min/day) during the commute to and from work have a protective effect against the increased risk of all-cause mortality [177]. These observations are complemented by findings that attribute a 39% lower all-cause mortality rate and a 34% lower CVD mortality rate to 2 hours or more of unstructured walking per week in otherwise low-active individuals with type 2 diabetes [178]. Further, in a prospective study involving >9,000 individuals from 40 countries, a 2000-step per day increase in daily life over 12 months was associated with an 8% lower cardiovascular event rate [179]. These observational results strengthen the evidence for promoting daily-life walking, especially because changes in ambulatory activity were assessed objectively using pedometers instead of questionnaires, which are known to have poor validity [180]. In this context, it has been suggested by very recent findings from cross-sectional and prospective studies that physical activity episodes of any length, even those shorter than the previously proclaimed minimum duration of 10 minutes, can yield important health benefits such as improvements in blood pressure [181,182], blood lipids [182,183], and metabolic syndrome [184].

Regarding glycemic control, a meta-analysis of 20 randomized controlled trials (866 participants) showed significant decreases in HbA_{1c} (0.5 percentage points) after ≥8 weeks of regular walking. These improvements were accompanied by significant decreases in diabetes-related risk factors such as BMI (0.91 kg/m^2) and diastolic blood pressure (1.97 mmHg) [185]. In general, it has been suggested that the duration of walking interventions, and those promoting increases in daily physical activity, should be ≥8 weeks with a weekly volume around the guideline-recommended

[13] (see 1.3.5) 150 minutes per week to effectively lower HbA_{1c} [186,187]. Higher frequencies (≥5 times per week compared to <5 times per week) of physical activity may yield additional benefits in HbA_{1c} reduction, independent of the overall weekly walking volume [186]; although even bouts of 10 minutes or less can have beneficial effects on glycemic control [182,184,188].

1.3.3 Effects of Structured Exercise

Regular aerobic training has been shown to reduce HbA_{1c}, triglycerides, LDL-cholesterol, hypertension, and systemic inflammation in type 2 diabetes [189,190]. In this regard, structured moderate-intensity exercise of ≥150 minutes per week is associated with greater improvements in glycemic control than that of <150 minutes per week [191], while glycemic improvements can be achieved even without weight loss [192]. As shown by the results of a meta-analysis of 21 randomized controlled trials, HbA_{1C} improvements that can typically be expected following aerobic exercise interventions of ≥8 weeks of duration are around 0.6 percentage points [193]. The magnitude of these improvements is comparable to those of drug monotherapy with decreases of 0.5-1.25 percentage points depending on the antidiabetic agent [194,195] and associated with a 22% decrease in microvascular complications risk and an 8% reduction in myocardial infarction rate. Endurance training can further prevent the decline in aerobic working capacity normally seen in untrained diabetics and thereby maintain or even improve quality of life [196]. Lower volumes may be equally effective when exercise is performed with vigorous to near maximal effort [197–200]. Even six sessions of high-intensity interval training (HIIT) consisting of 10×60 seconds of cycling at 90% of the maximal effort with 60 seconds of recovery over a 2-week period have been shown to markedly increase skeletal muscle GLUT4 expression and decrease blood glucose concentrations [198], despite a weekly training volume that is 50% lower than the recommended 75 minutes of vigorous physical activity [13] (see 1.3.5). While some studies suggest superiority of high-intensity exercise [197,201], to date it has not been conclusively evaluated whether higher intensities yield greater improvements in insulin sensitivity than moderate intensities [174], and studies that controlled for exercise volume by compensating lower intensities with longer duration found no additional benefit for HbA_{1c} following high-intensity endurance training [202,203]. If the potentially time-efficient high-intensity exercise strategy is pursued, patients with type 2 diabetes are advised to get pre-exercise medical clearance even if it would normally not be required before engaging in moderate-intensity physical activity [13]. Before designing high-intensity workouts for persistently inactive individuals, the potentially higher threshold to engage in these workouts should be considered. While the time-efficiency aspect may be appealing to those who are motivated to be physically active, the concurrent high-intensity character and thus higher perceived exertion [204] may present an additional barrier to those who lack physical activity enjoyment since high exertion and the related physical overload is precisely one of the reasons why these individuals do not enjoy physical activity.

Resistance exercise too has been associated with acute and chronic improvements in glycemic control [205–210], systemic inflammation [211], and endothelial function [212]. Although some studies suggest a slightly more pronounced effect of aerobic exercise on glycemic control [213], the results from large exercise interventions [214,215] and meta-analyses [189,191] indicate that the effects of weight training on HbA_{1c} of around 0.5 percentage points are comparable to those of aerobic exercise. Along with the improvements in long-term glycemic control, gains in lean body mass of 3-6 kg and increases in strength of about 50% have been reported [216], underlining the beneficial effect of resistance exercise with regard to diabetes-related sarcopenia and muscle weakness. Since improvements in muscle quantity and quality following resistance training are further associated with improvements in cardiorespiratory fitness [217], this form of exercise may be an attractive option for patients suffering from cardiovascular complications and those with a reduced exercise tolerance who are unable to perform a strict endurance exercise regimen [174]. In general, a combined training is recommended for optimal glycemic control and health outcomes [13,214]. While aerobic exercise should be the predominant form of exercise in most patients with type 2 diabetes and excess body fat to reduce adipose tissue and improve insulin resistance, resistance exercise can help to maintain lean body mass, especially when patients are on a calorie-restricted diet and should be incorporated into the exercise regimen at least twice per week [174]. Because acute effects of exercise on glycemic control usually wane after 48-72 hours [157], it is recommended not to let more than three days elapse in between exercise sessions to maintain a steady state of improved glycemic control [13]. Higher exercise frequencies may yield additional benefits [218], likely due to the fact that more exercise sessions in a week are usually accompanied by a greater exercise volume. Since resistance and endurance exercise has been shown to yield equal benefits with regard to glycemic control [189,191,214,215], exercise regimens can and should be tailored to the patients' individual preferences and functional abilities.

Although no randomized controlled trial data on the effects of structured exercise on mortality in type 2 diabetes exist, observational studies suggest an inverse association with all-cause and CVD mortality in a dose-response manner after adjusting for covariates such as BMI, smoking, alcohol use, and preexisting CVD and hypertension [219]. Even low volumes of 15 minutes of physical activity per day have been shown to significantly reduce mortality risk by 14% compared to inactive individuals and have, therefore, been proposed as the minimum amount of physical activity required to extend life expectancy [220]. This may be especially relevant for very inactive and unmotivated individuals for whom the guideline-recommended 150 minutes per week is, at least initially, an unrealistic and deterrent goal.

Beyond the distinct health benefits of structured exercise, lifestyle interventions with a strong physical activity component can reduce diabetes-related and all-cause health care services, such as hospitalizations, outpatient services, and use of prescription medication and thereby considerably lower medical costs with a direct positive impact on the economic and societal burden of type 2 diabetes [196,221].

1.3.4 Physical Activity Recommendations

Based on the existing evidence of the effectiveness of different physical activity and exercise modalities in individuals with type 2 diabetes, several international physical activity recommendations have been proclaimed. The following is a synthesis of the physical activity guidelines from the International Diabetes Federation (IDF) [222], American Diabetes Association (ADA) [13,133,223], European Association for the Study of Diabetes (EASD) [133,224], Canadian Diabetes Association (CAD) [225], and Francophone Diabetes Society (FDS) [226]:

- Asymptomatic patients who generally do not need pre-exercise medical clearance before engaging in low- or moderate-intensity physical activity, should be encouraged to engage in 150 minutes or more of moderate-intensity physical activity per week [13,133,222–227]. Moderate-intensity physical activity corresponds to 64-76% of the maximum heart rate [228] or 12-13 points on a 6-20-point rate of perceived exertion (RPE) scale [229].

- Shorter durations (minimum of 75 minutes per week) of vigorous-intensity physical activity may be a sufficient alternative for younger and more physically fit individuals if no cardiovascular or musculoskeletal contraindications are present [13,133,222–227]. Vigorous-intensity physical activity corresponds to 77-93% of the maximum heart rate [228] or 14-17 points on a 6-20-point RPE-scale [229].

- Physical activity sessions should be spread over at least 3 days per week with no more than 2 days in between sessions to permanently enhance insulin action [13,133,222–227]. Physical activity episodes of any duration may be included in the daily accumulated total volume of physical activity [230].

- For those who have participated in regular moderate-to-vigorous-intensity exercise and who are clinically stable, low-volume HIIT may present an alternative approach to continuous aerobic activity [13,231].

- Ideally, both aerobic and resistance exercise training should be performed for optimal glycemic and health outcomes and engagement in 2-3 weekly sessions of resistance exercise on nonconsecutive days is recommended [13,133,222–227]. Exercises should involve the major muscle groups with an initially recommended moderate intensity of 50–69% of the one repetition maximum [228] and one set of 10-15 repetitions per exercise. Heavier resistance (70-84% of one repetition maximum [228]) with more sets and 8-10 repetitions are recommended with increasing training progression for further improvements in glycemic control [13].

- In addition to general increases in structured exercise, adults with type 2 diabetes should be encouraged to increase total daily incidental (non-exercise) physical activity for additional benefits in glycemic control. Extended amounts of sitting time (>90 minutes) should be interrupted with short bouts of light activity, preferably every 30 minutes [13,223].

- Daily non-exercise physical activity of >7,500 steps is recommended. For further benefits in glycemic control, 3,000 steps should be taken at a brief walking pace of 100 steps per minute (equal to 30 minutes), preferably in addition to the incidental activity [232,233].

When designing physical activity programs for individual patients, the proclaimed recommendations are meant to provide guidance but should be tailored to the individual's current activity level, potential health restrictions, and personal interests [227]. Selecting appropriate volumes and modalities of physical activity for individual patients is challenging but extremely important because unrealistic, overwhelming targets often reduce patients' motivation and thereby directly affect their adherence to the program [174,234]. It is important to note that while meeting physical activity guidelines should be the long-term goal, even small initial increases in physical activity can be beneficial for glycemic control and general health and are most certainly better than no increases at all.

1.4 Improving Physical Activity Adherence in Diabetes

Despite the many individually relevant health benefits and the fact that regular physical activity is a proven cornerstone of a successful type 2 diabetes management (see 1.3), adherence to regular physical activity, especially in the long term, is very poor (see 1.1.1) with only about 25% of patients meeting physical activity recommendations [15]. The issue of poor long-term adherence extends to many research trials that aim to induce healthy behavior changes in low-motivation target groups. Typically, participants show encouraging responses to the treatment at first but have gradually increasing difficulties to adhere to the lifestyle changes over time despite initially volunteering to participate in the study. These adherence difficulties lead to premature dropout rates as high as 50% and disappointing long-term outcomes [135,235]. Identifying barriers to regular physical activity, as well as finding strategies to overcome these barriers and improve patients' physical activity adherence, is a major research challenge but crucial for a successful long-term diabetes management.

1.4.1 Barriers to Regular Physical Activity

Barriers to regular physical activity include those influenced by the individual's own decision making (internal barriers) and those independent of the own decision making progress (external barriers) [236,237]. Typical internal barriers include lack of interest, motivation or self-discipline [238–240], lack of physical activity enjoyment [238], as well as poor self-image and aversion to exercise facilities [241,242]. Further, poor overall health and acute health concerns such as

hypoglycemia or fear of injury or cardiovascular complications often keep patients with type 2 diabetes from being regularly active [236,241,243]. Additional factors that can influence physical activity participation include psychological problems such as fatigue and depression [243], lack of time [238,241,242,244], and insufficient knowledge about the benefits of physical activity [240,245], as well as difficulty to change well-established habits and/or a negative perception of the recommended new regimen [240]. In sedentary individuals with type 2 diabetes, an initially low level of aerobic fitness, a decreased insulin sensitivity, and a higher fat mass have further been identified as independent physiological predictors of dropout from exercise intervention studies, suggesting a need for researchers to be particularly proactive in encouraging these individuals to adhere to the intervention [135].

External barriers usually relate to missing social support and the associated lack of supportive and motivating companionship [236,241,245–247], as well as to environmental factors such as bad weather [236,238] or the absence of a physical activity-friendly infrastructure [241,244,246]. Cultural factors [245] and insufficient support from health care providers with a subsequent lack of knowledge and reinforcement can further influence exercise adherence negatively [247].

In a cross-sectional study with older adults, the three most frequently cited barriers to regular physical activity were poor health (57.7%), lack of company (43.0%), and lack of interest (36.7%) [239]. While the individually relevant internal and external barriers vary from person to person, the overall effect of the barriers is the same – the perceived cost of physical activity exceeds the expected benefits and therefore prevents individuals with type 2 diabetes from engaging in regular physical activity [236].

1.4.2 Changing Physical Activity Behavior

To improve the translation of research into practice and achieve a successful change in mid- to long-term physical activity behavior, it is indispensable to incorporate behavior change techniques into any physical activity-promoting intervention [236,248,249]. In recent years, behavior change interventions have become an essential component of effective practice in clinical medicine and public health [249,250], as incorporating individually applicable behavior change techniques can optimize the effectiveness of physical activity interventions and potentially help make them more economical [251]. It has been shown that structured behavioral interventions can significantly increase physical activity in adults with type 2 diabetes [252] and sustainably reduce HbA_{1c} over 24 months [253]. In addition, programs that target behavior change have been shown to be more effective in improving glycemic control in adults with long-duration diabetes than the non-behavioral control intervention [254].

When designing behavior change interventions, a systematic method is required that aims to comprehensively understand the nature of the behavior to be changed and provides an appropriate system of specific techniques that can make use of this understanding by targeting

the internal (psychological and physical) and external (immediate environment) mechanisms involved in the change of a particular behavior in a given context and a given population [249,250]. Particularly the identification of the behavioral context is key to the effective design and implementation of interventions and their long-term success [249,250].

By way of a systematic review of existing studies, ninety-three techniques have been identified as playing a role in the process of changing physical activity behavior [236]. In brief these techniques include: (realistic) goal setting, action planning, barrier identification, review of behavioral goals, rewards, focus on past success, feedback on performance, information on where, when and how to perform the behavior, use of follow up prompts, environmental restructuring, social support, fear arousal, and relapse prevention. Five of these behavior change techniques (in rank order of effect size) have particularly been shown to be associated with increased levels of physical activity in individuals with type 2 diabetes and a linked improvement in HbA_{1c}, namely (1) prompting focus on past success, (2) barrier identification/problem-solving, (3) use of follow-up prompts, (4) providing information on where/when to perform the physical activity behavior, and (5) prompting review whether physical activity goals were achieved, followed by revisions or adjustments [251].

It is important to note that the same techniques may serve different intervention functions [249], and that different behavior change techniques may interact with each other to amplify or reduce effectiveness [255]. The effectiveness of specific behavior change techniques further depends on how they are delivered, and it may vary distinctly depending on setting, target population [255], and personality [256], which further complicates the process of selecting appropriate and effective techniques. It needs to be understood, however, that while some techniques involve a greater cognitive burden than others, and thus may make utilization and consequently behavior change more difficult [257], the target behavior can in principle arise from combinations of any of the components of the behavior system [249]. It is therefore absolutely essential that those designing and applying intervention programs have a sufficient array of behavior change techniques at their disposal as well as the expertise to tailor them to the needs of the individual patient and the context in which they are most effective [251]. No matter which techniques are applied, the intention is to enhance the individual's self-efficacy, a key predictor of physical activity behavior in individuals with diabetes [258]. In combination with a supportive social and infrastructural environment, an increased self-efficacy can improve the effectiveness of physical activity-promoting interventions and increase long-term exercise adherence [236].

1.4.3 Modern Technologies to Support Behavior Change and Increase Exercise Adherence

Tools that use personal informatics to support physical activity behavior change are a growing area of research and practice [16,259]. These tools focus on collecting and interpreting personal information such as physical activity data and providing feedback to the user regarding the target behavior while still supporting individual autonomy in health decisions [13,16,236].

Personal informatics tools such as step counters have been widely studied as behavior-change tools in recent years, and it has been shown that their use can increase daily physical activity and yield health benefits such as decreases in BMI and blood pressure [260]. A meta-analysis of 12 trials and 1,458 participants showed that pedometers/accelerometers can significantly increase voluntary free-living physical activity (standardized mean difference of 0.57) in adults with type 2 diabetes [261], whereas using daily step goals, even when self-selected, is predictive of an increased physical activity adherence [262]. While a general dose-response association between accelerometer-based physical activity variables and HbA_{1c} has been reported [188], it is important to note that increases in daily steps are not always accompanied by improvements in glycemic control [261,262]. Even the positive activity-based findings for pedometers/accelerometers are not universal, and older adults (>60 years), especially, seem to benefit less from their use [251,257]. It is not that these devices are ineffective to support behavior change in this target group per se, rather that certain target groups require greater additional support to use them as effective self-monitoring tools, highlighting the importance of incorporating adequate behavior change techniques into physical activity-promoting interventions [251]. The results of a study [263] using a pedometer-based behavioral modification program with telephone support (following cognitive-behavioral therapy) in type 2 diabetes patients (62±9 years) show significantly increased daily physical activity (+2,744 steps/day) after a 24-week intervention that remained increased six months post-intervention (+1,872 steps/day). The support of a pedometer-based intervention with feasible, flexible, low-cost telephone support may thus be a suitable method to provide a successful physical activity promotion in type 2 diabetes patients [263].

Many modern activity trackers provide automated feedback and support through interactive tools to the user (via computer or mobile app) and thereby make use of behavior change techniques such as individualized goal-setting, prompts/cues, rewards, and focus on past success that are typically used in clinical behavioral interventions [264]. It has been shown that participants of various ages respond favorably to physical activity-promoting smartphone apps [265] and that the combination of a smartphone-based pedometer app with an automated and personalized feedback through short messages yields superior reductions in HbA_{1c} compared to the standard pedometer app without personalized feedback [266]. It has been suggested in this regard that technology-delivered and/or internet-based physical activity interventions are generally more effective for adults with type 2 diabetes with regard to increases in physical activity adherence than standard care because behavior change techniques are often incorporated and an improved self-monitoring is consequently enabled [267]. Given that the majority of individuals with type 2 diabetes has access to smartphones and the internet, technology-based support is further appealing for extending the reach of clinical interventions [267]. This can be of particular interest to those who are geographically isolated and do not have access to usual evidence-based physical activity interventions or those who have lower levels of social support and would benefit from the “social” interaction with other participants through the internet-delivered intervention [268].

In addition to the extended reach and the motivating character of many technology-based programs, their potential to make the delivery of behavior change-based physical activity interventions more affordable increases their potential for public health impact [268]. Conventional lifestyle programs have been shown to be principally cost-effective in preventing diabetes and more so than drug treatment, but generally do not appear to be cost-saving [144,269], or if so only after many years [270]. Although there is a shortage of studies that report cost-effectiveness data for technology-based physical activity interventions [271,272], it has been suggested that these interventions can, in fact, be cost-effective in the short term and distinctly more economical than conventional programs [268,273]. After initial production costs, technology-delivered interventions save costs related to study personnel and use of exercise facilities and likely become progressively cost-effective with increasing dissemination [268].

Despite the predominantly positive findings and the suggested economic viability, more research is needed to evaluate the long-term efficacy and efficiency of modern technologies in the prevention and treatment of type 2 diabetes conclusively and to determine which individuals benefit most from which technological approach and in which context. The greatest challenge for designers of health tracking technologies continues to be gaining and especially holding the attention of those who are inactive and not concerned or even curious about their own health (data) and to encourage them to become more sustainably active [16]. To promote behavior change successfully, any personal informatics application must convince the user that the behavior change will be beneficial and outweighs any barrier-related costs (see 1.4.1) or negative consequences of the unaltered behavior. The personal informatics application must further enable the user to develop self-motivation and confidence in the own ability to change the behavior (i.e., increase self-efficacy) [16]. For individuals who remain unmotivated and for whom personal informatics applications are not able to elicit the required changes in physical activity behavior, different approaches that address specific barriers or that somehow circumvent the need to change personal beliefs may be more successful [16].

1.4.4 Exergames and Gamification for Health

In recent years, physical activity-promoting games (exergames) and so-called “gamified” systems have increasingly been used and examined to trigger healthy behaviors in those who cannot be motivated through conventional physical activity-promoting interventions or even personal informatics by itself [16,274,275]. The gamified approach aims at making personal health and physical activity information a motivating and meaningful experience by turning specific health problems (i.e., physical inactivity) into challenges that are enjoyable to solve and lower the subjectively perceived cost of physical activity [16,276]. Rather than trying to convince the individual of the benefits of a physically active lifestyle, well-designed gamified approaches intertwine appealing benefits (i.e., in-game rewards) with health goals that may provide the missing cognitive and emotional stimulus to increase physical activity adherence.

Game designs that manage to increase players' physical activity-related self-efficacy and help them discover the enjoyment of physical activity, have the potential to support long-term behavior change beyond the use of the game [16].

It has been estimated that 60% of Americans play some type of video game and that 70% of players are adults (26% 50+ years) [277]. Even though the prevalence and demographics of playing exergames have not been sufficiently studied per se, sales figures indicate a broad and lasting appeal [268]. Exergames come in many different forms: motion-controlled console games (e.g., Nintendo Wii or Xbox Kinect) that include hand-held accelerometer controllers, floor-based mats or boards, and cameras that evaluate full-body movement or mobile smartphone games (e.g., Pokémon GO) that typically use GPS and built-in accelerometers to track the player's movement [268].

Numerous reviews have evaluated the effectiveness of console-based exergames in different target groups and have found predominantly promising results in laboratory studies [1,268,278,279]. Chapter 3, a systematic review that led to the first publication [1] of this Ph.D. project, discusses the effects of console-based forms of exergaming on different intensity parameters of physical activity in overweight adults in detail. Exergame interventions have been shown to increase physical activity [280], improve physical function [281], and support weight loss [282] in adults of different ages. While the results for physical activity outcomes vary greatly, it has been suggested that exergames may be effective as replacements for sedentary screen time [268]. Pokémon GO, as a recent representative of a mobile activity-inducing game, has shown inconclusive results regarding changes in physical activity behavior with sharp increases in daily steps initially [283–285] that were, however, not sustainable beyond five weeks of game use [286]. Very few studies have examined the effects of exergame use in populations with type 2 diabetes [1], but those that did suggest promising results. In a proof-of-concept study (Chapter 4), the suitability of selected Nintendo Wii Fit game modes to elicit effective exercise intensities in older adults with type 2 diabetes was demonstrated [2]. A recent feasibility study provided further preliminary evidence that four weeks of Nintendo Wii exergaming can increase overall physical activity, leg strength, and walking capacity [287], and a 12-week intervention found improvements in HbA_{1c}, fasting glucose, self-reported physical activity, and diabetes-dependent impairment following regular Nintendo Wii [288], suggesting a general benefit of exergame use in adults with type 2 diabetes. While exergame interventions have generally shown positive effects, it is noteworthy that the broad dissemination of exergames is not without distinctive hurdles [259]. First, game development is a cost- and time-intensive process especially when complex designs are incorporated that yield a large extent of individualization and that seek to generate the aforementioned intertwining of health objective and enjoyable gameplay. A second hurdle can arise when the demand of the game clashes with people's daily routines, particularly when the game is delivered through a dedicated device like a game console that requires the user to create committed space and time in their life for gameplay [259]. Enhancing existing systems or devices

(e.g., smartphones) through gamification could overcome these hurdles and is likely more cost-efficient. In addition, the mobile approach offers a better everyday life fit compared to the production of bespoke console games, as it simply reorganizes existing activities rather than adding additional demands to people's lives [259]. The results of a systematic review suggest that gamification can have positive effects on physical activity, particularly when applied in a well-conceived way that is tailored to the needs and interests of the target group [259].

When creating exergames or gamified systems, five core areas have been identified as being critical to consider, especially when targeting individuals with a predominantly very low physical activity motivation [289]. To lower the barrier of use, it is important to (1) enable an easy entry into use/play by creating an intuitive interface and by providing coaching mechanisms that allow an understanding of and engagement in the core mechanics without extensive and demotivating learning periods. Further, achievable short-term goals (2) and adequate challenges that match the individual skill level (3) should be included to foster long-term motivation through enhancement of self-efficacy. For this, an accurate assessment of the user's abilities by the game and a sufficient adaptability of the game mechanics are required. In addition, users should be provided with appropriate feedback on their exercise efforts and in-game achievements (4) and be encouraged and supported to interact with other players (5) for a long-term exergame adherence.

A recent systematic review showed that there is a wide variation in the use of behavior change techniques among health apps that use a gamified approach [290]. The most commonly used behavior change techniques that were included in the reviewed apps were self-regulatory techniques such as feedback, monitoring, goal setting, and planning, as well as reward and threat. The effectiveness of these control theory-linked [291] techniques in achieving behavior change has been demonstrated before [248,292]. It is important to note, however, that while rapid in-game feedback and rewards can reinforce and enhance player's physical activity-related self-efficacy, thereby promoting a continued use of the game even without immediate health improvements [16,293], such extrinsic goals also carry risks when they, in fact, lead to a decrease in the intrinsically motivated goal of being more active. In players who become so focused on in-game rewards that they adopt alternative behaviors (e.g., cheating) to achieve them, use of such incentives may be problematic for the development of an intrinsic physical activity motivation and thus sustained physical activity habits [16]. To address this problem and to promote long-term behavior change, it is essential that exergames and gamified systems include a wide array of behavior change techniques that cater for the needs of the individual user and collectively target the same outcome, so that deviations of the intended behavior (e.g., cheating to achieve rewards) can be avoided or at least reduced and the target behavior refocused. It is encouraging that a systematic review of behavior change techniques in smartphone apps found a median of 14 techniques in each smartphone game as it shows that app developers aim to incorporate these techniques and theoretically consistent technique combinations into the design of gamified systems [290]. Although more techniques are not necessarily better, there is a high potential for

more effective future apps through the use of appropriate combinations of the full repertoire of techniques [290]. A meta-analysis of 16 studies and 1,069 participants found the behavior change techniques action planning, instruction on how to perform the behavior, prompts/cues, graded tasks, and rewards to be particularly effective in changing physical activity behavior [294].

However, because the relationship between the behavior change technique content of an intervention and the resulting health behavior change is not simple [292], further research isolating the impact of behavior change technique-based gamification (e.g., randomized controlled trials) is needed to determine the optimum use of behavior change constructs in smartphone games in different target groups [259,290]. It has been noted in this regard that a multidisciplinary collaboration between game developers, behavior change experts, and public health specialists should be pursued in the development of future gamified health apps to make them more effective in targeting behavior change and especially in increasing physical activity-related intrinsic motivation [290].

In this Ph.D. project, following extensive preparatory research, a novel smartphone game was developed through a collaboration with international partners (game developers and behavior change experts) that is specifically designed for type 2 diabetes patients to encourage a healthier, more active lifestyle through gamified daily physical activity. It was hypothesized that the game application would motivate inactive type 2 diabetes patients for regular use and lead to higher increases in daily physical activity after 24 weeks than a control intervention consisting of a one-time lifestyle counseling. Further, it was hypothesized that the increased daily physical activity would be accompanied by improvements in glycemic control, aerobic capacity, and intrinsic physical activity motivation.

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Chapter 2

Aims and Hypotheses

Chapter 2 Aims and Hypotheses

The aims of this Ph.D. project were:

Aim 1: To systematically review the current evidence for the effectiveness of exergaming in overweight and type 2 diabetes and thus evaluate the suitability of these games to be used as tools for a guideline-concordant exercise promotion.

Aim 2: To evaluate the suitability of the Wii Fit Plus exergame to improve cardiorespiratory fitness in individuals with type 2 diabetes.

Aim 3: To develop a behavior change technique-based smartphone game that delivers individualized exercise and physical activity promotion with the intention to motivate inactive type 2 diabetes patients to become sustainably physically active and to plan a 24-week randomized controlled trial evaluating the game's effectiveness.

Aim 4: To assess the accuracy of the Garmin Vivofit 2 activity wristband as well as the iPhone SE and the Samsung Galaxy S6 Edge (as representatives for iOS and Android devices) to measure steps during various walking conditions.
The Garmin Vivofit 2 is used for the assessment of the primary outcome in the 24-week randomized controlled trial in both study groups. Smartphones (iOS and Android devices) are further used in the intervention group to measure daily physical activity as well as game-related activity throughout the intervention period.

Aim 5: To examine the effectiveness of the smartphone game to increase daily physical activity and improve glycemic control and aerobic capacity in inactive individuals with type 2 diabetes during a 24-week randomized controlled trial.

Aim 6: To further evaluate the effectiveness of the smartphone game regarding increases in intrinsic physical activity motivation and sustained improvements in physical activity adherence in inactive individuals with type 2 diabetes during a 24-week randomized controlled trial.

The hypotheses for this Ph.D. project were:

Hypothesis 1: Carefully selected Wii Fit Plus exercises are able to elicit exercise intensities in individuals with type 2 diabetes that concur with current physical activity guidelines.

Hypothesis 2: The Garmin Vivofit 2 activity wristband, iPhone SE, and Samsung Galaxy S6 Edge are valid for step detection in various walking conditions with constant as well as varying walking speeds.

Hypothesis 3: The use of the behavior change technique-based smartphone game is more effective in increasing daily physical activity (measured as steps per day) in inactive individuals with type 2 diabetes after 24 weeks than a control condition consisting of a one-time lifestyle counseling.

Hypothesis 4: The use of the behavior change technique-based smartphone game is more effective in improving glycemic control (measured as HbA_{1c}) in inactive individuals with type 2 diabetes after 24 weeks than a control condition consisting of a one-time lifestyle counseling.

Hypothesis 5: The use of the behavior change technique-based smartphone game is more effective in improving aerobic capacity (measured as oxygen uptake at the first ventilatory threshold) in inactive individuals with type 2 diabetes after 24 weeks than a control condition consisting of a one-time lifestyle counseling.

Hypothesis 6: The use of the behavior change technique-based smartphone game is more effective in improving intrinsic physical activity motivation (assessed with the Intrinsic Motivation Inventory) in inactive individuals with type 2 diabetes after 24 weeks than a control condition consisting of a one-time lifestyle counseling.

Chapter 3

Publication 1
Effects of Exergaming on Physical Activity in Overweight Individuals.

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Chapter 4

Publication 2

Cardiorespiratory Exertion While Playing Video Game Exercises in Elderly Individuals With Type 2 Diabetes.

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Chapter 5

Publication 3

Mobile Exergaming for Health – Effects of a Serious Game Application for Smartphones on Physical Activity and Exercise Adherence in Type 2 Diabetes Mellitus – Study Protocol for a Randomized Controlled Trial.

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Trials

STUDY PROTOCOL Open Access

Mobile Exergaming for Health—Effects of a serious game application for smartphones on physical activity and exercise adherence in type 2 diabetes mellitus—study protocol for a randomized controlled trial

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Abstract

Background: Exergaming is a novel approach to increase motivation for regular physical activity (PA) among sedentary individuals such as patients with type 2 diabetes mellitus (T2DM). Because existing exergames do not offer fitness-level adjusted, individualized workouts and are normally stationary (TV bound), thus not enabling PA anywhere and at any time, we developed a smartphone-based, game-like software application (MOBIGAME) specifically designed for middle-aged T2DM patients to induce a healthier, more active lifestyle as part of successful T2DM treatment and management. In a randomized controlled trial we aim to examine whether our smartphone-based game application can lead to increases in daily PA in T2DM patients that are persistent in the mid to long term and whether these increases are greater than those in a control group.

Methods: This study is designed as a randomized controlled trial. We plan to recruit a total of 42 T2DM patients [45-70 years, body mass index (BMI) ≥25 kg/m^2, low daily PA, regular smartphone use].
The experimental intervention (duration 24 weeks) includes individualized multidimensional home-based exercise and daily PA promotion administered through MOBIGAME. The control intervention consists of a one-time standard lifestyle counseling including the promotion of baseline activities.
The primary outcome is daily PA measured as steps per day. Secondary outcome is exercise adherence measured via the usage data from the participants' smartphones (experimental intervention) and as self-recorded exercise log entries (control intervention).
We will test the hypothesis that there will be differences between the experimental and control group with respect to post-interventional daily PA (as well as all other outcomes) using analysis of covariance. For each analysis, an estimate (with 95% confidence interval) of the difference in outcome between both groups will be reported.

Discussion: This research will investigate the effectiveness of a novel smartphone-based, game-like software application to be used as a way to promote regular daily PA among inactive T2DM patients. The results of this trial may have important implications for future PA-promoting interventions and provide relevant information for the general transferability of such applications to be used as part of the treatment in other chronic diseases.

(Continued on next page)

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(Continued from previous page)

Trial registration: ClinicalTrials.gov, NCT02657018. Registered on 11 January 2016. Last status update on 3 May 2016. Kofam.ch, SNCTP-number:SNCTP000001652. Registered on 21 January 2016.

Keywords: Type 2 diabetes, Physical activity, Exergaming, Exercise adherence, Diabetes management

Background

Overweight and Type 2 Diabetes mellitus—defining the target group

Overweight and obesity have become a global public health issue over the past decades reaching worldwide prevalences of 39% (overweight) and 13% (obesity) in 2014 and thereby having more than doubled since 1980 [1]. Along with these increases, type 2 diabetes mellitus (T2DM), a common comorbidity of overweight and obesity, has also seen dramatic increases in prevalence. In 2012, 9.3% of the US population was diagnosed with T2DM and 27.5% with prediabetes, the precursor stage to T2DM [2]. The direct and indirect medical costs accrued by patients with T2DM in the US in 2012 accounted for an estimated $245 billion, while people diagnosed with diabetes created 2.3 times higher average medical expenditures than people without diabetes, underlining the enormous financial burden that is caused by this disease.

Both obesity and T2DM are associated with a high level of inactivity [3, 4] that aggravates the physical and mental health status and constitutes a crucial factor in the development of several comorbidities such as hypertension, dyslipidemia, cardiovascular disease, and kidney and nerve disease [2]. In 2008, 9% of all premature deaths worldwide were attributed to physical inactivity, making its impact comparable to that of smoking, an established risk factor [5]. Physical inactivity is furthermore responsible for 7% of the burden of disease from T2DM [5], and it has been shown that decreased maximum oxygen consumption (VO_{2max}) is among the earliest indicators of insulin resistance and T2DM [6], thus representing an important risk factor for disease progression. It has further been shown that participation in regular physical activity (PA) improves blood glucose control [7, 8] and can prevent or delay onset of T2DM [9–12] and its comorbidities [13, 14]. Individuals who engage in regular PA, such as the American College of Sports Medicine (ACSM) recommended 30 min of brisk walking on 5 days per week, have a 30% lower risk of developing T2DM as compared to sedentary individuals [13, 15]. In individuals with T2DM, increased glucose uptake into active muscles during exercise as well as acute improvements in systemic insulin action lasting from 2 to 72 h post exercise have been reported [13]. Chronic effects of both aerobic and resistance training include improvements in insulin action, blood glucose control and fat oxidation [13].

In addition to the T2DM-induced impairments in the individual's glucose metabolism, severe decreases of skeletal muscle mass have been reported in older adults with T2DM, demonstrating the negative effects of the disease on body composition [16–18]. These losses of muscle mass are most profound in the extremities and especially in the lower limbs, while they are independent of body weight change over time [16]. In general, the loss of muscle mass is paralleled by significant decreases in muscle strength [19]. However, a 50% more rapid decline in the knee extensor strength was found in older adults with T2DM compared to non-diabetics of the same age even after controlling for losses of leg muscle mass [19]. This indicates a more rapid decline in muscle quality, suggesting that T2DM may result in impairments in muscular function of the lower extremities as well, not necessarily accompanied by a loss of muscle mass [19]. In addition to reduced levels of muscle strength, patients with T2DM often show reduced levels of aerobic exercise capacity due to an impaired recruitment of skeletal muscle capillaries [20] and an impaired bioenergetics capacity of skeletal muscle mitochondria [21]. In patients with poor disease management and existing microvascular complications, these impairments are even further increased and significantly add to the cardiovascular risk [22]. Factors such as reduced muscle strength, decreased aerobic capacity and rapid accumulation of lactate during exercise as a result of the impaired muscle energetics might also be responsible for early muscle exhaustion, lower exercise tolerance and fatigue in T2DM [23]. Especially peripheral fatigue of the skeletal muscles, which arises from a combination of neurological, musculoskeletal and metabolic changes, such as reductions in glycogen stores, reduced oxygen consumption during activity and changes in muscle fibers induced by physical inactivity and aging, are of great importance in T2DM [23]. Fatigue has far-reaching and serious consequences for patients with T2DM as it interferes with self-reported quality of life [24] and diabetes self-management [23, 24]. Fatigue further leads to greater physical inactivity [25] and thus further facilitates muscle atrophy and declines in muscle strength especially in the lower limbs [16–20]. Reduced muscle quality and lower aerobic capacity subsequently amplify fatigue with all of its physiological and psychological ramifications [23], ultimately resulting in a vicious cycle that needs to be broken since the effects of regular PA

in T2DM are very promising [7–15], especially since increases in muscle mass of the lower limbs are crucial for improvements in insulin sensitivity and thus successful T2DM management [26].

Exergaming as a motivating way to increase exercise adherence—reaching the target group

For any PA-promoting lifestyle intervention to be effective, motivation to start and adhere to the lifestyle changes is crucial. As explained before, T2DM patients usually show very low levels of PA [4]. Lack of motivation, missing social support and disease-related implications such as fatigue or pain are the main reasons why patients with T2DM cease to participate in PA promoting programs [27]. Exergames, the coupling of PA and video gaming, offer an enjoyable and promising new approach to increase PA in individuals that are among the least likely to engage in regular PA [28, 29]. It has been shown that these games can enhance health-related learning and even behavior change [28] because they are experiential and interactive and immerse the player in worlds that offer compelling challenges and immediate progress feedback, ultimately leading to improved diabetes self-management and better health outcomes [28, 30]. The Nintendo Wii Fit™ Plus exergame has been shown to motivate elderly patients with T2DM to engage in increased voluntary and regular PA and consequently improve long-term blood glucose control (HbA1c), body composition and quality of life [31]. It has also been demonstrated that exergames such as "Dance Dance Revolution" meet vigorous PA requirements for improving or maintaining physical fitness in a wide range of adults [32]. In a previous study with T2DM patients [33], we were able to show that selected Nintendo Wii Fit™ Plus exercises (Boxing, Obstacle Course and Cycle Island, played for bouts of 10 min each) bear the potential to produce exercise intensities that correspond to moderate-intensity PA [67-70% of the maximum heart rate (HR_{max}) and a mean oxygen consumption (VO_{2mean}) of 40% of the peak oxygen consumption (VO_{2peak}) previously established in an all-out treadmill test]. A moderate to strong correlation between treadmill VO_{2peak} and both exergame VO_{2peak} and exergame VO_{2mean} in the same study indicated that subjects with a higher fitness level were able to exercise at a higher intensity during exergame play than individuals with a lower fitness level. These results suggest that carefully selected Wii Fit™ Plus game modes can potentially induce health benefits similar to common aerobic exercise and would thus be able to help improve the glucose metabolism and reduce the risk of premature all-cause as well as cardiorespiratory mortality in T2DM patients.

In a systematic review [34] it has further been shown, however, that the current state of research in this field contains significant research gaps. The true effectiveness of the currently available exergames in regard to changes in objectively measured intensity parameters of PA [i.e., VO_2, energy expenditure, metabolic equivalent (MET), heart rate or activity counts] remained unclear as a result of the vastly differing study designs and greatly varying exergame expositions used in the respective studies. It was further noted that future exergame interventions will need to be conducted in a home-based setting rather than in the laboratory to fit into and be part of one's daily routine. This is necessary to truly examine the suitability of exergames to promote daily PA. In addition it was pointed out that future exergames would only be able to contribute to a healthier, more active lifestyle if they keep players motivated in the long term. This lasting motivation is especially important among a target group that is likely to be sedentary, such as that of T2DM patients who usually do not show a lot of intrinsic motivation to be physically active [34]. At the same time, future exergames, unlike the currently available exergames, need to feature game modes with a minimum duration of 10 min, as suggested by current guidelines [35], and an exercise intensity that corresponds to moderate PA [35] to be able to offer effective workout alternatives for the target group of T2DM patients [34]. To meet the different fitness levels of the different players, future exergame designs should further offer more tailored intensity levels and a more individualized intensity progression than the currently available exergames do.

Development of the MOBIGAME application

To address the shortcomings of existing exergames we—a group of researchers at different universities, from the fields of sports medicine and (serious) game as well as behavioral design, in collaboration with a long-standing, commercial serious game development studio—developed a mobile smartphone-based, game-like software application and platform (MOBIGAME) specifically designed for the needs of T2DM patients and those at risk of developing T2DM, with the goal to induce a healthier, more active lifestyle in the target group.

The use of smartphones and mobile apps especially among middle and older age groups has grown exponentially in the past years [36] with 50% of casual gamers being between 35-64 years [37]. These age groups are also disproportionately impacted by chronic diseases; 60% of adults aged 50-64 years have at least one chronic condition [37] such as obesity and T2DM [2]. Using these technologies to provide tools for diabetes prevention and management is timely and offers a cost-effective opportunity to directly reach a larger segment of the target population than traditional diabetes prevention programs. At the same time, smartphones' integrated sensors and actuators as well as wearable sensor devices enable personalized diabetes prevention and can thereby significantly improve sustainability and dissemination of such intervention programs [38].

It has been shown [38] that the replacement of the group sessions in a diabetes prevention intervention by a mobile app in combination with in-person sessions, focusing on lifestyle-enhancing personal skills, is able to induce increases in daily PA of up to 3100 steps per day in an 8-week period compared with baseline. Even after 20 weeks daily PA remained elevated at approximately 2500 steps per day over baseline. It is noteworthy, however, that after the peak in daily PA at week 8, mean daily steps continuously decreased until the end of the intervention while this decline was paralleled by a likewise continuous decrease in adherence to the mobile app [38]. Adherence decreased almost linearly from 85% at week 1 to 40% at week 20. There is good reason to believe that this decline in adherence influenced the amount of daily PA negatively. In fact, it is possible that adherence levels would have been higher and more persistent in the study population of T2DM patients if a more game-like and thus more enjoyable approach had been used.

The effectiveness of a smartphone-based gaming application in increasing players' daily PA is currently demonstrated by the enormous success of Pokémon GO [39], which attracted over 65 million users within the first week of its launch [40]. While this app undeniably leads to an at least GPS-tracked increase in daily PA (since steps are not measured, other ways to search for Pokémon, such as driving, cannot be ruled out), it is missing fundamental components to make it a safe exercise tool. First, some public spaces designated for Pokémon use are simply inappropriate or even dangerous. This has led to several accidents while playing Pokémon GO due to inattention to surroundings while walking or even driving [40, 41], presenting serious risks especially to the more vulnerable, often easily distracted pediatric population [42]. Second, the app does not take the player's cardiorespiratory fitness or possible health restrictions into account when placing Pokémon in the surrounding environment. Especially for low-fitness players with chronic diseases, such as T2DM, the distances that need to be covered in order to find Pokémon may cause an unhealthy physical overexertion in the short-term and lead to overuse injuries in the long term.

Therefore, for it to be a safe exercise tool especially for individuals with chronic diseases, an interactive smartphone game needs to feature a structured, guideline-concordant and fitness-adjusted exercise intervention that uses a variety of the device's sensors to track and further tailor the player's PA. While safely promoting regular physical activity as part of a lifestyle change, this approach could help further reduce staff expenses compared to interventions using in-person sessions [38] or cognitive-behavioral telephone support sessions led by a psychologist [43] while still ensuring an effective diabetes prevention and long-term treatment.

The MOBIGAME project sought to implement evidence-based sports scientific knowledge into the production of an entertaining and interactive mobile software application that offers individualized and structured exercise regimens and that can be played at home as well as on the go. Special regard was paid to exercises that can be tracked via the mobile phone's sensors (camera, accelerometer/pedometer, position sensor, noise recognition or Global Positioning System, GPS) to design a clearly exercise-oriented game that is challenging and also responds to an individual player while including compliance, monitoring and motivational aspects. A key component of the application is the integration of exercise tests such as the 1-min Sit-to-Stand Test (STS) [44] and the 6-Minute Walk Test (6MWT) [45] to assess the exercise-related capabilities of each individual user. In the application, these tests are used as baseline measurements to assess the user's fitness level in a home-based setting and thereby make it possible to build tailored exercise programs for each individual user, even those with severely compromised fitness. Exercise regimens integrated into the game application include strength and endurance workouts as well as balance and flexibility exercises and follow the ACSM and European Association for Cardiovascular Prevention & Rehabilitation (EACPR) principles of exercise training [46, 47]. Additionally, daily PA is promoted and tracked via the user's smartphone sensors. Personalized daily (and weekly) step goals are set for each user. The suitability of the developed strength exercises including the different intensity/difficulty levels has been evaluated in a qualitative user study ($N = 12$) with the target group (unpublished data). In this user study, first the baseline tests were conducted, and the individual fitness levels were assessed using population-based reference values [44]. Based on the results of the baseline tests, and hence the fitness assessment of the participant, exercises and respective difficulty levels were selected from a pool of upper-limb, lower-limb, core and back exercises. The main objective of the user study from the sports medical point of view was to validate the categorization of the different difficulty levels and to evaluate whether the exercises that were selected based on the results of the STS were in fact feasible for each participant and thus concurrent with our fitness assessment. From the game and behavioral design's, as well as from the game developers' point of view, the main objective of the user study was to assess the playability of the game concept and the appeal to the target group.

The motivational approach chosen for MOBIGAME to increase PA while obeying the abovementioned principles follows the promotion of the players' self-efficacy and specifically their personal mastery [48–50]. Rather than directly targeting a particular behavior (i.e., increased PA), successful exergames target mediators (i.e., self-efficacy), which, in turn, affect the behavior and then the health outcome of interest [51]. In this context, self-determination, namely (1)

perceived competence (the player's actions are responsible for the success in the game), (2) perceived autonomy (the player feels in charge of the own choices in the game) and (3) relatedness (a sense of belonging or connection), has repeatedly shown a strong relationship with the experience of enjoyment as well as sustained engagement and lasting behavior change in multiple domains [52, 53]. The enjoyment arising in the context of the game experience supports and facilitates the behavior change as it creates a positive emotional state of playful enjoyment in which the player is intrinsically motivated, meaning that the value of the experience is the experience itself, rather than the experience being instrumental in achieving something else [52].

Through the use of MOBIGAME, the players will further learn that their regular PA is directly responsible for the achievements in the game and thus has an immediate and noticeable impact [54]. The gameplay design thus represents a kind of "reflection-on-action" approach [55] in which the players' motivation leads to adjustments in real-life behaviors (i.e., walking more steps per day) in response to events or incidents in the game's story line.

As MOBIGAME uses sensor tracking to verify the execution and completion of workouts that requires a specific, sensor-dependent (camera, accelerometer or position sensor) position of the device for each exercise, an actual gamification of the exercises such as a visualization of the execution on the phone's screen is not feasible and the adaption of the proposed movement-based game guidelines [56] not always possible. Since the screen of the average smartphone is rather small compared to a TV, however, gamification of the exercises as used in traditional exergames such as Nintendo Wii or Xbox Kinect would also not present an acceptable option for use by our target group. Therefore, the game guidelines [56] were taken into account during the development of the game design, but adapted to suit the idea of our mobile game application. Embedding structured and individualized strength and endurance workouts as well as promotion of daily PA into the story line of a mobile phone-based game, which uses self-efficacy as a key motivational aspect by giving additional meaning to the player's PA, offers a promising and feasible solution to increase PA and to be effective in the target group in the long term.

Main hypothesis

The experimental intervention (use of MOBIGAME) is more effective for increasing daily PA measured as steps per day than a control intervention after 24 weeks.

Methods

Study overview: target group, setting, design and registration

The study targets patients with non-insulin-dependent diabetes mellitus, 45-70 years of age, with a body mass index (BMI) ≥25 kg/m^2, who use a smartphone regularly and show low and irregular daily PA. The study aims to include a total of 42 German-speaking patients in the Basel (Switzerland) metropolitan area. The setting of the intervention is the patients' everyday environment (home, work, places of leisure time activities), where the MOBIGAME application is used and the included exercises are carried out. The study is a prospective randomized controlled trial and has been registered with the US National Institute of Health's Protocol Registration and Results System (PRS) on https://clinicaltrials.gov/(NCT02657018) as well as with the Federal Office of Public Health's (FOPH) portal for human research in Switzerland on http://www.kofam.ch/ (SNCTP-number:SNCTP000001652). For a study flow diagram, see Fig. 1. The SPIRIT checklist is provided as Additional file 1. Scientific lead, study management and coordination, patient information and recruitment in cooperation with the Clinic of Endocrinology, Diabetes and Metabolism of the University Hospital Basel, measurements and statistical analyses are performed by the Department of Sport, Exercise and Health of the University of Basel.

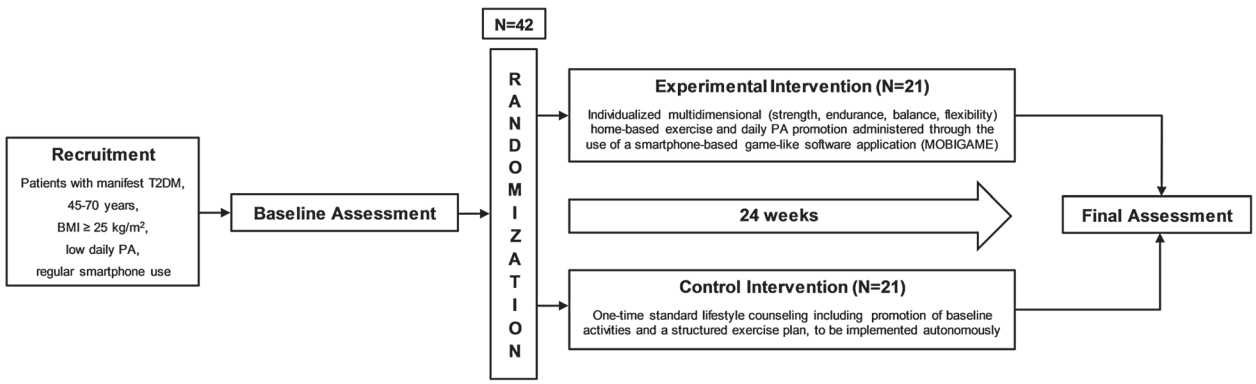

Fig. 1 Study flow chart. T2DM, type 2 diabetes mellitus; BMI, body mass index; PA, physical activity

Eligibility criteria

This study aims at tertiary prevention and therefore patients have to be diagnosed with a manifest non-insulin-dependent diabetes mellitus (doctor diagnosed) to be eligible to participate. They further have to be overweight (BMI ≥25 kg/m^2), between 45 and 70 years of age, have used a smartphone regularly during the last year before the study and give their written informed consent. Because questionnaires will be filled out as part of this study, sufficient proficiency of German is required. Patients will be excluded if any one of the following criteria is applicable:

- Impaired physical mobility (participants have to at least be able to walk short distances indoors without a walking aid and without help of another person).
- Regular PA before the study (≥150 min moderate intensity daily PA per week or >1 endurance or strength training session per week of more than 30 min in duration).
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.).
- Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders, dementia, etc., of the participant.
- Resting systolic blood pressure >170 mmHg, resting diastolic blood pressure >100 mmHg.
- Participation in other clinical studies in the last 4 weeks.

Experimental and control intervention

Overview

The duration of the intervention is 24 weeks. In the experimental group the intervention consists of:

1. Individualized multidimensional (strength, endurance, balance, flexibility) home-based exercise and daily PA promotion administered through the use of MOBIGAME following established PA guidelines [47].
2. Consultations provided by a sports medical expert via telephone, including personal attention and instruction as well as technical support

In the control group the intervention consists of:

1. One-time lifestyle counseling (standard of care) including the promotion of baseline activities of daily life [57] as well as a structured exercise plan including strength and endurance exercises with moderately increasing intensity and duration, essentially comparable to the content of MOBIGAME, which is to be implemented autonomously.
2. Consultations provided by a sports medical expert via telephone, including personal attention and instruction.

Common aspects for both groups

In both groups a sports medical expert will provide a given number of personal exercise consultations on the telephone (weeks 1 and 2) as well as a face-to-face consultation at week 0, thus guaranteeing that the control group receives the same number of consultations as the experimental intervention group. For an overview of the study schedule, see the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule [58] (Fig. 2).

Experimental intervention details

The experimental intervention aims at improving participants' motivation to exercise in the short and especially in the mid to long run through the use of MOBIGAME and thereby increasing daily PA. MOBIGAME features numerous different exercises (see Table 1) and exercise regimens including strength and endurance workouts as well as balance and flexibility exercises (a total of over 130 exercises) that concur with generally accepted PA guidelines [46, 47]. The strength exercises span over a wide range of different difficulty and intensity levels. Each exercise contains up to 15 variants with up to 30 different levels regarding repetitions, bouts and duration for each variant. All exercises are designed in a way that makes it possible for players with any fitness level to gradually progress with their workout routine while increasing workout intensities at an individualized pace.

Endurance workouts include a wide variety of walking exercises with different walking speeds and exercise modalities as well as aerobic workouts (Table 1). Walking exercises are to be conducted outdoors and include continuous trainings as well as interval trainings. Since the 6MWT speed is used as a reference, the proposed walking speeds during the workouts are individually adjustable (e.g., 70% of 6MWT speed). To prevent players from being inattentive to their surroundings because of smartphone distraction, walking exercises are not visualized on the smartphone's screen. Instead, players are advised to keep the phone in their pocket throughout the exercise, which in addition will guarantee a more accurate tracking of the players' step count during the exercise. Before the start of each walking exercise, along with the exercise instruction, the players are further advised to ensure a safe environment that is suitable for the upcoming walking exercise. This precaution in design is based on prior research on location-based games that involve explorative, walking activities in public space; it had been shown that there was a need to focus the player's attention away from the gaming device's screen during such gameplay situations to avoid dangerous encounters [59]. Aerobics moves can be executed with or

TIMEPOINT	Recruitment	Baseline assessment		Intervention		Final assessment	
	t_0	t_1	t_2 (t_1 + 1 week)	*Telephone interview 1* (t_2 + 1 week)	*Telephone interview 2* (t_2 + 2 weeks)	t_3 (t_2 + 24 weeks)	t_4 (t_3 + 1 week)
ENROLLMENT							
Eligibility screen	✓						
Informed consent	✓						
Randomization			✓				
INTERVENTIONS							
Experimental			●	—	—	●	
Control			●	—	—	●	
ASSESSMENTS							
Demographics		✓					
Anthropometrics		✓				✓	
Blood pressure		✓				✓	
Resting ECG		✓				✓	
Medical examination		✓				✓	
Blood parameters		✓				✓	
6MWT		✓				✓	
Bike spiroergometry		✓				✓	
Accelerometry		●	— ●			●	— ●
Self-determination			✓				✓
HRQOL			✓				✓
Fatigue			✓				✓
Macrovascular analysis			✓				✓
Microvascular analysis			✓				✓
STS			✓				✓
Isometric leg strength			✓				✓
Personal exercise consultation				✓	✓		
Acceptance of intervention							✓

Fig. 2 Schedule of enrollment, interventions and assessments according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT). 6MWT, 6-Minute Walk Test; ECG, electrocardiogram; HRQOL, health-related quality of life; STS, Sit-to-Stand Test

without arm movement, indoors as well as outdoors. The combination of indoor and outdoor exercises in an exergame application is a novelty and offers a vast variety of different endurance workout opportunities to meet individual exercise preferences. Instructional videos are available for all exercises (strength, aerobics, balance and flexibility) to ensure correct and safe execution. The algorithms for the individualized exercise training are based on the ACSM and EACPR principles of exercise training [46, 47] and several exercise intervention studies in normal and overweight subjects and patients [60–63]. The training progression in the game is monitored through the repetition of the baseline tests and subsequent adaptions in the exercise/intensity selection. Specific test scores are linked to specific exercises and difficulty levels, so that for example players with higher scores in the STS will get a higher (entry) difficulty level for a specific leg strength exercise than players with a lower score. In addition to these adaptions, the user has the option to rate the intensity of each exercise upon its completion, directly affecting the intensity of the next workout. The rating scale used is a simplified version of the 15-point Borg Scale [64]. In simple terms, a rating of "too hard" will

Table 1 Overview of exercises included in MOBIGAME

Category	No.	Exercise (no. of variants)
Strength	1	Hip/knee extension, dynamic (15)
	2	Knee extension, static (3)
	3	Leg lift, frontal/lateral (9)
	4	Arm elevation (7)
	5	Arm abduction (7)
	6	Elbow extension/shoulder protraction (6)
	7	Back extension, dynamic (6)
	8	Upper back/shoulder extension, static (4)
	9	Abdominals, static (5)
	10	Abdominals, dynamic (10)
Endurance		**Aerobics**
	1	March (2)
	2	Tap (6)
	3	Step touch (4)
	4	Out-In (2)
	5	V-step (2)
	6	Box-step (2)
	7	Grapevine (2)
	8	Leg curl (2)
	9	Knee lift (2)
	10	Front kick (2)
	11	Heel dig (2)
		Walking
	1	Continuous (1)
	2	Interval (4)
Flexibility	1	Chest/upper back (2)
	2	Torso (1)
	3	Neck (2)
	4	Lateral torso (1)
	5	Ischiocrural muscles (2)
Balance	1	Two-leg stand (5)
	2	Tandem stand (5)
	3	One-leg stand (5)

Data captured in bold indicates that all Aerobics exercises as well as the two Walking exercises are sub-categories of the Endurance exercises

result in a lower difficulty/intensity level in the next workout; a rating of "too easy" will result in a higher difficulty/intensity level in the next workout. Five consecutive ratings of "just right" of the same exercise will result in the suggestion of a higher intensity level in the next workout. The combination of objective as well as subjective measures to control the training progression was chosen to enable unbiased feedback to the player through the repetition of the baseline tests while keeping the player in control of the game at all times, thereby facilitating the long-lasting enjoyment and high levels of self-efficacy that are known to positively influence exercise adherence [49].

A key element of the story line of MOBIGAME is the restoration of a garden. The garden used to be a beautiful place until the Schweinehund came and destroyed it, causing all of the animals that used to live in the garden and help maintain it to leave. In German, "innerer Schweinehund" (inner swine hound) is used as a self-depreciating idiom denoting a form of lazy procrastination, usually of the physical kind, that needs to be overcome to get yourself going. The player's task is now to help restore the garden by planting trees and flowers and thereby attracting the animals to come back into the garden while at the same time taming the Schweinehund. The garden as the main setting was purposefully chosen as gardens and the activity of gardening have been shown to be highly appealing to the target group [65] and to be effective in reducing stress and stress related-illness such as cardiovascular diseases, depression, reduced immune function and chronic fatigue [66]. In this regard, it has been shown that simply viewing a green space through a window can relax people and reduce stress levels [66, 67]. In our approach, the viewing of this green space (i.e., the garden) occurs through the smartphone screen. Particularly the engagement in gardening activities is very effective in alleviating stress and has been shown to significantly decrease cortisol levels [68]. Research has further shown that nurturing plants from seed to maturity evokes feelings of curiosity, competence and enjoyment, all of which contribute to successful stress management [69, 70]. While we are aware that artificial gardening on a smartphone screen is not identical to an actual gardening experience, the positive and de-stressing character of this activity may still partially be transmitted to the player The animals are humanized (walk upright, wear clothes), always friendly and very likable and represent typical human character traits. Some have even acquired typical human vices such as laziness, sulkiness, contempt or moodiness that the player can help them break by playing the game regularly and thus being regularly physically active. Every activity (in-app workouts as well as steps walked during the day) is rewarded with water or building materials needed to restore the garden. When designing the game, close attention was paid to defined principles and mechanisms such as the inclusion of rules, clear but challenging goals, fantasy, progressive levels of difficulty, interactivity, player control, uncertainty, feedback and a social element [71, 72]. The game mechanics are further anchored in the 40-item CALO-RE taxonomy of behavior change techniques [73]. In this regard particularly "goal setting," "action planning" and "providing rewards contingent on successful behavior" (i.e., the player sets the goal to complete a super-challenge that requires regular activity on several consecutive days in order to receive a special reward), as well as "providing feedback on performance" (i.e., all of the player's activity and achieved goals are recorded and summarized in a general overview), are implemented

in the game mechanics to help players integrate more PA into their daily routines. "Environmental restructuring" is used quite visibly in the main story line (restoring of the garden) while at the same time and more subtly leading to the development of exercise habits and routines ("prompting practice") that are supported by the "use of follow-up prompts" (i.e., reminder notifications). The players are encouraged to seek support from the humanized animals to achieve their goals ("elicit social support") and to keep the Schweinehund away, as failing in doing so will interfere with a successful garden restoration ("fear arousal"). As its ability to provide (lasting) enjoyment is critical to the success of any game, the focus was laid most importantly on this specific factor [74]. While it has been pointed out that for serious games the fun may only need to exceed its traditional analog (health class, lectures from care providers, etc.) to be considered successful [75], we aimed to create an appealing exergame that players want to play because it gives them pleasure by featuring just the right balance between fun and seriousness [51, 76]. Figures 3, 4, 5, 6, 7, 8 and 9 show screenshots of MOBIGAME to illustrate how the gameplay and exercises work from the user perspective.

At the end of the baseline examination, MOBIGAME is installed on the participants' smartphones (Fig. 2). The participants only receive very basic instructions on how to use and control the app since MOBIGAME was designed to be self-explanatory including a built-in tutorial that explains all of the game's features to the player at the appropriate time. Participants further do not receive any instructions on how often to use the app because this study seeks to evaluate the motivating character of MOBIGAME by itself and thereby its suitability to increase regular PA.

Control intervention details

The control intervention focuses on promoting daily PA through a one-time lifestyle counseling, which will be administered by a sports medical expert. All participants in the control group receive a booklet containing information on the benefits of regular PA for health, opportunities to integrate more PA into the daily routine and illustrations of recommended exercises and activities (comparable to the exercises included in MOBIGAME) as well as 24 weekly exercise logs [77] to check off completed workouts and record additional activities. Increases in daily PA in the control group are possible but are not expected to be of the same extent or persistence as in the experimental group because a daily reminder and the motivating character of a game are missing.

Study data

Characterization of participants

Baseline data of participants are assessed during the recruitment process and within the baseline assessment (see Fig. 2). Demographic data (sex, age, socioeconomic status, smoking status), anthropometric data (weight, height, waist and hip circumference, body composition) and resting blood pressure are assessed by a sports medical expert. Medical history (including drug history and concomitant medication) as well as allergies are assessed during a general physical examination by a physician. PA is assessed using the Freiburg Questionnaire of physical activity [78] as part of the screening during recruitment.

Primary outcome

The primary outcome is daily PA measured as steps per day after 24 weeks. It is assessed in a 1-week tracking period during the week before the start of the intervention as well as during the first week after the 24-week intervention using a VivoFit 2 pedometer wristband (Garmin International Inc., Olathe, KS, USA). The displays of the wristbands in both groups will be irreversibly blackened out so that the daily activity can only be viewed by the study personnel via the wristband's software and a motivating character of PA feedback by the device can be ruled out.

Secondary outcome

Participants' exercise behavior as well as patterns of MOBIGAME use is analyzed in the intervention group via the app's usage log. The log can be accessed through each participant's smartphone to draw conclusions regarding

Fig. 3 Illustration of the gaming concept of MOBIGAME

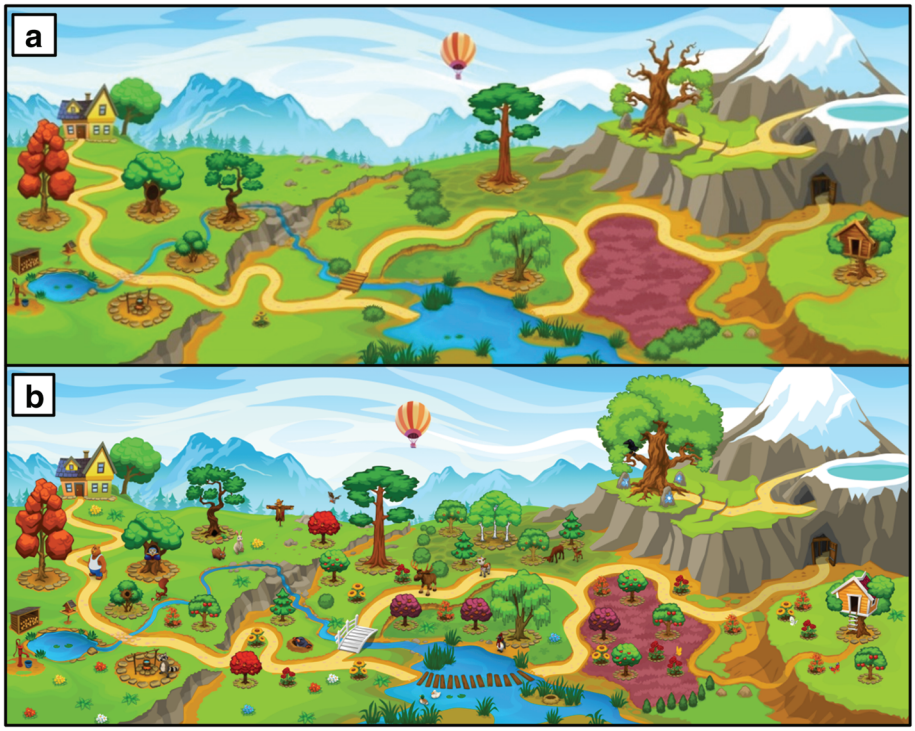

Fig. 4 Illustration of the undeveloped garden before starting the exercise (**a**) and the fully developed garden as a result of regular exercise (**b**)

the sustainability of player motivation as well as exercise adherence. The usage data will give information about whether goals of daily PA as well as exercise goals are met, how many workouts are completed, how many workouts are done voluntarily and what influence the suggestions of specific workouts as well as the reminder to be physically active have on players' exercise behavior. The usage data are further used to analyze which workouts are preferably chosen, which are less popular and whether MOBIGAME use can help players reach and maintain 150 min of moderate PA per week.

In the control group, adherence to the exercise regimen, as suggested during the one-time lifestyle counseling, will be self-recorded by the participants in 24 weekly exercise logs (see above).

Further outcomes are described in detail in Additional file 2.

Timeline

The duration of the entire MOBIGAME project is 50 months (January 2014 to February 2018). Development of MOBIGAME was completed in February 2016. Recruitment of participants started in January 2016 and is expected to end in June 2017 (18 months). Examinations started in August 2016. The last participant is expected to finish the intervention in December 2017. Altogether, the period between "first patient in" and "last patient out" is 20 months.

Sample size

Determination of sample size was based on the primary outcome. On the basis of a previous study [43] and our own experience, we assumed that the expected difference in daily PA after 24 weeks between participants in the experimental intervention and those in the control group would be 2500 steps per day. We further assumed that the standard deviation given either study group would be 3000 steps per day [43]. By including daily PA (steps per day) at baseline as a covariate in the analysis, we aim to further reduce error variability and therefore assumed that the correlation between baseline and outcome daily PA will be 0.7. With a significance level of 0.05 (2-sided), the sample size needed to attain a targeted power of 90% for showing superiority of the experimental intervention over control was determined as a total of 34 participants (17 in each group). While we aim to achieve complete capture of all data from all participants, it is unavoidable that some participants will fail to provide outcome data. We will therefore increase the proposed sample size by 20%, so that we will include a total of 42 participants (21 in each group).

Recruitment

Participants are recruited in cooperation with the Clinic of Endocrinology, Diabetes and Metabolism of the University Hospital Basel, Switzerland as well as on the basis of the database of the Diabetesgesellschaft Region Basel, Switzerland. Further, subjects will be recruited

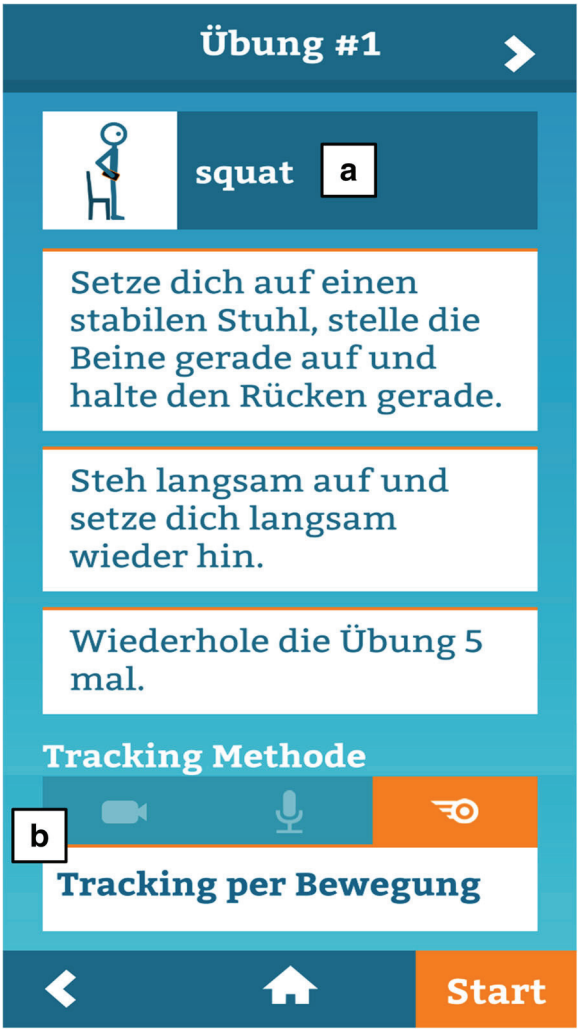

Fig. 5 Screenshot of the exercise mode: (**a**) Step-by-step instructions, including a video of an animated stick figure, are available for all exercises to ensure correct execution. (**b**) Tracking of exercise execution via camera, audio sensor or motion sensor tracking

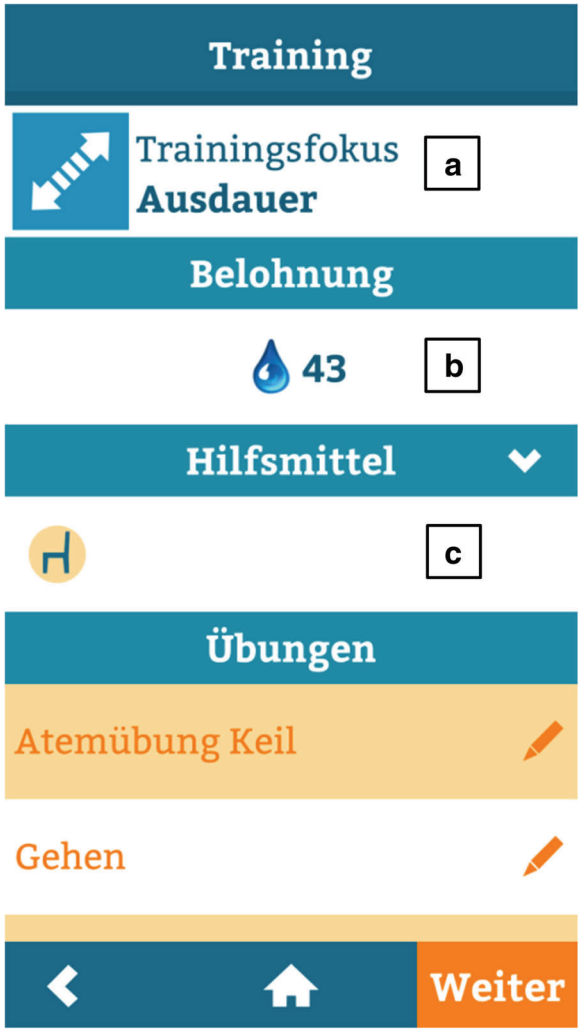

Fig. 6 Screenshot of the exercise mode: Training focus (**a**), type of in-app reward (**b**) and required materials (**c**) are clearly stated before the start of the training

through online and newspaper advertising as well as by word of mouth. Patients who seem to be eligible based on their medical records are contacted via email, telephone or personal inquiry. They then receive a questionnaire via email to verify insufficient levels of PA as well as other general eligibility before an appointment for the first day of examination, including the personal assessment of final eligibility, is scheduled at the Department of Sport, Exercise and Health of the University of Basel.

Assignment of interventions

Allocation and blinding

Participants are allocated at random and in equal numbers to one of the two groups. To achieve this, permuted block randomization with randomly varying block sizes is applied. The randomization list was generated in advance using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and the R add-on package blockrand version 1.3 [79] and was transmitted using sequentially numbered, opaque, sealed envelopes [80] by a study assistant not involved in the measurement appointments. Another study assistant receives the envelope on the second visit after all measurements are completed and immediately prior to the distribution of MOBIGAME or the one-time lifestyle counseling, respectively. Through the randomly varying block sizes, which were deliberately not disclosed, study assistants involved in both the measurement appointments and the distribution of MOBIGAME or the one-time lifestyle counseling, respectively, as well as the investigator organizing the appointments cannot know which upcoming participant will be allocated to which of the two groups. All other study personnel and all outcome assessors (with the exception of the telephone

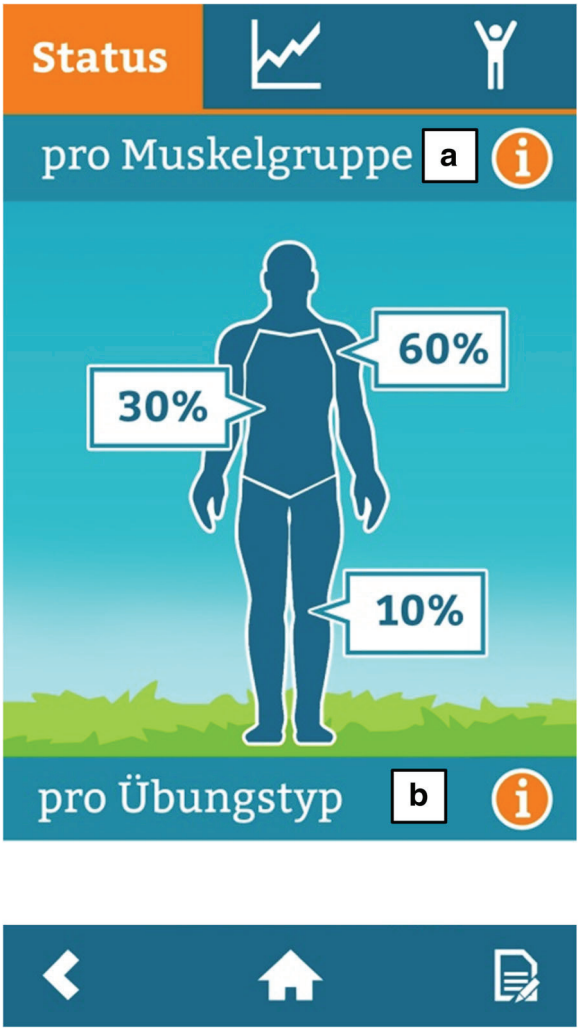

Fig. 7 Screenshot: Overview of completed exercises by muscle group (**a**) or by type of exercise (**b**)

Fig. 8 Screenshot of activity overview: (**a**) Average steps and average minutes of activity per week, month (displayed) or year. (**b**) Day view of steps walked, daily step goal and information if step goal was reached

interviewers) are blinded with respect to group allocation. No unblinding procedures are intended, except for adverse events that require medical care. A blinding of participants regarding group allocation is not possible. However, to minimize performance bias, participants do not receive detailed information about the other intervention [81].

Data collection

All measurements of this study are performed by standardized procedures and the assessment staff uses standardized instructions for all measurements to ensure equal testing conditions for all participants. For a description of the study instruments, see study data (above).

To promote participant retention and complete outcome data from all participants, including those who discontinue or deviate from intervention protocols, a total incentive of up to 450 CHF per individual as compensation for their time participating in the study will be provided to all participants. The incentive is not awarded at one time, but is delivered as the participant progresses through the study (150 CHF after completion of the baseline assessment and an additional 300 CHF after completion of the final assessment following the 24-week intervention).

Data management

To ensure anonymous data handling, sensitive patient data have been previously encoded into a string variable. Data are secured by passwords and only accessible by the responsible staff. The obtained data are digitally stored, backed-up and archived at the Department of Sport, Exercise and Health of the University of Basel. All activity and participant usage data collected by MOBIGAME are stored on the phone's hard drive and encrypted (and thus secured) with a password chosen by the participant.

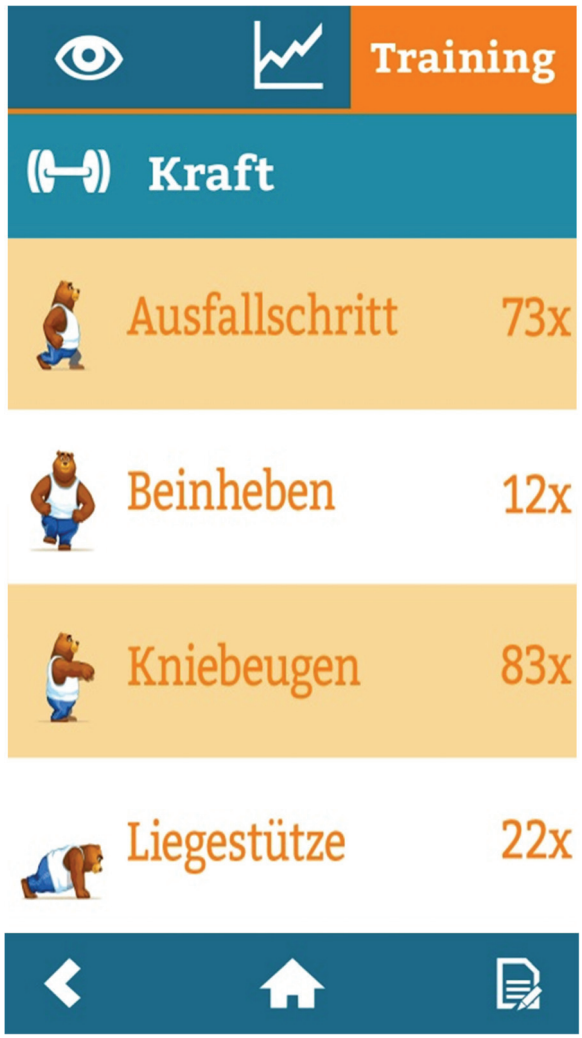

Fig. 9 Screenshot of training overview: Total number of completed strength exercises. Exercises displayed are lunge ("Ausfallschritt"), leg lift ("Beinheben"), squat ("Kniebeuge") and push-up ("Liegestütze")

Entering of this password—and thereby the participant's consent—is required before exporting these data for analysis post intervention.

Statistical methods

The statistical analysis will conform to the pre-specified statistical analysis plan described below. Following the intention-to-treat analysis strategy, participants will be analyzed in the groups exactly as randomized.

Descriptive analysis

A flow chart of the participants' progress through the trial will be used for reporting [82]. The number of screened T2DM patients who fulfill the eligibility criteria and the number included in the primary, secondary and further analyses as well as the reasons for exclusion from these analyses will be reported. Summary statistics will be provided for baseline and outcome data, as appropriate. Continuous variables will be summarized using the mean and standard deviation for normally distributed data or the median and interquartile range for non-normally distributed data. Frequency counts and percentages will be used for categorical data. Visual inspection of box plots of steps per day and further outcomes will be used to identify possible outliers in each group (experimental vs. control) to be excluded in sensitivity analyses.

Main analyses

The main analyses will be performed on the assumption that missing outcome data are missing at random and therefore will be based on complete cases only.

The primary outcome of daily PA (steps per day) after the 24-week intervention and further outcomes will be analyzed by analysis of covariance (ANCOVA) [83]. The results will be presented as differences in outcome (with 95% confidence intervals) between participants in the experimental intervention and those in the control group, adjusted for the corresponding values at baseline. In the case of chance imbalances at baseline, this will remove a possible bias in the estimate of the effect of experimental intervention over control, while, at the same time, yielding a more precise estimate and accordingly more powerful test for the difference between groups.

Normality will be assessed using normal quantile-quantile plots of the residuals, and to assess variance homogeneity, we will use Tukey-Anscombe plots. If the residual plots indicate departure from model assumptions, suitable transformations of the outcome will be considered [84].

For the secondary outcome, each group will be analyzed descriptively with respect to program adherence.

Finally, correlations between MOBIGAME adherence and acceptance of MOBIGAME (TAM questionnaire score, see Additional file 2) will be analyzed using Spearman's rank correlation coefficient.

Sensitivity analyses

The effect that any missing outcome data might have on results will be assessed through sensitivity analyses based on imputed data sets. Dropouts (essentially, participants who are lost to follow-up) will be included using imputation methods that allow for the uncertainty about the imputed values. While a few missing values generally present a minor nuisance, a substantial number of missing values is a major threat to a trial's integrity [85]. If omitting all patients with incomplete data will result in a large proportion of the data being discarded, we will use multiple imputation where missing data are replaced by a set of plausible imputations generated from the patient's available data [86]. To achieve this, imputation models will need to be developed based on the majority of patients with complete data. Variables included in these models

will be carefully chosen, and the study team will discuss whether this choice makes the underlying assumption that any systematic difference between the missing and the observed outcome data can be explained by differences in observed (baseline) data plausible. Rubin's rules will be used to combine results across ANCOVA models based on the imputed data sets (at least five imputed data sets will be created) and so give an overall estimate of the effect of experimental intervention over control on the primary and further outcomes.

Statistical software

Up-to-date versions of SAS (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria) will be used for statistical analysis and graphics.

Quality assurance and monitoring

Written standard operating procedures are used for all measurements to ensure data quality. The state of recruitment, patient participation and consent withdrawals are reported regularly to the project manager. Data completeness and plausibility as well as control of correct randomization/allocation of patients are verified regularly. Any deviation from expected standards are reported to and discussed with the project manager.

Ethical considerations

The health risks of MOBIGAME use are negligible. To minimize the risk for any cardiorespiratory adverse events, all participants are required to undergo an extensive physical examination including resting and exercise electrocardiography (see Additional file 2) before receiving MOBIGAME as part of the intervention treatment. Overload of soft tissue may be in principle possible but seems very unlikely because of the implemented training structure that begins with very light intensity and duration and is based on the individual results from the baseline testing (6MWT and STS). Training progression is also tailored and can be individually and manually adjusted at any time, thereby further minimizing the risk for adverse events. In addition, at first use of MOBIGAME the player is instructed to contact the primary care physician (or study personnel) should any unexpected adverse events occur during use and to call the emergency number for emergencies.

In contrast, the potential benefits of MOBIGAME use significantly exceed the risk of adverse events and include increased cardiorespiratory fitness and leg strength, improved glucose metabolism and diabetes management as well as lower cardiovascular risk and ultimately an improved quality of life. Accident insurance is provided by the University of Basel for all participants.

Discussion

PA is a crucial component in the prevention as well as treatment of T2DM [7–12] and its comorbidities [13–15]. Despite the many individually relevant health benefits, adherence to PA-promoting intervention programs in T2DM is generally low and their mid- to long-term effectiveness therefore often limited [27]. On the basis of our extensive review of the current exergaming literature [34] and our own preliminary work examining the intensity of indoor exergaming on cardiorespiratory exertion in T2DM individuals [33], it has been shown that serious exergames as well as mobile app-based programs [38] principally have the potential to be effective treatment options, especially because they seem to at least partly solve the adherence problem [28, 29]. The MOBIGAME application is a milestone in the exergaming approach as it is the first such application seeking to improve physical activity in T2DM individuals by offering individualized and structured strength and endurance workouts as well as balance and flexibility exercises, which are embedded in the game's story line. All workout intensities are based on the fitness assessment of the player through established field tests that are also part of the story line. MOBIGAME offers the unique opportunity to more sustainably improve adherence to exercise through game enjoyment combined with convenience and individualized goals that give the users immediate feedback and credit for their accomplishments and thereby increase motivation to progress in the game [55]. In contrast to traditional exergames, MOBIGAME offers a large variety of sensor-tracked exercise modes that facilitate workouts indoors as well as outdoors and thus gives the users the opportunity to be physically active wherever they are.

This study will comprehensively evaluate the effectiveness of MOBIGAME as a highly innovative, mobile and individualized home-based treatment option for T2DM patients on sustainably improving daily PA (primary outcome) and several health parameters in the mid to long term. The study aims to assess whether a cutting-edge exergaming application, developed by sports scientists and professional game developers in a close collaboration over the course of 24 months, is superior to traditional home-based patient guidance. If so, this application may cover a gap in the treatment of those patients with T2DM not willing or not able to participate in structured group programs and could at the same time reduce time-consuming and personal-intensive face-to-face as well as telephone consultations (or at best make them redundant). Last but not least, this study will add considerably to the understanding of whether a mobile phone-based game application is an option to sufficiently address the problem of program adherence in PA-promoting interventions and provide relevant information for the general transferability of this application for use in other chronic diseases.

Trial status

At the time of manuscript submission (Version 1, 27 October 2016), examinations have started (see timeline).

Additional files

Additional file 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist. (DOC 121 kb)

Additional file 2: Study data – further outcomes. (DOCX 49 kb)

Abbreviations

6MWT: 6-Minute Walk Test; ACSM: American College of Sports Medicine; ANCOVA: analysis of covariance; BMI: body mass index; EACPR: European Association for Cardiovascular Prevention & Rehabilitation; EKNZ: Ethics Committee Northwest/Central Switzerland; FACIT: Functional Assessment of Chronic Illness Therapy; FOPH: Federal Office of Public Health; HbA_{1c}: glycated hemoglobin; HDL: high-density lipoprotein; HOMA: Homeostasis Model Assessment; HR_{max}: maximum heart rate; HRQOL: health-related quality of life; IMI: Intrinsic Motivation Inventory; LDL: low-density lipoprotein; MET: metabolic equivalent; PA: physical activity; PRS: Protocol Registration and Results System; RPE: ratings of perceived exertion; RVA: retinal vessel analyzer; SF-36: 36-Item Short Form Health Survey; SNSF: Swiss National Science Foundation; STS: Sit-to-Stand Test; T2DM: type 2 diabetes mellitus; TAM: Technology Acceptance Model; VO_{2max}: maximum oxygen consumption; VO_{2mean}: mean oxygen consumption; VO_{2peak}: peak oxygen consumption

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Availability of data and materials

All data will be archived electronically under the responsibility of the Department of Sport, Exercise and Health of the University of Basel, Switzerland. The data set generated and analyzed during the study will be available from the corresponding author upon reasonable request.

Authors' contributions

CH, AST, SW and JH specified the research plan for development and evaluation of the MOBIGAME concept. CH, AST and JS initiated, planned and conceptualized the present study. CH and AST applied for the research grant. All co-authors supported the grant application and substantially contributed to the conception and design of the study by giving relevant intellectual input on all aspects of the study. CH drafted the manuscript, tables and figures; JS ("Sample size", "Statistical methods", "Allocation and blinding", and "Data collection") and HH ("Microvascular function") participated in drafting the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the version to be published.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

We intend to publish the results of this study in a relevant peer-reviewed journal. All participants give their consent for publication in the consent form. However, every attempt will be made to ensure the participants' anonymity.

Ethics approval and consent to participate

All participants have to give their written informed consent before being included in the study and can discontinue their participation at any time without giving reason. A withdrawal of consent will not affect the participant's subsequent medical assistance and treatment. The research is carried out in accordance with the Declaration of Helsinki [87] as well as the ICH-GCP guidelines [88]. The protocol was approved by the Ethics Committee of Northwest/Central Switzerland (EKNZ) on 23 January 2016 (reg. no. EKNZ 2015-424). In case of substantial amendments of the study protocol, approval by the EKNZ will be sought before implementation.

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Additional File: Study Data– Further Outcomes

The following parameters are measured at baseline as well as after the 24-week intervention:

Self-determination

Consisting of intrinsic motivation, perceived competence, perceived choice, and perceived usefulness, self-determination is measured via the Intrinsic Motivation Inventory (IMI) score. The IMI is a multidimensional Likert-type rating scale that assesses the central motivational structures underlying self-determination [1]. It has been shown to possess good internal consistency (Cronbach's alpha = 0.92) and test-retest reliability (intraclass correlation coefficient = 0.77) in other populations [1] and has been used in previous virtual reality physical activity studies [2–6].

Aerobic capacity

Aerobic capacity is measured as $\dot{V}O_{2peak}$ during an all-out bike spiroergometry using the mobile METALYZER 3B spirometry system (Cortex Biophysik GmbH, Leipzig, Germany). After a 3-minute warm-up phase at 25 W, workload increases by 15 W/min until subjects' subjective exhaustion. Pedaling frequency has to be above 60 rpm throughout the entire test. Respiratory gas parameters are measured breath-by-breath; ratings of perceived exertion (RPE) [7] and blood pressure are measured at rest, after warm-up and every two minutes until exhaustion. The blood lactate concentration is measured at rest and at maximum performance as well as one, three, and five minutes after the end of the exercise test. Throughout the entire duration of the test and until exertion, cardiac function is monitored with a 12-channel electrocardiogram.

Maximal 6-minute walking distance

Maximal 6-minute walking distance is assessed with the 6-minute walk test, an established measure of functional exercise capacity commonly assessed in T2DM [8].

Leg strength endurance

Leg strength endurance is assessed as the maximum number of repetitions in the Sit-to-Stand Test [9].

Maximal isometric force

Maximal isometric force and rate of force development are measured in a double-limb leg press on an isokinetic dynamometer (D&R Ferstl, IsoMed 2000, Hemau, Germany) [10]. During the measurement, the seat back is reclined to 50°. Hip and knee angles are individually adjusted at 90° and 100°, respectively, while the hip is additionally fixed with a belt. The testing condition consists of two maximal contractions of five seconds with a recovery time of 30 seconds in between two contractions [10]. As decreases of skeletal muscle mass and muscle quality especially in the lower limb are common in older adults with T2DM [11] and often contribute to fatigue [12]

and a reduced HRQOL [13], the assessment of leg strength is an important outcome of the MOBIGAME intervention.

Glucose metabolism

Glucose metabolism (fasting glucose, glycated hemoglobin (HbA_{1c}), fasting C-peptide, fasting insulin levels) measured by standard laboratory analysis of venous blood. The Homeostasis Model Assessment (HOMA) index is used to quantify insulin resistance and ß-cell function by implicating the measured fasting insulin and fasting glucose concentrations.

Inflammatory markers

Inflammatory markers such as total cholesterol, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, triglycerides, apolipoprotein B, irisin, adiponectin and interleukin-6 levels, measured by standard laboratory analysis of venous blood.

Macrovascular function

Macrovascular function (peripheral and central blood pressure, pulse wave reflection as augmentation index and arterial stiffness as aortic pulse wave velocity) is assessed using a cuff-based oscillometric measurement device (Mobil-O-Graph, I.E.M GmbH, Stolberg, Germany) by the application of the ARCSolver algorithm to pulse wave signals acquired with the Mobil-O-Graph device [14]. Peripheral and central blood pressure, pulse wave reflection as augmentation index and arterial stiffness are commonly used as independent predictors to assess the cardiovascular risk [15]. These methods are valid and reliable ways to assess arterial stiffness, central blood pressure and pulse wave reflection in a Caucasian population [14,16].

Microvascular function

Microvascular function (retinal vessel diameters) is analyzed using the Retinal Vessel Analyzer (RVA, IMEDOS Systems, Jena, Germany). Two valid images from the retina of the left and the right eye with an angle of 30° and with the optic disc in the center are taken per visit in order to analyze retinal vessel diameters as previously described [17] and applied in a previous study [18] using a special analyzing software (Vesselmap 2, Visualis, Imedos Systems). Reliability of retinal vessel diameter analysis has been shown to be high, with inter-observer and intra-observer intraclass correlation coefficients for arteriolar and venular diameter measurements ranging from 0.78 to 0.99 [17,19]. Retinal vessel diameter analysis has been used as a microvascular biomarker and independent predictor of cardiovascular risk and mortality [20–22].

Health-related quality of life

Health-related quality of life (HRQoL) is assessed via the 36-Item Short Form Health Survey (SF-36). This patient-reported survey features a set of generic, coherent, and easily administered quality-of-life parameters, while its vitality scale specifically addresses fatigue measures [23].

Fatigue

Fatigue is measured by use of the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale. It has demonstrated reliability and sensitivity to change in patients with a variety of chronic health conditions with a high test-retest reliability (intraclass correlation coefficient = 0.95) and a high internal validity (Cronbach's alpha = 0.96) [24].

Acceptance of intervention

To evaluate the participants' perceived acceptance of the MOBIGAME intervention and to find possible correlations with adherence levels, an abridged version [25] of the technology acceptance model (TAM) questionnaire is used in addition in the intervention group post-intervention [26].

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Chapter 6

Publication 4
Validity of Activity Trackers, Smartphones, and Phone Applications to Measure Steps in Various Walking Conditions.

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Chapter 7

Publication 5

Behavior Change Technique-based Smartphone Game Sustainably Increases Daily Physical Activity in Type 2 Diabetes Patients – A Randomized Controlled Trial.

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Abstract

Objective

Many type 2 diabetes patients show insufficient levels of physical activity (PA) and are often unmotivated to change PA behaviors. We investigated whether a newly developed, commercially released smartphone game delivering an individualized exercise and PA promotion can generate sustained improvements in daily PA (steps/d).

Research Design and Methods

Inactive, overweight type 2 diabetes patients (n=36), 45-70 years of age, who regularly use smartphones were randomly assigned to either the intervention group or the control group (one-time lifestyle counseling). Participants were instructed to play the game or implement the recommendations from the lifestyle counseling autonomously during the 24-week intervention period. The primary outcome was daily PA (steps/d) change over 24 weeks.

Results

Daily PA increased by an average of 3,998 (SD 1,293) steps/d in the intervention group and by an average of 939 (SD 1,156) steps/d in the control group. The adjusted difference between the two groups was 3,128 steps/d (95% CI 2,313, 3,943; P<0.001). The increase in daily PA was accompanied by an increase in aerobic capacity (adjusted difference of oxygen uptake at the first ventilatory threshold of 1.9 ml/(kg·min), 95% CI 0.9, 2.9; P<0.001). Glycemic control (HbA_{1c}) did not change over the course of the intervention.

Conclusions

A novel, self-developed smartphone game, delivering multidimensional home-based exercise and PA-promotion, significantly increases daily PA (steps/d) and aerobic capacity in inactive type 2 diabetes patients after 24 weeks. The ability of the game to elicit a sustained PA motivation may be relevant for other inactive target groups with chronic diseases.

Introduction

In recent years, type 2 diabetes has developed into a global health burden that presents one of the great health care challenges of our time [1]. In 2014, over 400 million adults worldwide had diabetes mellitus, predominantly of type 2 [2], representing a key determinant of morbidity and mortality in both developed and developing countries [1]. The direct annual cost of diabetes was an estimated $825 billion in 2014 [3] and makes up as much as 20% of the total health care expenditures in many countries [4], underlining the disease's enormous economic burden.
Regular physical activity (PA) is a cornerstone of a successful diabetes management, and its beneficial health effects with regard to glycemic control, comorbidities, and physical functioning are well documented [5]. Despite the apparent benefits of regular PA, only 25% of adults with type 2 diabetes meet PA recommendations and 40% are physically inactive, engaging in less than ten minutes of moderate or vigorous activity per week during work, leisure time, or transportation [6]. Physical inactivity not only increases the risk of type 2 diabetes by over 100% but also significantly contributes to the development of several comorbidities such as hypertension, dyslipidemia, and cardiovascular disease [6] and a 1.5-fold increased risk of all-cause mortality [7]. Lack of motivation and lack of PA enjoyment, as well as aversion to exercise facilities, missing social support, and health concerns such as hypoglycemia or fear of injury, are the main reasons that keep patients with type 2 diabetes from becoming more physically active or cause them to discontinue participation in a PA promoting program [8]. Motivating and enjoyable low-threshold forms of PA are therefore desperately needed to encourage this target group to become and sustainably be more physically active.

In recent years, PA-promoting games (exergames) have increasingly been used and examined to encourage regular PA in those who cannot be motivated through conventional PA-promoting interventions [9]. By making PA an enjoyable and meaningful experience, this "gamified" approach aims to attenuate the negative perception of PA, as often the case in inactive target groups, and thereby lowers the subjectively perceived cost of being physically active [9]. Console-based exergaming has been shown to improve glycemic control, quality of life, and subjectively (questionnaire) assessed PA in type 2 diabetes [10]; however, evidence is very limited and longer-term results of any gamified approach regarding objectively (accelerometer) measured increases in PA are missing [11]. In addition, current exergames seldom offer exercise modes that concur in intensity and duration with established exercise guidelines and fail to provide a sufficient extent of individualization that is required for an effective and safe training in patients with chronic diseases who often have a significantly lower fitness level than healthy target groups [11]. Further, for exergames, and more generally, for serious games with a behavioral intervention objective to be enjoyably effective, they need to engage their intended audience in terms of narrative premise, gameplay, and storytelling [9].

To address these design challenges, as well as the shortcomings of existing exergames, we developed a mobile smartphone-based game application specifically designed for type 2 diabetes patients with the goal to encourage a healthier, more active lifestyle through gamified daily PA [12]. The aim of this randomized controlled trial (RCT) was to assess the effect of the game on daily PA (steps/d) in physically inactive individuals with type 2 diabetes. We hypothesized that the use of the game application would lead to higher increases in steps/d after 24 weeks than a control intervention consisting of a one-time lifestyle counseling. Secondary aims were to assess the effect of the game on glycemic control, circulating cardiovascular risk factors, and aerobic capacity.

Research Design and Methods

Study design

This 24-week RCT (2-arm) was conducted in accordance with the Declaration of Helsinki [13] between August 2016 and April 2018 at the Department of Sport, Exercise and Health of the University of Basel, Switzerland. The study was registered at ClinicalTrials.gov (NCT02657018) and approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, Reg.-No. EKNZ 2015-424). We used permuted block randomization with randomly varying block sizes to allocate participants at random and in equal numbers to one of the two groups. The randomization list was generated in advance using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and the R add-on package 'blockrand' version 1.3 and transmitted using sequentially numbered, opaque, sealed envelopes by a study assistant not involved in the measurement appointments. All outcome assessors were blinded with respect to group allocation. The detailed study protocol can be found in a previous publication [12].

Participants

Participants were recruited in cooperation with several hospitals, doctor's offices, and diabetes care centers in the Basel metropolitan area, as well as through online and newspaper advertising. Participants were eligible to participate if they met the following inclusion criteria: (I) physician-diagnosed and medically treated non-insulin-dependent diabetes mellitus, (II) body mass index ≥25 kg/m^2, (III) 45-70 years of age, (IV) <150 min of moderate-intensity PA per week, and (V) regular smartphone use during the last year before the study to ensure that participants were familiar with the use of smartphones and would represent a realistic target group for a PA-promoting smartphone game. Exclusion criteria were insulin treatment as well as health risks that contraindicate exercise testing [14], impaired physical mobility, and acute infections or injuries. Eligible participants received detailed information about purpose and procedures of this study and gave written informed consent before participation.

Intervention

Participants in the intervention group received a novel, self-developed smartphone game that was commercially released under the name "Mission: Schweinehund". The game includes individualized multidimensional (strength, endurance, balance, flexibility), exercise and daily PA (walking) promotion following established PA guidelines [15]. A key component of the game's PA-related content is the integration of exercise tests such as the 1-min Sit-to-Stand Test [16] and the Six Minute Walk Test [17]. These tests assess the fitness level of each individual user at baseline and periodically during play and allow building tailored exercise regimens with appropriate entry levels and individualized rates of intensity progression. Execution of in-game exercises (130 exercise variations) and daily PA are tracked via the phone's sensors (camera, accelerometer, and gyroscope). Key elements of the game's storyline are the restoration of a garden (used as a metaphor for the own body) and the taming of the Schweinehund (in German, a self-depreciating idiom denoting one's weaker self, often referring to the lazy procrastination regarding PA), both of which can be achieved through regular in-game PA and the related in-game rewards. The game mechanics are anchored in the CALO-RE taxonomy of behavior change techniques [18], whereby the progression in the storyline is independent of the player's initial fitness level but depends rather on the regularity of game use and the meeting of personalized PA goals. A detailed description of the game's content with regard to the exercise regimen and game design is provided in a previous publication [12]. Because the game was designed to be self-explanatory and to encourage regular use through the motivating character of the game design, participants in the intervention group were only provided with very basic instructions on how to use and control the game but not on how often or when to use it.

Participants in the control group received a one-time lifestyle counseling including the promotion of baseline activities of daily life [19], as well as a structured exercise plan including strength and endurance exercises with moderately increasing intensity and duration, essentially comparable to the content of the game, that was to be implemented autonomously.

Outcome Measures

Participant Characteristics

At baseline and after the 24-week intervention, all participants underwent a clinical examination including medical history and a physical examination consisting of measurements of height, body mass, body fat content via bioelectrical impedance analysis (InBody 720, JP Global Markets GmbH, Eschborn, Germany), resting blood pressure (BP), and resting electrocardiography (ECG). To verify that participants met the PA-related inclusion criteria, habitual PA was assessed at the first measurement appointment using the Freiburg Questionnaire of PA [20].

Glycemic Control and Circulating Cardiovascular Risk Factors

During the clinical examination and after an overnight fast of ≥8 hours, blood samples were drawn by venipuncture of the cubital fossa of the right or left arm by trained medical staff. Directly after collection, blood samples were transported to the laboratory of the University Hospital Basel, Switzerland for further analysis. Analyzed parameters included HbA_{1c}, total cholesterol, low- (LDL) and high-density lipoprotein (HDL), and triglycerides.

Aerobic Capacity

Following the clinical examination, participants underwent a cardiorespiratory fitness test on a bicycle ergometer (ergoselect 200, ergoline GmbH, Bitz, Germany) to assess the maximum oxygen uptake ($\dot{V}O_{2peak}$) and the first ventilatory threshold (VT1) [21]. After a 3-minute warm-up phase at 25 W, workload increased linearly (ramp protocol) by 15 W/min until participants' exhaustion. Respiratory gas parameters were analyzed breath-by-breath (MetaMax 3B, Cortex Biophysik GmbH, Leipzig, Germany). Ratings of perceived exertion according to the 6-20 Borg Scale [22] and BP were measured at rest, after warm-up, and every two minutes until exhaustion. Blood lactate concentration was measured (Super GL Ambulance, Hitado Diagnostic Systems, Moehnesee, Germany) at rest and at maximum performance as well as one, three, and five minutes after the end of the test. Cardiac function was monitored with a 12-channel ECG throughout the entire test (Custo med GmbH, Ottobrunn, Germany). Maximal exhaustion was accepted if at least two of the following four criteria were met: (I) respiratory exchange ratio ≥1.1; (II) blood lactate concentration >8 mmol/l; (III) RPE ≥18; and (IV) maximum heart rate (HRmax) >95% of predicted HRmax [208 − 0.7 × age (years)] [23].

Daily Physical Activity

After the cardiorespiratory fitness test, participants received a Vivofit 2 accelerometer wristband (Garmin International Inc., Olathe, KS, USA) with the instruction to wear it continuously during the following week for the assessment of the daily PA. The Garmin Vivofit has previously been shown to be valid for step detection in various walking conditions with constant as well as varying walking speeds [24,25]. To eliminate any impact of a step count feedback on the participants' PA behavior, the devices' displays were irreversibly blackened out. In addition to the accelerometer wristbands, participants received a diary to record any non-wear time during the monitoring period. Only days with uninterrupted wear were considered for data analyses. Day 0 (the day participants received the device) of the monitoring period was not considered for data analyses, as is common in the assessment of PA, because participants are known to change their activity pattern on the initial day of data recording [26].

Statistical Analyses

Summary statistics were calculated to characterize the study sample and for pre- and post-intervention data as appropriate. Continuous data were summarized using the mean (standard deviation, SD) or the median (interquartile range, IQR). The primary outcome of daily PA (steps/d) after the intervention and further outcomes were analyzed by analysis of covariance [27]. Results are presented as differences in outcome (with 95% confidence intervals, CI) between participants in the intervention group and those in the control group, adjusted for the corresponding values at baseline. Correlations between total in-game training (min) and outcome measures were analyzed using Spearman's rank correlation coefficient. R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses and graphics with the significance level set to 0.05 (2-sided).

Sample Size

For the sample size calculation, we hypothesized that the expected difference in daily PA (primary outcome) after 24 weeks between participants in the intervention group and those in the control group would be 2,500 steps/d with an SD in either group of 3,000 steps/d [28]. By including daily PA (steps/d) at baseline as a covariate in the analysis, we aimed to further reduce error variability and therefore hypothesized that the correlation between baseline and outcome daily PA would be 0.7. With a significance level of 0.05 (2-sided), the sample size needed to attain a targeted power of 90% for showing superiority of the experimental intervention over control was determined as a total of 34 participants (17 in each group).

Results

Participant Flow and Characteristics

Sixty-eight participants were assessed for eligibility (Figure 1). Thirty-two subjects were excluded because they did not meet inclusion criteria (n=19) or declined to participate (n=13). All remaining participants (n=36) were randomly assigned to either the intervention group (n=18) or the control group (n=18). Baseline characteristics of study participants were balanced between both groups (Table 1). All participants received antidiabetic drug treatment prior to enrollment in the study and did not change medication during the intervention period. One participant was lost to follow up due to medical reasons not related to the study. Thirty-five participants completed the study and were included in the analysis of the primary outcome.

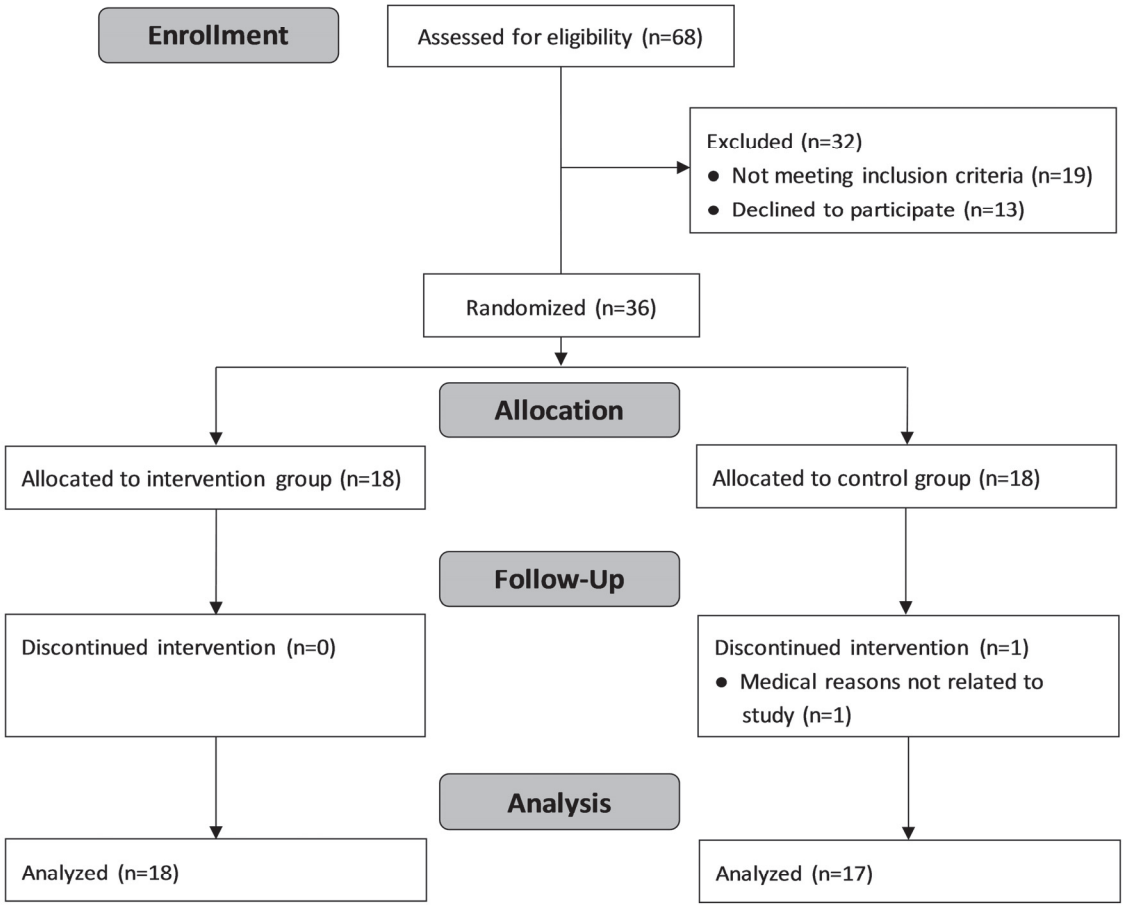

Figure 1: *Flow diagram of study participants.*

Table 1: Baseline characteristics of study participants.

		Intervention (n=18)		Control (n=18)	
		n	Median (IQR)	n	Median (IQR)
Basic					
Sex	Female	8		9	
	Male	10		9	
Age (years)		18	57 (53, 60)	18	60 (54, 63)
Height (m)		18	172 (166, 177)	18	172 (165, 177)
Weight (kg)		18	93 (89, 96)	18	98 (88, 111)
BMI (kg/m^2)		18	31 (29, 34)	18	33 (30, 36)
Fat mass (%)		18	39 (35, 43)	18	35 (33, 43)
MVPA (min/week)		18	45 (0, 60)	18	38 (0, 68)
Medical Record					
Diabetes duration (years)		18	3.3 (1.4, 4.3)	18	4.1 (1.5, 7.0)
Antidiabetic drug intake		18		18	
Metformin		18		18	
DPP-4-inhibitor		7		6	
Thiazolidinedione		-		1	
SGLT2 inhibitor		-		1	
GLP-1 receptor agonist		1		2	
Sulfonylurea		2		1	
Antihypertensive drug intake		12		11	
Lipid-lowering drug intake		4		7	

Abbreviations: IQR, interquartile range; BMI, body mass index; MVPA, moderate-to-vigorous physical activity; DPP-4, dipeptidyl peptidase 4; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide 1.

Changes in Daily Physical Activity

All participants wore the accelerometer wristband continuously for a minimum of five full days. Daily PA increased by an average of 3,998 (SD 1,293) steps/d in the intervention group and by an average of 939 (SD 1,156) steps/d in the control group during the 24-week intervention (Table 2). The adjusted difference of the increase in daily PA between both groups was 3,128 steps/d (95% CI 2,313, 3,943; P<0.001) in favor of the intervention group.

Changes in Glycemic Control

HbA_{1c} remained unchanged at 6.2% (SD 0.7) in the intervention group and increased by 0.1 percentage points (SD 1.3) in the control group during the intervention period with an adjusted difference of -0.9 percentage points (95% CI -1.5, -0.2; P=0.016) in favor of the intervention group. There were no apparent changes in total, LDL-, and HDL-cholesterol, or triglycerides over the course of the intervention in either group.

Changes in Aerobic Capacity

Relative $\dot{V}O_{2peak}$ increased by 1.4 ml/(kg·min) (SD 2.0) in the intervention group and decreased by 0.3 ml/(kg·min) (SD 1.1) in the control group during the intervention period with an adjusted difference of 1.9 ml/(kg·min) (95% CI 0.7, 3.0; P=0.002) in favor of the intervention group. Absolute values did not change significantly in either group with an adjusted difference of 0.10 l/min (95% CI, -0.02, 0.23; P=0.110) between both groups. Relative and absolute $\dot{V}O_2$ at VT1 increased by 1.8 ml/(kg·min) (SD 1.2) and 0.13 l/min (SD 0.09) in the intervention group and decreased by 0.1 ml/(kg·min) (SD 1.4) and 0.03 l/min (SD 0.15) in the control group. The adjusted difference between the two groups was 1.9 ml/(kg·min) (95% CI 0.9, 2.9; P<0.001) and 0.14 l/min (95% CI 0.05, 0.23; P=0.003) in favor of the intervention group. Increases in workload at VT1 were observed for both groups post-intervention, with an adjusted difference between both groups of 10.8 W (95% CI 7.1, 14.5; P<0.001) in favor of the intervention group.

Changes in Anthropometric and Further Physiological Parameters

Total body fat mass decreased by 2.7 kg (SD 2.5) in the intervention group and by 0.9 kg (SD 3.4) in the control group. The adjusted difference between the two groups was -2.1 kg (95% CI -4.2, 0.0; P=0.045) in favor of the intervention group. Skeletal muscle mass did not change significantly in either group during the intervention with an adjusted difference of 0.2 kg (95% CI -1.0, 1.5; P=0.710). No apparent changes were observed for resting HR as well as for systolic or diastolic BP at rest.

Table 2: Effects of game use compared to a one-time lifestyle counseling on daily physical activity, aerobic capacity and anthropometric, metabolic and physiological parameters.

Outcome	Intervention (n=18)		Control (n=17)		Adjusted difference* (95% CI)	P value
	Pre-intervention (mean (SD))	Post-intervention (mean (SD))	Pre-intervention (mean (SD))	Post-intervention (mean (SD))		
Steps per day	5,785 (793)	9,783 (1,334)	5,612 (1,192)	6,552 (1,280)	3,128 (2,313, 3,943)	<0.001
Total body fat mass (kg)	35.1 (8.7)	32.4 (9.1)	38.7 (10.6)	37.9 (9.8)	-2.1 (-4.2, 0.0)	0.045
Skeletal muscle mass (kg)	32.1 (5.7)	32.7 (5.8)	34.1 (6.6)	34.5 (7.0)	0.2 (-1.0, 1.5)	0.710
HbA_{1c} (%)	6.2 (0.6)	6.2 (0.7)	6.9 (0.7)	7.0 (1.0)	-0.9 (-1.5, -0.2)	0.016
Total cholesterol (mmol/l)	4.9 (0.9)	5.1 (0.8)	4.6 (1.0)	4.8 (0.9)	0.2 (-0.4, 0.7)	0.546
HDL cholesterol (mmol/l)	1.2 (0.2)	1.2 (0.3)	1.3 (0.3)	1.3 (0.2)	0.0 (-0.1,0.2)	0.463
LDL cholesterol (mmol/l)	2.8 (0.9)	3.0 (0.9)	2.5 (0.9)	2.7 (0.8)	0.1 (-0.4, 0.6)	0.740
Triglycerides (mmol/l)	2.0 (0.9)	1.9 (0.8)	1.9 (1.0)	1.8 (0.9)	0.0 (-0.4, 0.4)	0.951
HR at rest (bpm)	66 (10)	64 (10)	68 (11)	69 (9)	-3 (-7, 1)	0.099
SBP at rest (mmHg)	136 (14)	133 (15)	134 (12)	134 (14)	-3 (-9, 4)	0.384
DBP at rest (mmHg)	88 (8)	85 (8)	86 (8)	87 (9)	-3 (-7, 1)	0.180
$\dot{V}O_{2peak}$† (ml/(kg·min))	24.0 (4.3)	25.5 (3.5)	23.2 (4.1)	22.9 (4.0)	1.9 (0.7, 3.0)	0.002
$\dot{V}O_2$ at VT1‡ (ml/(kg·min))	15.4 (2.5)	17.2 (2.6)	15.0 (1.7)	14.9 (2.2)	1.9 (0.9, 2.9)	<0.001
Workload at VT1‡ (W)	82.2 (17.3)	95.6 (15.7)	84.8 (15.8)	87.1 (15.9)	10.8 (7.1, 14.5)	<0.001

Abbreviations: SD, standard deviation; CI, confidence interval; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; $\dot{V}O_{2peak}$, peak oxygen uptake; $\dot{V}O_2$, oxygen uptake; VT1, first ventilatory threshold.

*Analysis of covariance comparing post-intervention values between the intervention group and the control group adjusted for the corresponding pre-intervention values.

†Pre- and post-intervention data available in 17/18 participants in the intervention group and in 13/17 participants in the control group.

‡Pre- and post-intervention data available in 13/17 participants in the control group.

Strong positive correlations were found between total time of in-game training and change in daily PA (steps/d) (r_s=0.91) as well as change in workload at VT1 (r_s=0.66), indicating that those who used the game as a training tool more, increased their daily PA and aerobic capacity more than those who used the game less (Figure 2).

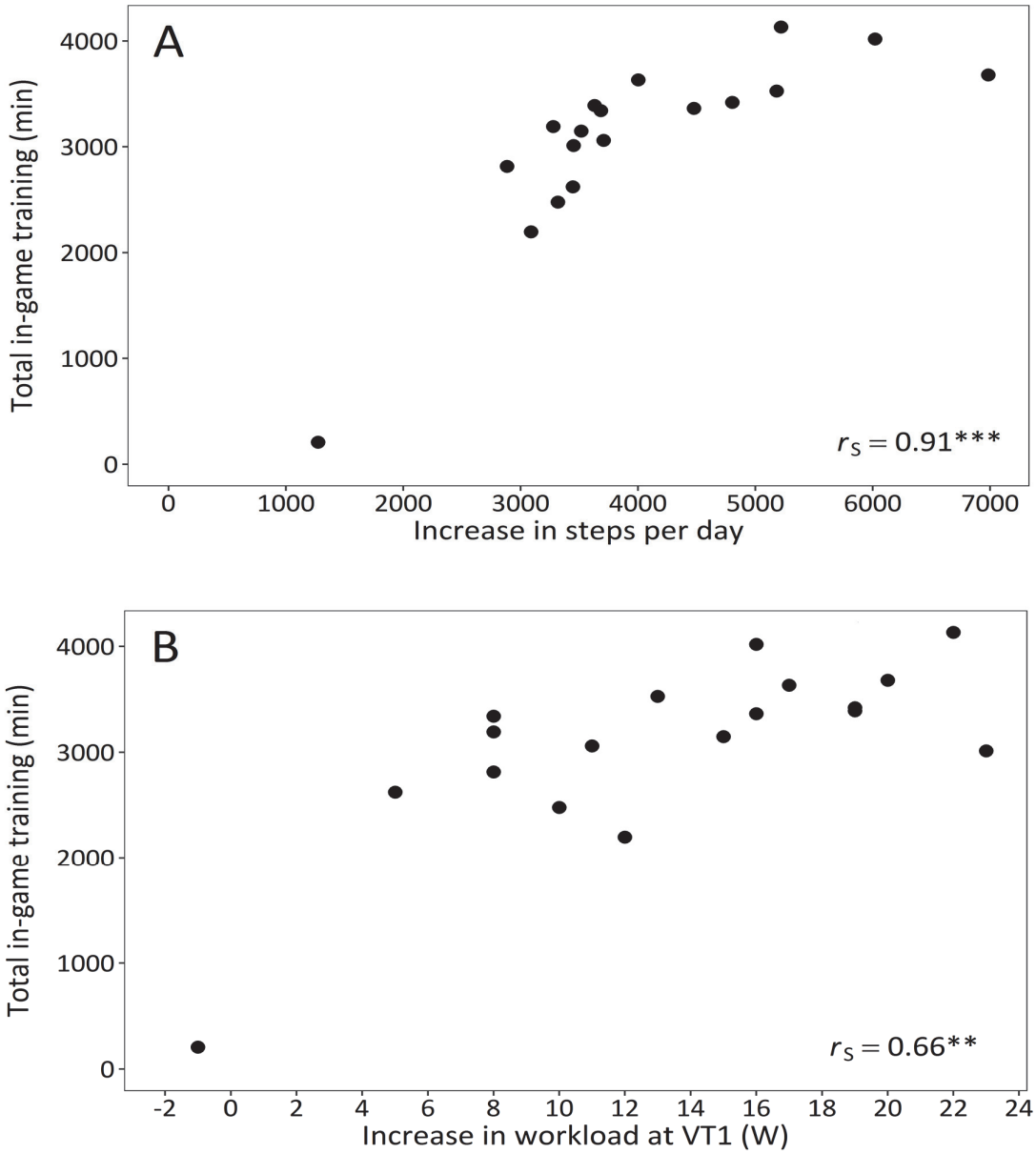

Figure 2: *Correlation between total in-game training (min) and (A) increase in steps per day and (B) increase in workload at VT1 (W).*
***P<0.01 and ***P<0.001 (Spearman's rank correlation coefficient).*

Conclusions

In this RCT, the use of a novel, self-developed smartphone game that included individualized exercise and daily PA promotion led to a significantly higher increase in daily PA (+3,000 steps) after 24 weeks than a control intervention consisting of a one-time lifestyle counseling. The magnitude of the shown increase in steps/d is comparable to that of a 24-week pedometer-based behavioral modification program including a face-to-face session and regular telephone follow-ups (+2,800 steps) [28] and provides strong evidence that a smartphone game that incorporates personalized PA recommendations and step count goals in the storyline can generate meaningful and sustained improvements in daily PA in a previously inactive target group. Increases of 2,000 steps/d in daily life over a 12-month period have been shown to be of clinical relevance in patients with an impaired glucose tolerance as they are associated with an 8% lower cardiovascular event rate [29]. The strong positive correlation (r_s=0.91) between the total time of in-game training and the increase in steps/d in the intervention group suggests that indeed the game played a decisive role in motivating participants to become and remain more physically active.

The increased amount of daily PA in this study was accompanied by an improvement in aerobic capacity. Relative $\dot{V}O_2$ (ml/(kg·min)) at VT1 increased by 11.7% and absolute $\dot{V}O_2$ (l/min) by 9.2%, indicating a de facto improvement in aerobic capacity. The increased $\dot{V}O_2$ enabled participants to generate an 18% higher workload (+14.7 W) at VT1. A higher $\dot{V}O_2$ at VT1 has been shown [30] to be inversely and independently associated with fatal cardiovascular and all-cause mortality events, underlining the clinical relevance of the found improvements in aerobic capacity. Relative $\dot{V}O_{2peak}$ (ml/(kg·min)) increased as well (+6.3%) but was not accompanied by significant increases in absolute $\dot{V}O_{2peak}$ (l/min). This is not surprising, as the game was not designed to improve $\dot{V}O_{2peak}$, but rather to improve basic endurance through increases in daily PA. The slight change in relative $\dot{V}O_{2peak}$ was likely due to a decrease in body weight caused by the significant reduction in total body fat mass of 2.7 kg (7.7%) during the intervention. The reduction in body fat mass in our study was modest when compared to an intensive 12-week lifestyle intervention consisting of dietary changes, exercise, cognitive-behavioral modifications, and medication adjustments, which showed an average reduction in body fat mass of 15% [31]. It is important to note however, that the reduction in body fat mass in the aforementioned study and congruent with other large lifestyle interventions targeting weight loss [32], was accompanied by a loss in lean body mass of 2.3 kg (3.5%), while in our study skeletal muscle mass was preserved. Because type 2 diabetes is associated with a 3-fold increased risk of sarcopenia [33], preservation of muscle mass is crucial and should be the focus of any lifestyle intervention to prevent an accelerated functional decline and maintain independent functioning, a central component of health-related quality of life [34]. It is therefore advisable to design lifestyle interventions to target weight loss more moderately and incorporate sufficient amounts of regular PA to prevent possible diet and inactivity-related losses of skeletal muscle mass.

Despite the strong increase in daily PA and the associated improvement in aerobic capacity, no improvements in glycemic control were found. While significant decreases in HbA_{1c} of 0.5 percentage points following walking interventions of durations between 8 and 36 weeks have been found in a recent meta-analysis [35], an inconclusive glycemic control benefit of step goal/pedometer use in type 2 diabetes, similar to our findings, has also been reported before [36]. This recent meta-analysis [36] found no association between step goal/pedometer-mediated increases in daily PA and improvements in glycemic control despite average increases in daily PA of 3,200 steps/d. A recent RCT [37] that promoted daily PA through pedometers and physician-prescribed step count goals did find reductions in HbA_{1c} of 0.38 percentage points following a 1,200-step-per-day increase in daily PA (60% lower increase than our study) after one year. It is possible that the longer intervention duration of one year in that study [30] played a role in eliciting the improvements in HbA_{1c} and that our study would have yielded similar improvements in a comparable timeframe. This assumption is supported by the findings of a recent study [38] investigating the effects of a novel online game delivering diabetes self-management education content to patients with diabetes that showed the greatest impact on HbA_{1c} in the six months after completing the intervention (12 months after baseline). It is thus conceivable that a similar time lag applies to our study through which it may take more time than 24 weeks before the gradual adoption of health-improving PA-behaviors induced by the game leads to glycemic improvements that are reflected in a lower HbA_{1c}. It can further be conjectured that a higher exercise intensity, as may be the case in certain console-based exergames [39], would have elicited (more detectable) improvements in glycemic control, comparable to the 0.3 percentage point reduction in HbA_{1c} found after only 12 weeks of autonomous exergame use [10]. However, because this may have then potentially affected the adherence to the game over 24-weeks and subsequently compromised the shown increases in PA, we deliberately designed our game to be mainly of low-intensity character to lower the threshold for regular use in our inactive, low-motivation target group and to support a sustained change in PA behavior. In addition, it is noteworthy, that the participants of the studies included in the aforementioned meta-analysis [35] and those of the exergame intervention [10] had a markedly higher average HbA_{1c} at baseline than did the participants in the intervention group of our study. Average HbA_{1c} values of 6.9-8.1% [35] and 7.1% [10] leave more room to improve glycemic control through increases in daily PA than does a baseline value of 6.2% that indicates a medically already well-controlled HbA_{1c}. The fact that HbA_{1c} actually slightly increased in our control group despite unchanged medication, along with the significant adjusted difference of -0.9 percentage points in favor of the intervention group, further suggests that the PA promotion through the game is more effective than a one-time lifestyle counseling and at the very least contributes to a successful stabilization of a well-adjusted glycemic control.

Our study has a number of strengths, including the novelty of the smartphone game-based intervention, the longer-term intervention of 24 weeks, and the objective one-week assessment of daily PA. The individualized, fitness level-adjusted training regimen and PA promotion were administered remotely via the game and without the need of physical contact between study personnel and participants. This may set a potential precedent for future PA-promoting interventions with the potential for a wide and easy dissemination even in geographically dispersed health care settings. As initial increases in daily steps have been shown to diminish during the subsequent weeks with a return to baseline values after six weeks in other PA-promoting game apps such as Pokémon GO [40], the fact that our study found significantly increased daily PA after 24 weeks, measured objectively by accelerometers, is a major strength that suggests a longer-term sustainability of the game-induced increases in daily PA.

A limitation of our study is that because enrollment required regular smartphone use before the study, the generalizability of our results might be limited, as individuals who are less technologically proficient were not considered. However, it is reasonable to speculate that individuals who do not use smartphones regularly would not typically play smartphone games in their daily life, and since we aimed to test the effectiveness of the game in a real-life setting, we consider the choice of our target group to be justified. Another limitation is that we do not know for sure which conceptual ideas and behavior change mechanics incorporated into the game have caused the increase in daily PA. This would be important knowledge for the design of future game applications targeting changes in PA behavior in unmotivated, inactive target groups.

In summary, our RCT demonstrates that a novel, behavior change technique-based smartphone game delivering multidimensional home-based exercise and PA-promotion significantly increases daily PA (steps/d) and aerobic capacity after 24 weeks and seems to contribute to the stabilization of a medication-supported diabetes treatment. The playful approach of the game seems to elicit a sustained PA motivation that could be beneficial to other inactive target groups with and without chronic diseases.

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Conflict of Interest and Funding

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Chapter 8

Publication 6

Effectiveness of a Behavior Change Technique-based Smartphone Game to Improve Intrinsic Motivation and Physical Activity Adherence in Type 2 Diabetes Patients: A Randomized Controlled Trial.

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Publication 6

Effectiveness of a Behavior Change Technique-based Smartphone Game to Improve Intrinsic Motivation and Physical Activity Adherence in Type 2 Diabetes Patients: A Randomized Controlled Trial.

Abstract

Background

Regular physical activity (PA) is an essential component of a successful type 2 diabetes treatment. However, despite the manifest evidence for the numerous health benefits of regular PA, most patients with type 2 diabetes remain inactive, often due to low motivation and lack of PA enjoyment. A recent and promising approach to help overcome these PA barriers and motivate inactive individuals to change their PA behavior is PA-promoting smartphone games. While short-term results of these games are encouraging, the long-term success in effectively changing PA behavior has to date not been confirmed. It is possible that an insufficient incorporation of motivational elements or flaws in gameplay and storyline in these games affect the long-term motivation to play and thereby prevent sustained changes in PA behavior. We aimed to address these design challenges by developing a PA-promoting smartphone game that incorporates established behavior change techniques and specifically targets inactive type 2 diabetes patients.

Objective

To investigate if a self-developed, behavior change technique-based smartphone game designed by an interdisciplinary team is able to motivate inactive individuals with type 2 diabetes for regular use and thereby increase their intrinsic PA motivation.

Methods

Thirty-six inactive, overweight type 2 diabetes patients (45-70 years of age) were randomly assigned to either the intervention group or the control group (one-time lifestyle counseling). Participants were instructed to play the smartphone game or to implement the recommendations from the lifestyle counseling autonomously during the 24-week intervention period. Intrinsic PA motivation was assessed with an abridged 12-item version of the Intrinsic Motivation Inventory (IMI) before and after the intervention. In addition, adherence to the game-proposed PA recommendations during the intervention period was assessed in the intervention group via the phone-recorded game usage data.

Results

Intrinsic PA motivation (IMI total score) increased significantly in the intervention group (+6.4 (SD 4.2; P<0.001) points) while it decreased by 1.9 (SD 16.5; P=0.623) points in the control group. The adjusted difference between both groups was 8.1 (95% CI 0.9, 15.4; P=0.029) points. The subscales 'interest/enjoyment' (+2.0 (SD 1.9) points, P<0.001) and 'perceived competence' (+2.4 (SD 2.4) points, P<0.001) likewise increased significantly in the intervention group while they did not change significantly in the control group. The usage data revealed that participants in the intervention group used the game for an average of 131.1 (SD 48.7) minutes of in-game walking and for an average of 15.3 (SD 24.6) minutes of strength training per week.

Conclusions

In inactive individuals with type 2 diabetes, a novel smartphone game incorporating established motivational elements and personalized PA recommendations elicits significant increases in intrinsic PA motivation that are accompanied by de-facto improvements in PA adherence over 24 weeks.

Introduction

Diabetes mellitus affects over 400 million adults worldwide [1] with 90-95% of all cases being attributed to type 2 diabetes [2]. The disease is associated with numerous complications and comorbidities that drastically increase direct and indirect medical costs and considerably contribute to the disease's enormous financial strain worldwide [3].

Regular physical activity (PA) with its proven positive effects on glucose and lipid metabolism, blood pressure, cardiovascular complications, and quality of life, is a key component of a successful diabetes treatment [4]. Despite these health benefits, and even though diabetes patients are usually encouraged by their physicians to increase PA, long-term adherence to PA-promoting programs is generally poor, and the level of regular PA remains low [2,5]. Physical inactivity has been estimated to be responsible for between 6% and 10% of the world's type 2 diabetes prevalence [6] and to increase the risk of all-cause mortality by an estimated 60% [7]. Lack of infrastructure, missing social support, health concerns, and especially low motivation and lack of PA enjoyment are the main deterrents that keep patients with type 2 diabetes from effectively changing their PA behaviors [8,9]. As intrinsically motivated individuals have been shown to have higher PA engagement and better PA adherence than those who are primarily motivated by external factors [10], PA-promoting programs should aim particularly at helping patients to increase their PA enjoyment and consequently increase intrinsic motivation for regular PA [11].

A promising approach that has increasingly been examined in recent years to promote regular PA in unmotivated, inactive target groups is exergames. Through the enjoyable game experience, console-based exergames have been shown to motivate inactive type 2 diabetes patients to voluntarily engage in more regular PA and thereby improve their glycemic control and overall health status [12]. Very recently, PA-promoting game apps such as Pokémon GO have entered the market that likewise aim at sustaining PA habits through gamified incentives. While Pokémon GO certainly has the potential to increase daily PA, it should be noted that the game-related initial increases of daily PA of 25% in the first week have been shown to gradually diminish in subsequent weeks and return to baseline after only six weeks [13]. It is possible that the game design does not include a sufficient degree of narrative, gameplay, or storytelling, which are required to sustainably motivate the player to play the game and consequently to make a PA-promoting game effective in the long term [14]. To address these design challenges, with an interdisciplinary team featuring sports scientists, gamification researchers, professional game developers, and clinical professionals, we developed a novel smartphone game that incorporates established motivational elements [15] and behavior change techniques [16] to encourage inactive type 2 diabetes patients to adopt a healthier, more active lifestyle.

The purpose of this study was to investigate if the behavior change technique-based smartphone game is able to motivate inactive individuals with type 2 diabetes for regular use and thereby to increase their intrinsic PA motivation. We hypothesized that use of the game would lead to greater improvements in intrinsic PA motivation than a control intervention consisting of a one-time lifestyle counseling.

Methods

Study design

This 24-week randomized controlled trial was conducted in accordance with the Declaration of Helsinki [17] between August 2016 and April 2018 at the Department of Sport, Exercise and Health of the University of Basel, Switzerland (ClinicalTrials.gov Identifier: NCT02657018) and was approved by the local ethics committee (EKNZ 2015-424). Written informed consent was obtained from all study participants prior to inclusion in the study. The primary aim of this study was to investigate the effect of the novel PA-promoting smartphone game on accelerometer-assessed daily PA (steps per day) in inactive type 2 diabetes patients. The results for the primary outcome as well as regarding changes in glycemic control and aerobic capacity have been reported elsewhere (personal communication by Christoph Höchsmann, June 2, 2018). Secondary aims were to assess the effect of the game on the predefined [18] further outcomes 'intrinsic PA motivation' and 'PA adherence'. Participants were allocated at random to either the intervention or the control group using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) and the R add-on package 'blockrand' version 1.3 to apply permuted block randomization with randomly varying block sizes. The randomization list was generated in advance and transmitted by a person not involved in the study using serially numbered, sealed, opaque envelopes. All outcome assessors were blinded with respect to the group allocation. Because 50% of diabetes participants generally drop out of exercise programs within three months [19], we chose an intervention duration of 24 weeks, which distinctly exceeds the critical timeframe of 3 months and consequently would allow the assessment of the longer-term physical activity adherence. The detailed study protocol can be found in a previous publication [18].

Recruitment

Physically inactive, overweight (body mass index ≥25 kg/m^2) type 2 diabetes (non-insulin-dependent) patients between 45 and 70 years of age were recruited in cooperation with various hospitals, doctor's offices, and diabetes care centers in the Basel metropolitan area and via online and newspaper advertising. Eligible participants were required to have used a smartphone regularly during the year before the study to ensure that they were technologically proficient enough to represent a realistic target audience for a PA-promoting smartphone game.

During the eligibility screening, participants underwent a medical examination including height, body mass, body fat content (bioelectrical impedance analysis; InBody 720, JP Global Markets GmbH, Eschborn, Germany), and resting blood pressure (BP) measurements as well as resting electrocardiography (ECG). To verify insufficient levels of PA before the study (<150 minutes of moderate-intensity PA per week), participants filled out the Freiburg Questionnaire of PA [20] as part of the eligibility screening. Present health risks that contraindicate exercise testing [21] as well as an impaired physical mobility, acute infections, or injuries excluded participants from participating in the study.

Intervention

After the baseline assessment, the self-developed and commercially released smartphone game 'Mission: Schweinehund' was installed on the phones of the participants in the intervention group. The game was designed to be self-explanatory and motivate for regular use through its game mechanics. Therefore, participants only received basic instructions regarding the game controls but not relating to an intended frequency or duration of use during the intervention period. The goal of the game is to restore a decayed garden by planting trees and flowers. In doing so, the player attracts animals that used to live in the garden to come back and help with the restoration. At the same time, the Schweinehund, the game's adversary, is kept in check. In German, 'innerer Schweinehund' (inner swine hound) refers to the weak or lazy part of one's nature, often regarding PA, that has to be overcome to get yourself going. The garden setting was deliberately chosen as its restoration stands metaphorically for the restoration of the player's body through regular PA. In addition, it has been shown that gardening is among the target group's preferred forms of physical activity [22] and that gardening-themed games are quite popular and comprehensible to a wide range of players because of their straightforward mechanics [23,24]. In the game, regular PA is rewarded with water or building materials that are needed to restore the garden and to proceed in the storyline. When designing the game, close attention was paid to the inclusion of established motivational elements [15] and behavior change techniques [16]. In addition to the rewards for successful PA behavior, goal setting, action planning, feedback on performance, as well as prompts and cues were incorporated into the game mechanics to support sustained changes in PA behavior.

The game's PA content includes in-game workouts as well as the promotion of daily PA. In-game workouts consist of 130 variations of strength, endurance, balance, and flexibility exercises whose execution, as well as daily PA, is tracked via the phone's sensors (camera, accelerometer, and gyroscope). To allow an individualization of the PA-related content of the game, exercise tests such as the 1-minute Sit-to-Stand Test [25] and the Six Minute Walk Test [26] assess the player's fitness level at baseline and periodically during play.

Based on the results, an algorithm selects appropriate entry levels and tailored rates of intensity progression for the exercise regimens as well as for the daily PA goals that can, however, be manually adjusted by the player to fit personal preferences and potential physical limitations. An individualization of the exercise regimen is crucial because unrealistic, overwhelming targets often reduce patients' motivation and thereby directly affect adherence [27]. Regularity of PA and relative improvements rather than high absolute values determine the progression in the game and thereby make game success independent of the individual fitness level.

Participants in the control group received a one-time lifestyle counseling to promote baseline activities of daily life [28]. Further, control group participants were provided with a structured exercise plan consisting of strength and endurance exercises with moderately increasing intensity and duration, essentially comparable to the content of the game that was to be implemented autonomously during the intervention period. A detailed description of the game including screenshots can be found in a previous publication [18].

Outcome Measures

Intrinsic Physical Activity Motivation

Intrinsic PA motivation was measured with an abridged 12-item version of the Intrinsic Motivation Inventory (IMI) [29] at baseline and after the 24-week intervention. The questionnaire included the four subscales 'interest/enjoyment', 'perceived competence', 'perceived choice', and 'value/usefulness'. These subscales have been used before to assess participants' subjective experience regarding participation in a TV exercise program [30] as well as to examine the motivational pull of video games [31]. The interest/enjoyment subscale is considered the true self-report measure of intrinsic motivation, while perceived competence, perceived choice, and value/usefulness are viewed as positive predictors of intrinsic motivation [30]. The items of each subscale were modified to fit the content of this study and were rated on a 7-point Likert scale ranging from 1 (*not at all true*) to 7 (*very true*). This yielded total scores between 3 and 21 for each subscale and between 12 and 84 for the entire questionnaire. Higher scores indicated a more internally motivated, self-regulated PA behavior.

Physical Activity Adherence

In the intervention group, adherence to the game-proposed PA recommendations was assessed during the intervention period via the recorded usage data from the participants' phones. Usage data included daily PA (steps per day), completed and canceled in-game workouts as well as patterns and total duration of game use.

The accuracy of iPhones and Android phones to detect steps during various walking conditions independent of the placement on the body has been confirmed in a previous study of ours [32]. For in-game walking, stride cadence was measured to assess periods of moderate-to-vigorous-intensity walking defined as ≥100 steps/minute [33].

Statistical Analysis

Summary statistics were calculated to characterize the study sample and for pre- and post-intervention data as appropriate. Continuous data were summarized using the mean (standard deviation, SD) and median (interquartile range, IQR). Intrinsic PA motivation (IMI total score and scores for all four subscales) after the intervention was analyzed by analysis of covariance [34]. Results are presented as differences in outcome (with 95% confidence intervals, CI) between participants in the intervention group and those in the control group, adjusted for the corresponding values at baseline. PA adherence was analyzed descriptively using the median, IQR, and range to illustrate game-related as well as overall-recorded daily PA per week during the 24-week intervention period. A linear regression model was used to assess the relationship between total in-game training (min) and change in IMI total score. All statistical methods used to compare the groups for intrinsic PA motivation in the present report were pre-specified and registered. R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses and graphics with the significance level set to 0.05 (two-sided).

Sample Size

A sample size calculation based on the primary outcome was conducted for this study. Since intrinsic PA motivation and PA adherence are secondary outcomes, the corresponding analyses presented in this report have to be considered explorative, and we reported the evidence in the data for the hypothesized effect of the game use on intrinsic PA motivation and PA adherence.

Results

Participant Flow and Characteristics

Figure 1 illustrates the participants' flow through the study. Sixty-eight subjects were assessed for eligibility. Nineteen did not meet the inclusion criteria and 13 declined to participate, leading to the exclusion of 32 subjects. All remaining participants (n=36) were randomly assigned to either the intervention group (n=18) or the control group (n=18) (Figure 1). Baseline characteristics of study participants were balanced between the two groups (Table 1). One participant dropped out of the study before follow-up due to medical reasons not related to the study. Thirty-five participants completed the study and were included in the analyses.

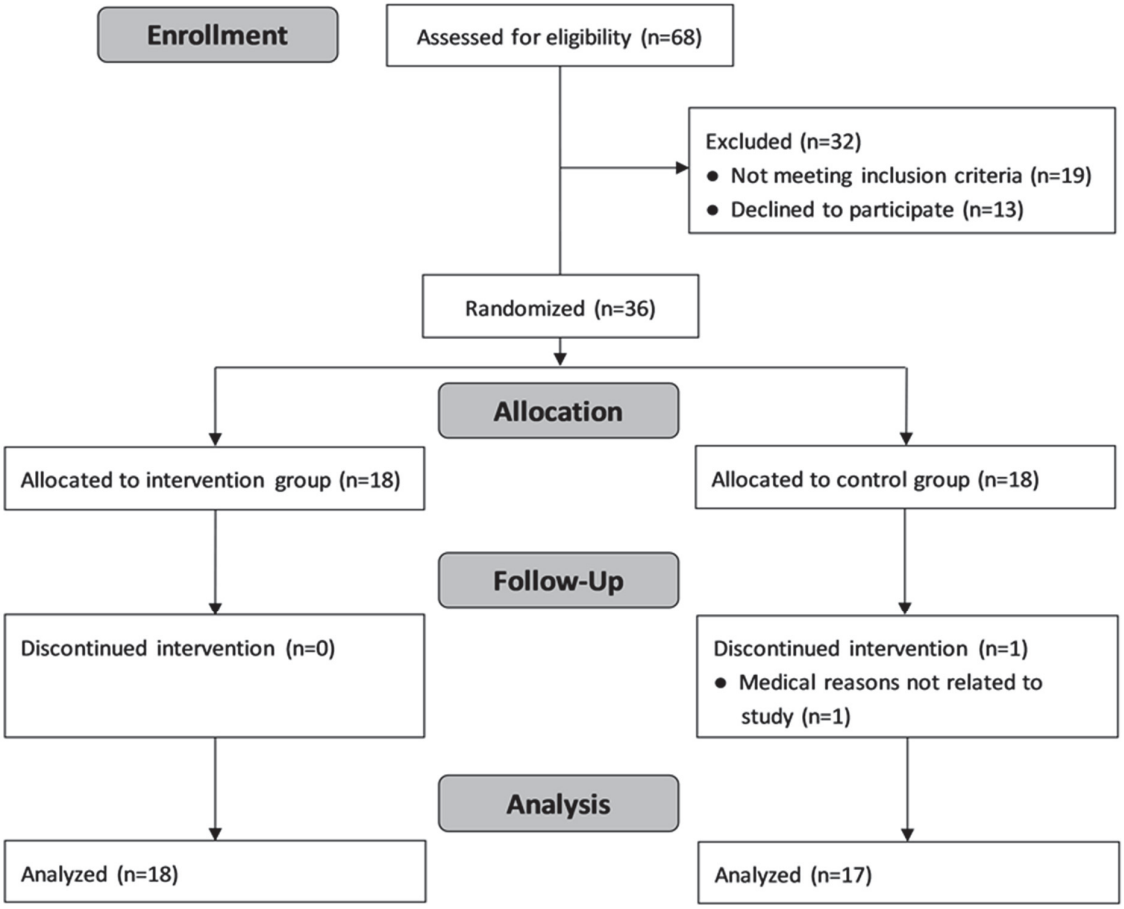

Figure 1: *Flow diagram of study participants.*

Table 1: Baseline characteristics of study participants.

		Intervention (n=18)		Control (n=18)	
		n	Mean (SD)	n	Mean (SD)
Characteristic					
Sex	Female	8		9	
	Male	10		9	
Age (years)		18	56 (5)	18	58 (6)
Height (m)		18	171 (7)	18	172 (8)
Weight (kg)		18	93 (12)	18	100 (16)
BMI (kg/m^2)		18	32 (4)	18	34 (5)
Fat mass (%)		18	38 (7)	18	38 (7)
MVPA (min/week)		18	39 (34)	18	37 (31)
Diabetes duration (years)		18	4 (4)	18	5 (4)

Abbreviations: SD, standard deviation; BMI, body mass index; MVPA, moderate-to-vigorous physical activity, PA, physical activity

Changes in Intrinsic Physical Activity Motivation

Figure 2 shows pre- and post-intervention data as mean and IQR for the IMI total score and all four subscales. Intrinsic PA motivation (IMI total score) increased significantly by an average of 6.4 (SD 4.2; P<0.001) points in the intervention group and decreased by an average of 1.9 (SD 16.5; P=0.623) points in the control group with an adjusted difference between the two groups of 8.1 (95% CI 0.9, 15.4; P=0.029) points. The subscales 'interest/enjoyment' (+2.0 (SD 1.9) points, P<0.001) and 'perceived competence' (+2.4 (SD 2.4) points, P<0.001) likewise increased significantly in the intervention group while they did not change significantly in the control group. The adjusted difference between the two groups was +2.0 (95% CI 0.0, 4.1; P=0.049) points for 'interest/enjoyment' and +2.9 (95% CI 0.6, 5.2, P=0.015) points for 'perceived competence'. The value/usefulness subscale showed a significant adjusted difference of +2.7 (95% CI 0.3, 5.2; P=0.030) points in favor of the intervention group despite non-significant changes in either group. The perceived choice subscale increased significantly by 1.2 (SD 2.4) points in the intervention group; however, with a non-significant adjusted difference of +0.7 (95% CI -1.3, 2.6; P=0.914) points between the two groups.

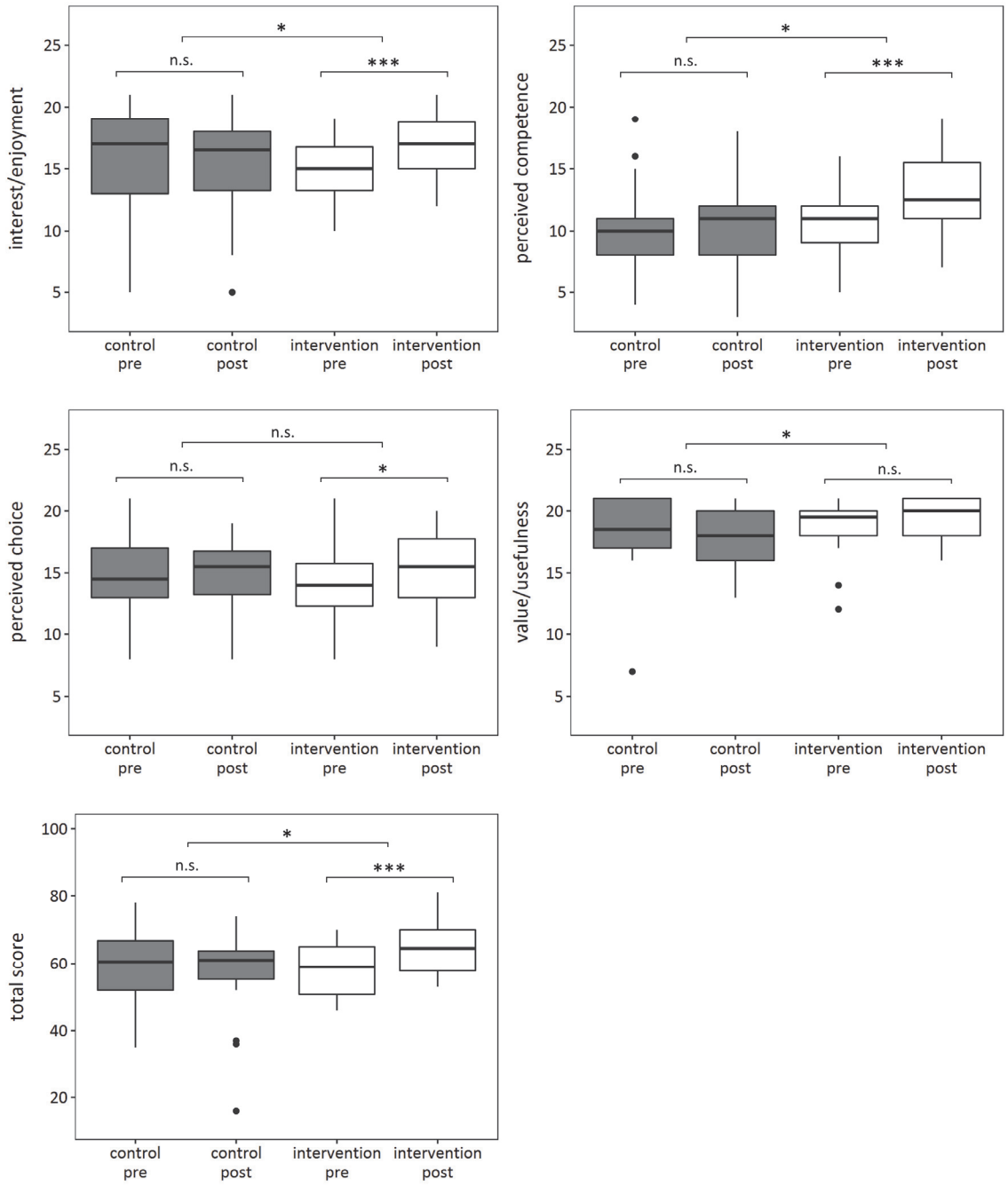

Figure 2: *Illustration of the group-dependent change in total Intrinsic Motivation Inventory score and for the subscales 'interest/enjoyment', 'perceived competence', perceived choice', and 'value/usefulness'. *, P<0.05; ***, P<0.001; n.s., not significant.*

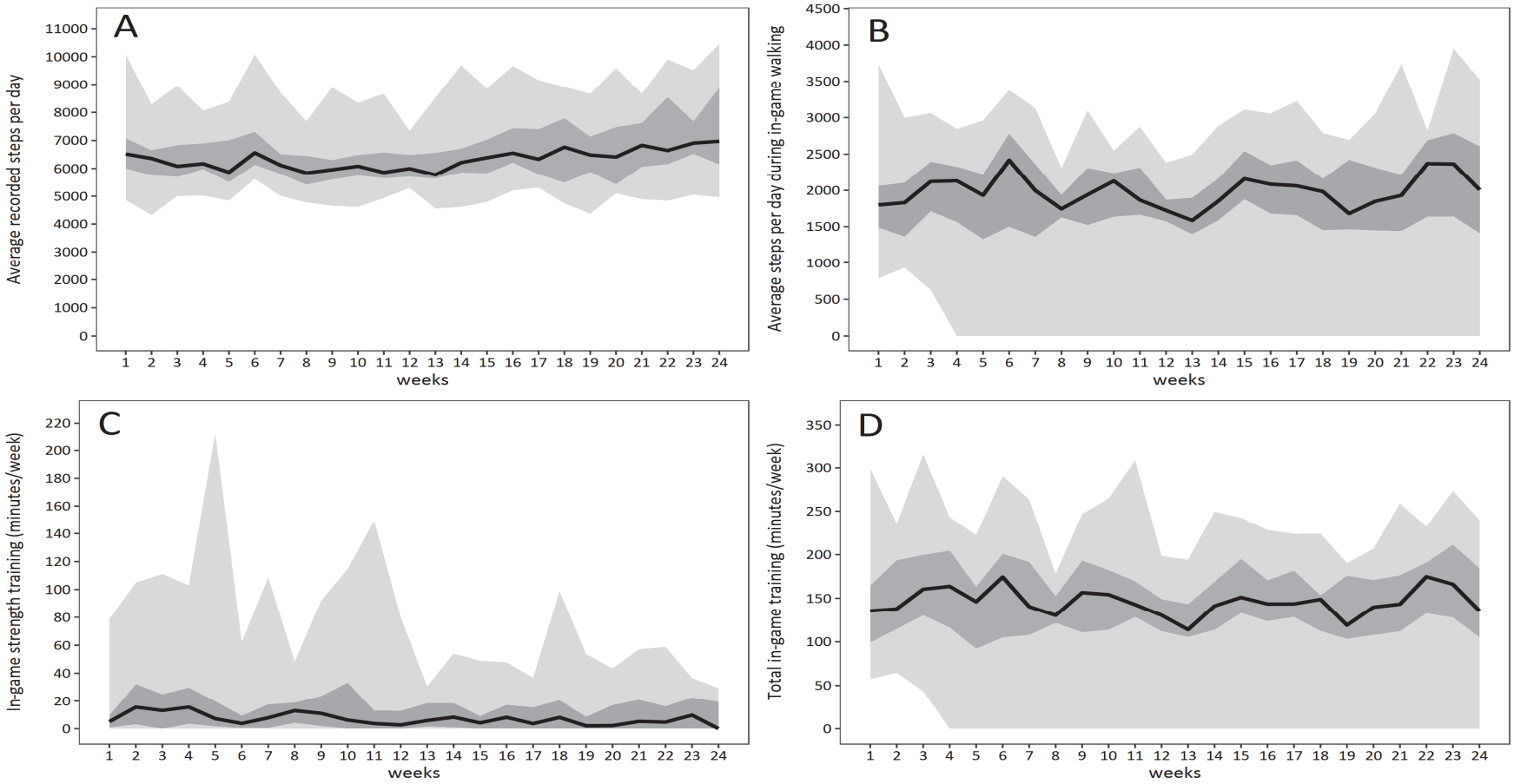

Figure 3: *Illustration of phone-recorded PA data during the intervention period. A: weekly average of total steps per day, B: weekly average of steps per day during in-game training, C: average duration (minutes) of in-game strength training per week, D: total duration (minutes) of in-game training per week.*

Physical Activity Adherence

Figure 3 illustrates the usage data regarding daily PA as well as patterns and total duration of in-game training as median, IQR, and range. On average, the participants' phones recorded 6,559 (SD 1,182) steps per day during the 24-week intervention period (panel A). Panel B shows the weekly steps during in-game walking, averaged per day, with an average of 1,893 (SD 723) daily steps. Participants performed an average of 4.9 (SD 1.3) in-game walking trainings per week (average duration of 26.8 (SD 8.2) minutes per training), adding up to a total average duration of 131.1 (SD 48.7) minutes of in-game walking per week. The analysis of the stride cadence revealed that on average 83.7% (SD 3.5%) of all in-game walking was done at a cadence of ≥100 steps/minute, indicating an average weekly amount of 109.8 (SD 43.4) minutes of moderate-to-vigorous-intensity in-game walking. One participant stopped playing the game after the third week and consequently did not produce any usage data beyond that time. We did not exclude this participant from the analyses because we consider non-use as much of an important outcome as regular use. Participants engaged in an average of 6.8 (SD 6.4) strength workouts per week with a total average duration of 15.3 (SD 24.6) minutes per week (panel C). In total participants used the game for an average of 143.1 (SD 59.1) minutes of training per week (panel D). Overall 70.4% of strength workouts and 96.5% of walking workouts were completed and 82.6% of all in-game workout reminders led to a completed workout on the same day. The linear regression model (Figure 4) found a significant positive association between total in-game training (min) and change in IMI total score (β=0.0028; 95% CI 0.0007, 0.0049; P=0.010; R^2=0.34). This indicates that for every additional 30 minutes of in-game training per week during the 24-week intervention period, the change in the total IMI score increased by 2.0 (95% CI 0.5, 3.5) points.

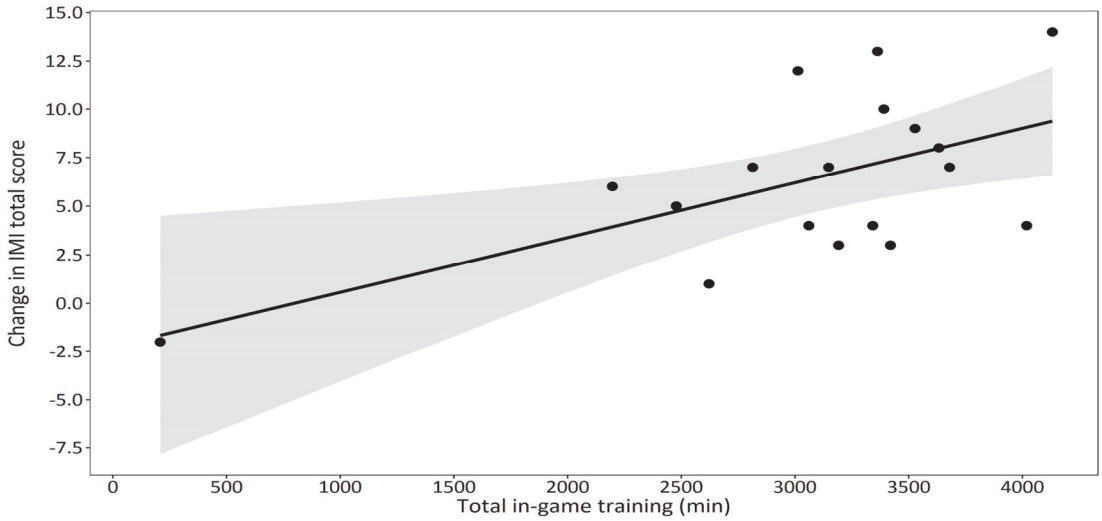

Figure 4: *Linear regression model illustrating the relationship between total in-game training (minutes) and change in Intrinsic Motivation Inventory total score.*

Discussion

Principal Findings

The results of this randomized controlled trial show that a novel smartphone game whose storyline is based on established motivational elements and behavior change techniques can significantly improve intrinsic PA motivation and lead to stable increases in PA in inactive type 2 diabetes patients over a 24-week period. Participants in the intervention group showed significant increases in the IMI total score as well as in the subscales 'interest/enjoyment', 'perceived competence', and 'perceived choice', indicating improvements in true PA-related intrinsic motivation as well as in factors that predict intrinsic motivation. There was no significant change in the value/usefulness subscale in the intervention group; however, it is noteworthy that the baseline value of this intrinsic motivation-predicting subscale was relatively high (18.7 points) and thus did not leave a lot of room for improvement in a scale with a maximum score of 21 points. The average recorded amount of 143 minutes of total in-game training per week during the intervention phase underlines the game's strong potential in motivating formerly inactive type 2 diabetes patients (39 minutes of moderate-to-vigorous PA per week at baseline) to meet and sustainably adhere to established PA recommendations [4].

Interpretation of Results

Intrinsic PA motivation increased significantly in the intervention group during the 24-week intervention period. A comparison of the magnitude of these improvements with other studies is difficult since no studies exist that used the IMI to assess changes in intrinsic motivation in game-based interventions that promote PA. However, it has been shown in a cross-sectional study [30] that enjoyment and perceived competence of performing a television exercise program (i.e., higher intrinsic motivation) are the most predictive factors to more frequent participation in the program. The recorded in-game training data in our study support this finding. By illustrating the direct impact of the game-induced increase in intrinsic PA motivation on the weekly PA behavior, the usage data give a more tangible meaning to the shown increase in the relatively abstract IMI scores going beyond the primarily predictive value of the IMI.

The analysis of the recorded usage data further shows that participants walked an average of 1,893 steps per day during in-game training. This is distinctly more than what has been reported for other PA-promoting smartphone games such as Pokémon GO even when assuming that the reported maximal increase of 955 steps per day was entirely attributable to Pokémon GO-related walking [13]. Further, and in contrast to Pokémon GO, which showed a gradual decline of daily steps back to baseline values after only six weeks following the abovementioned initial increase in

daily PA, the amount of both in-game steps and overall recorded daily steps in our study was considerably more consistent.

Average daily in-game steps between 1,619 and 2,206 throughout the intervention period indicate a substantially better PA adherence that becomes especially meaningful when considering the distinctly longer timeframe of 24 weeks. The stable, objectively measured increases in weekly PA during the intervention period, along with the positive association between total in-game training (min) and change in IMI score, further confirm the previously indicated [30,35] importance of pursuing improvements in intrinsic motivation through an increased PA enjoyment especially in behavioral interventions targeting inactive and unmotivated individuals. By being a motivating and enjoyable experience, the subjectively perceived cost of PA is lowered and people are encouraged to engage in regular PA based on their personal intrinsic motivation [14,36]. It can be conjectured that our game's narrative and gameplay are more elaborate and that the motivational elements incorporated into our storyline are more successful in motivating players for a long-term use than those of Pokémon GO. It is further possible that our approach of tailoring the in-game PA recommendations and exercises to the fitness level of each player avoided feelings of incapability and failure that result from overwhelming PA volumes and intensities and instead enabled players to experience PA-related competence by being able to complete suitable workouts and meet appropriate and realistic PA goals. The effectiveness of our game is highlighted by the fact that 83.7% of all in-game walking (110 min/week) was of moderate-to-vigorous intensity (≥100 steps/minute) and therefore most likely suitable to improve aerobic fitness [37] and to prevent morbidity and premature mortality [38]. This weekly amount of moderate-to-vigorous-intensity walking is equal to an average duration of 15.6 minutes per day, which has been shown to be associated with a 14% reduction in all-cause mortality and has therefore been proposed as the minimum amount of PA required to extend life expectancy [39].

The average amount of time spent in in-game strength exercises was distinctly lower than that of in-game walking throughout the intervention period. While the completion rate of strength workouts was considerably lower than that of walking workouts (70.4% vs. 96.5%), the shorter average engagement in strength workouts is also due to how these workouts were designed. In contrast to walking workouts, which were designed to be of sufficient intensity and duration to improve aerobic fitness [4,37] while avoiding a demotivating physical overload, strength workouts were designed to be brief bouts of activity to interrupt prolonged times of sedentary behavior that could be easily integrated into the daily routine and be performed anywhere and without extensive equipment.

This design choice is supported by recent findings, showing that interrupting prolonged sitting by brief bouts (2-5 minutes) of PA every 20-30 minutes can yield improvements in glycemic control in inactive individuals with an impaired glucose regulation that are persistent for up to 22 hours [40,41]. On average, participants made use of this design feature approximately seven times per week with an average duration of around 2.5 minutes per workout and thereby made clinically relevant changes to their sedentary daily routine.

Overall, the game encouraged an average amount of 143 minutes of in-game activity per week and thereby supported type 2 diabetes patients who had been physically inactive for many years in adopting and adhering to a physically active lifestyle that corresponds to established PA guidelines [4].

Limitations and Implications for Future Research

A limitation of this study is that we have no objectively measured record of any additional PA beyond the phone-recorded PA. While participants used the game extensively as a training tool and accrued close to the guideline-recommended amount of 150 minutes of moderate-intensity PA per week during in-game training alone, it would have been interesting to see if participants engaged in any additional structured, moderate-intensity PA outside of the game. Further, while the phones recorded daily steps with a likely high accuracy when they were placed on the body [32], we have no record of the number of steps that were taken when they were not. Though participants were encouraged to carry their phones with them as much as possible (i.e., reminder function of the game), and based on the average daily step counts it is likely that they did most of the time, it is quite conceivable that especially when participants were at home or at work they did not always carry their phones on them. These periods without phone wear time likely led to an underestimation of unknown magnitude of the true number of daily steps. Therefore, future smartphone-based studies should consider measuring daily steps additionally with an accurate accelerometer with a high potential for a good wear-time compliance such as an activity wristband [32]. A further limitation is that we do not know for sure which conceptual ideas and motivational elements incorporated into the game have indeed caused the increased intrinsic PA motivation and led to the improved PA behavior. While it is justified to argue that the ensemble of all behavior change mechanics was crucial for the success of the game, a more detailed analysis would have been important knowledge for future game designs. Finally, a follow-up assessment after an appropriate interim period should be considered to evaluate the effectiveness of the game regarding the sustainability of the improvements in PA adherence beyond the 24-week intervention period.

Conclusions

In summary, our randomized controlled trial shows that a novel smartphone exergame that incorporates established motivational elements and personalized PA recommendations in the storyline can generate significant increases in intrinsic PA motivation in inactive individuals with type 2 diabetes. The clinical relevance of the game-induced increases in intrinsic PA motivation is highlighted by the associated de-facto and stable improvements in PA adherence during the 24-week intervention period that demonstrate the game's suitability in successfully encouraging persistently sedentary individuals to meet and adhere to established PA guidelines. The combination of playful elements and an individualized PA promotion has high potential to be successful in other inactive, unmotivated target groups with and without chronic diseases.

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Conflict of Interest and Funding

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Chapter 9

Discussion

Chapter 9 Discussion

This chapter summarizes the main findings of the four publications [1–4] and the two papers that have been submitted for publication [5,6], discusses them in their scientific context and provides prospects for future research.

9.1 Synopsis

Figure 1 illustrates the five steps of this Ph.D. project. After extensive preparatory work (systematic review (step 1) and data analysis of a previously conducted pilot study (step 2)), an innovative smartphone game was developed through an international and interdisciplinary cooperation (step 3). The game delivers individualized physical activity content through an elaborate storyline that is based on established motivational components. As the smartphone game tracks and rewards daily physical activity, we assessed the accuracy of these devices to measure steps during various walking conditions in a validation study (step 4). In this validation study, we additionally assessed the validity of an activity wristband (Garmin Vivofit 2), as this device was intended to be used to measure the primary outcome (steps per day) in the subsequent intervention study. In addition to daily physical activity, the 24-week intervention study (step 5) assessed the effectiveness of the smartphone game to improve aerobic capacity, glycemic control, intrinsic physical activity motivation, and physical activity adherence.

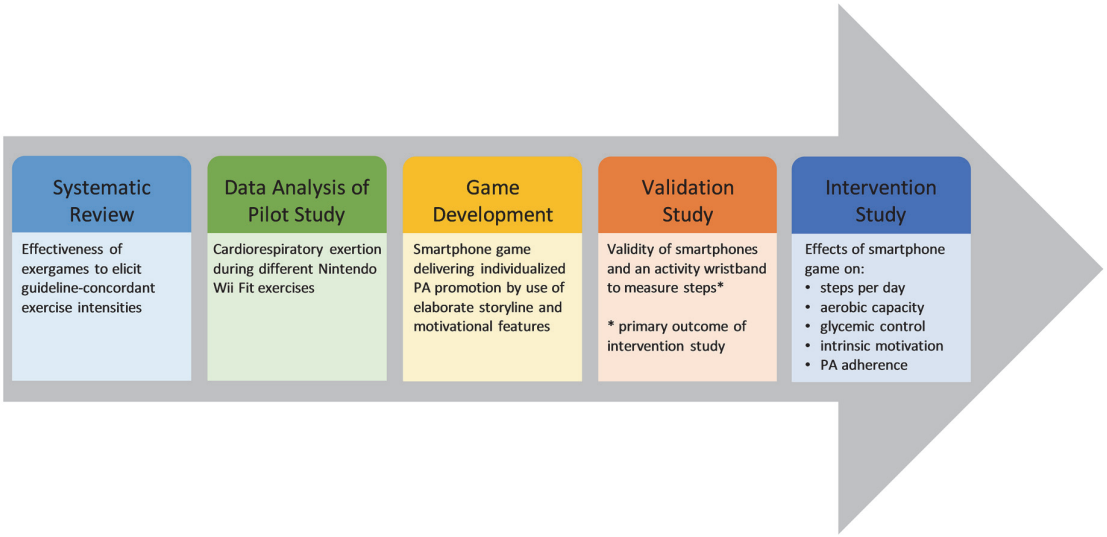

Figure 1: *Illustration of this Ph.D. project's 5-step process. PA, physical activity*

9.1.1 Aim 1: Systematically reviewing the current evidence for the effectiveness of exergaming in overweight and type 2 diabetes. [1]

The first aim was to systematically review the current evidence for the effectiveness of exergaming on physical activity in overweight and type 2 diabetes individuals. All of the 11 studies included in the systematic review showed increases in either oxygen uptake ($\dot{V}O_2$), energy expenditure, or heart rate during exergame play, suggesting a general suitability of exergames to be used as effective exercise tools. At the same time, exergaming was rated generally as more enjoyable than generic physical activity, suggesting an additional motivational benefit of these games. The magnitude of the effect on physical activity-related intensity parameters varied significantly, however, between game modes and consoles as well as because of the vastly differing durations of exergame activity between studies. Exergame-induced increases in $\dot{V}O_2$ compared to resting values were 49% in some game modes while they reached up to 204% in others. The amount of energy expended during exergame play likewise differed vastly (1.5- to 5-fold) between studies due to the different game modes and consoles as well as the varying durations of exergame play. In most of the included studies, the mean generated energy cost did, however, not reach or exceed three METs, suggesting that most of the used exergames do not allow overweight individuals to reach exercise intensities that correspond to moderate physical activity and consequently are not suitable to meet established guidelines. A general lack of adequate individualization of the intensity and difficulty level was noted for all exergames, making most game modes unsuitable for effective training and potentially unsafe for inactive individuals with chronic diseases and a likely reduced fitness level. Of all included studies, only one had a low risk of bias and 10 out of 11 studies were of cross-sectional nature. No studies were found investigating the (long-term) changes in objectively measured parameters of physical activity in type 2 diabetes patients. Based on the current literature (at the time the systematic review was conducted), it was therefore not possible to evaluate mid- to long-term effects of exergames on intensity parameters of physical activity in overweight individuals with or without type 2 diabetes, and a positive effect of a possible enjoyment of exergame use on physical activity adherence could only be conjectured.

9.1.2 Aim 2: Evaluating the suitability of the Wii Fit Plus exergame to improve cardiorespiratory fitness in individuals with type 2 diabetes. [2]

For the second aim, data from a previously conducted proof-of-concept study was analyzed to evaluate the suitability of the Nintendo Wii Fit Plus exergame as a tool to improve cardiorespiratory fitness in individuals with type 2 diabetes. The carefully selected Wii Fit Plus exercises (Boxing, Obstacle Course, and Cycle Island – played for bouts of 10 minutes each) elicited peak $\dot{V}O_2$ values of around 60% of the maximally reached values as established during an all-out treadmill test. Mean $\dot{V}O_2$ was just above 40% of the maximally reached treadmill values during all exercises. Mean heart rate (between 98 and 103 bpm – equating to 67-70% of maximum treadmill heart rate) and respiratory exchange ratio (between 0.81 and 0.86) likewise lay in a range of

moderate aerobic exercise. In addition, a moderate-to-strong positive correlation between the peak treadmill $\dot{V}O_2$ and both peak and mean exergame $\dot{V}O_2$ values was found. This indicated that subjects with a higher fitness level were able to exercise at a higher intensity during exergame play than individuals with a lower fitness level, suggesting, at least in part, the potential for an individual intensity adjustment without a visible ceiling effect.

9.1.3 Aim 3: Developing a behavior change technique-based smartphone game that delivers individualized exercise and physical activity promotion with the intention to motivate inactive type 2 diabetes patients to become sustainably physically active and planning a 24-week randomized controlled trial evaluating the game's effectiveness. [3]

The third aim was to develop a physical activity-promoting smartphone game based on behavior change techniques and to plan a 24-week randomized controlled trial examining the effectiveness of the game in improving daily physical activity (primary outcome) and other physiological and psychological/motivational outcomes. The game was developed through a collaboration with international partners to create a motivating, fitness level-adjusted exercise tool specifically designed for the needs of inactive type 2 diabetes patients and thereby addressing the noted shortcomings (see Aim 1) of current exergames. The game's content with regard to the game design and physical activity content is illustrated in Figure 2.

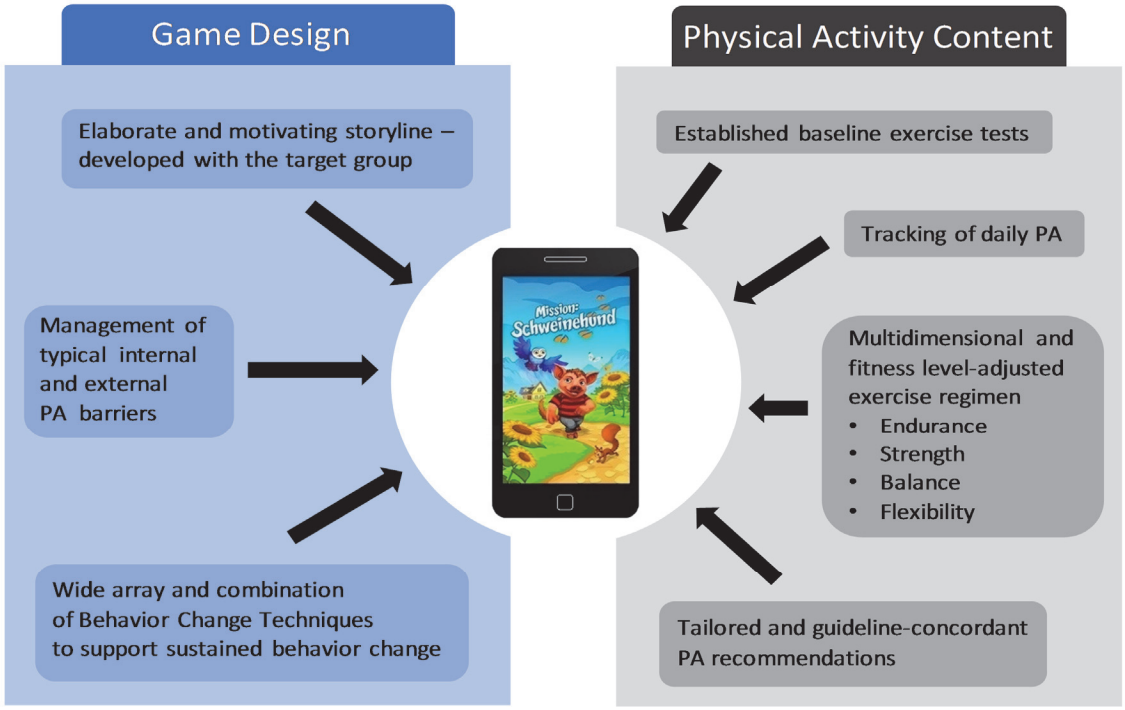

Figure 2: *Illustration of the content of the smartphone game. PA, physical activity*

In the game, the player's individual fitness level is assessed through established exercise tests that are conducted at first use and periodically during play to allow setting an appropriate entry level as well as an individualized rate of intensity progression of the game's physical activity-related content. Execution of in-game exercises and daily physical activity are tracked via the phone's sensors (camera, accelerometer, gyroscope, and audio sensor). The key element of the game's storyline is the restoration of a decayed garden (used metaphorically for the own body) and the taming of the game's adversary, the Schweinehund (in German, a self-depreciating idiom denoting one's weaker self, often referring to the lazy procrastination regarding physical activity). Both can be achieved through regular in-game physical activity and by meeting the game-recommended, individualized physical activity goals. The game mechanics are based on established behavior change techniques to motivate for regular long-term use and support sustained changes in physical activity behavior. During the 24-week randomized controlled trial, participants in the intervention group are instructed to play the game while no specific instructions regarding intended frequency or duration of play are given, however, to be able to evaluate the motivational potential of the game accurately and in a real-life setting. Participants in the control group receive a one-time lifestyle counseling and a structured exercise plan. The exercise plan was essentially comparable to the physical activity-related content of the game and was to be implemented autonomously during the intervention period.

9.1.4 Aim 4: Assessing the accuracy of the Garmin Vivofit 2 activity wristband as well as the iPhone SE and the Samsung Galaxy S6 Edge to measure steps during various walking conditions. [4]

The fourth aim was to conduct a validation study to assess the accuracy of the Garmin Vivofit 2, iPhone SE, and Samsung Galaxy S6 Edge (as a representative for Android devices) to measure steps in various walking conditions. This side project was conducted because the Garmin Vivofit 2 is used to measure the primary outcome (steps per day) of the 24-week randomized controlled trial and because iPhones and Android devices are used in the intervention group as the carrier medium for the game and subsequently to measure daily game-related and other physical activity. The tested walking conditions included treadmill walking at 1.6, 3.2, 4.8, and 6.0 km/h (five minutes each) as well as free walking (620 m walking course with stops, different inclines, and several flights of stairs) at a self-chosen walking speed (mean speed 4.73 km/h). Twenty participants were included in the study and equipped with the devices (Garmin Vivofit 2, on the wrist of the non-dominant arm; iPhone SE, in the right pants pocket, in a shoulder bag, in a backpack; Samsung Galaxy S6 Edge, in the left pants pocket) while performing the different walking conditions. The Garmin Vivofit 2 and iPhone SE showed good accuracy for treadmill walking ≥3.2 km/h (<3% deviation from video recordings) and for free walking thus being suitable to measure steps at normal, fast, and even slow walking speeds. The Samsung Galaxy S6 Edge showed good accuracy (<3% deviation from video recordings) for treadmill walking ≥4.8 km/h and for free walking,

demonstrating suitability to measure steps during normal and fast walking. The good validity of the iPhone SE was found independently of the phone's position (pants pocket, backpack, shoulder bag), suggesting a broad versatility of the device for physical activity measurement in various settings.

9.1.5 Aim 5: Examining the effects of the smartphone game on daily physical activity, glycemic control, and aerobic capacity in inactive individuals with type 2 diabetes. [5]

The fifth aim was to examine the effectiveness of the novel smartphone game to increase daily physical activity and improve glycemic control and aerobic capacity in inactive individuals with type 2 diabetes during a 24-week randomized controlled trial. Participants in the intervention group increased their daily physical activity by an average of 3,998 (SD 1,293) steps per day, averaging 9,782 (SD 1,334) steps per day after the intervention. The control group showed post-intervention increases in daily physical activity of an average of 939 (SD 1,156) steps per day, remaining insufficiently active, however, with an average of 6,551 (SD 1,280) per day. The significant adjusted difference between the two groups of 3,128 steps per day (95% CI 2,313, 3,943; P<0.001) underlines the game's potential to elicit a sustained increase in daily physical activity. The increase in daily physical activity was accompanied by an increase in aerobic capacity with an adjusted difference in oxygen uptake at the first ventilatory threshold of 1.9 ml/(kg·min) (95% CI 0.9, 2.9; P<0.001) in favor of the intervention group. A strong positive correlation was found between total duration of in-game training and both increase in steps per day (r_s=0.91; P<0.001) and increase in workload at the first ventilatory threshold (r_s=0.66; P<0.01). Glycemic control measured as HbA_{1c} did not change during the intervention period. However, the significant adjusted difference in HbA_{1c} of -0.9 percentage points (95% CI -1.5, -0.2; P=0.016) in favor of the intervention group suggests that regular use of the game may support a stabilization of glycemic control in medically well-controlled patients.

9.1.6 Aim 6: Examining the effects of the smartphone game on intrinsic physical activity motivation and physical activity adherence over 24 weeks in inactive individuals with type 2 diabetes. [6]

The sixth aim was to analyze further predefined outcomes of the 24-week randomized controlled trial to examine the effectiveness of the game in increasing the intrinsic physical activity motivation and to evaluate the game's potential in eliciting sustained improvements in physical adherence. Intrinsic physical activity motivation was assessed with an abridged 12-item version of the Intrinsic Motivation Inventory (IMI) in both groups. In addition, adherence to the game-proposed physical activity recommendations during the intervention period was assessed in the intervention group via the phone-recorded game usage data. Participants in the intervention

group significantly increased their total IMI score by 6.4 (SD 4.2; P<0.001) points while the same score decreased in the control group by 1.9 (SD 16.5; P=0.623) points during the intervention period. The adjusted difference between the two groups was 8.1 (95% CI 0.9, 15.4; P=0.029) points in favor of the intervention group. The subscales 'interest/enjoyment' (+2.0 (SD 1.9) points, P<0.001) and 'perceived competence' (+2.4 (SD 2.4) points, P<0.001) likewise increased significantly in the intervention group whereas they did not change significantly in the control group. The usage data revealed that participants in the intervention group used the game for an average of 131.1 (SD 48.7) minutes of in-game walking and for an average of 15.3 (SD 24.6) minutes of strength training per week, totaling in 143.1 (SD 59.1) minutes of in-game training per week and underlining the game's potential in motivating formerly inactive type 2 diabetes patients to meet and sustainably adhere to established physical activity recommendations. Figure 3 illustrates the intervention outcomes that were found following 24-weeks of regular game use.

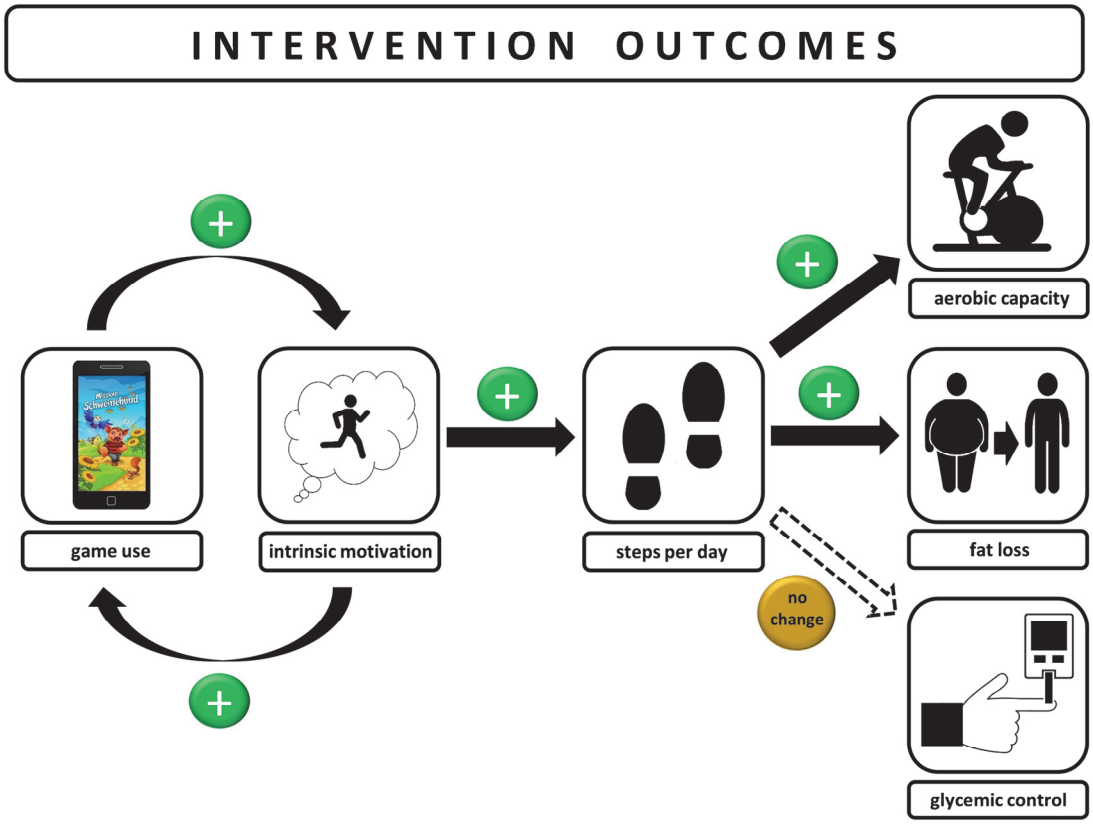

Figure 3: *Illustration of the intervention outcomes of the 24-week randomized controlled trial. Black arrows indicate significant results and dotted arrows indicate inconclusive results. No significant change in glycemic control was found; however, a significant adjusted difference between both groups suggests superiority of the intervention group.*

9.2 General Discussion

9.2.1 Rationale to Develop a Smartphone-based Exergame

The results of the systematic review [1] along with the data from the pilot study [2] showed that console-based exergames are acutely able to elicit exercise intensities that are of sufficient intensity to improve cardiorespiratory fitness and thus have the potential to yield important health benefits in overweight individuals with type 2 diabetes. Because these games make physical activity a motivating and meaningful experience that is generally perceived as more enjoyable than generic physical activity [1], they are potentially well suited to encourage physical activity in those who cannot be motivated through conventional physical activity-promoting interventions [7]. The fact that 50% of casual gamers are between 35-64 years [8] further supports the use of these games to promote physical activity not just in adolescents and young adults but also in middle-aged individuals. While general suitability was demonstrated, the systematic review also revealed several content-related shortcomings of current exergames as well as a distinct research gap regarding the effectiveness of these games to promote physical activity in the long term, as no studies with intervention durations longer than 12 weeks exist [1]. Content-related shortcomings particularly pertain to the general lack of individualization of the game-related workout intensity, which makes them unsuitable and potentially unsafe for low-fitness individuals with chronic diseases and often-concurrent physical limitations. In addition, because commercially available exergames understandably prioritize game enjoyment over workout effectiveness to meet sales figures and elicit long-term use, structured exercise regimens are usually missing and a guideline-concordant long-term training is consequently not possible. Therefore, to be able to use the promising exergaming approach as an effective workout option for individuals with chronic diseases and a low fitness, a tailored and more serious physical activity-promoting game was needed. In this Ph.D. project, it was attempted to address the challenge of combining structured and guideline-concordant physical activity content with an enjoyable game experience, which is undoubtedly essential to motivate players for regular use, and thereby elicit sustained improvements in physical activity behavior.

While designing the game, close attention was paid to physical activity barriers that commonly occur among inactive type 2 diabetes patients to create an attractive exercise option that intends to overcome these typical barriers and thereby lowers the perceived cost of being physically active. The motivating and enjoyable game experience targets the typical physical activity barriers ‘lack of physical activity enjoyment’ [9] and ‘lack of physical activity motivation’ [9–11] that are highly prevalent among inactive type 2 diabetes patients. Further, the physical activity barrier ‘aversion to exercise facilities’ [12,13] is bypassed by offering a multidimensional, home-based, and tailored exercise regimen through the game, whereby a potentially ‘poor self-image’ [12,13] has a much smaller impact on someone’s motivation to exercise when the workout happens in a familiar home environment. In addition, the choice of the smartphone as the carrier medium offers a higher degree of convenience and flexibility to the player than a television-bound

exergame. Because a mobile device allows in-game physical activity in short bouts anywhere and anytime, it helps overcome the barrier 'lack of time' [9,13]. The very likable, humanized animals that are an essential component of our game's storyline offer supportive and motivating companionship to the player and thereby may at least partly compensate for the 'missing social support' [12,14] that keeps many type 2 diabetes patients from engaging in regular physical activity. Finally, the tailored exercise regimen along with the generally low-threshold entry level and the individualized intensity progression minimize the risk of physical overload and thereby lower the often-perceived 'fear of injury or disease-related complications' [14,12].

While the game effectively changed the targeted behavior of daily physical activity [5,6] and thereby demonstrated its successfulness from a scientific point of view, the economic efficiency of our approach is more challenging to evaluate. In general, technology-delivered interventions become progressively cost-effective with increasing dissemination, when the cost savings related to study personnel and use of exercise facilities outweigh the initial, often high production costs [15]. Considering that our study included only 36 participants, of which 18 received the game, the production costs of approximately one million CHF are certainly not yet justified. However, the fact that only about 850 (0.2%) (personal communication by Verein DIAfit Schweiz, June 6, 2018) of the approximately 450,000 adults with type 2 diabetes in Switzerland [16] currently participate in one of the 35 physical activity-promoting outpatient diabetes rehabilitation programs, illustrates the potential to reach a much larger number of patients with a serious gaming approach than the number of participants that were included in our study. Further, while participation in such physical-activity-promoting programs is certainly encouraged and has been shown to reduce annual medication- and hospitalization-related health care costs by 50% (1,300 CHF to 700 CHF) [17] in type 2 diabetes patients, the cost of these programs for the health care system must not be neglected. Although participation in these programs is usually covered by the health insurance in Switzerland and the costs consequently do not affect patients directly, the amount of approximately 1,600 CHF per patient for the 12-week (three 1-hour sessions per week) DIAfit program (personal communication by Verein DIAfit Schweiz, June 6, 2018) is a significant financial strain on the health care system. These resulting costs are not necessarily compensated for by the related medication- and hospitalization-related savings especially considering that a successful diabetes rehabilitation usually involves a distinctly longer timeframe than 12 weeks and is likely a life-long process. If our game was further disseminated to approximately 650 patients (0.15% of all type 2 diabetes patients in Switzerland), the overall production costs of approximately one million CHF would be equal to 1,538 CHF per patient and would consequently break even with the costs of a one-time participation of 650 patients in the 12-week DIAfit program. Because production costs are one-time costs and because maintenance costs and technical support for a commercially released game that has undergone extensive beta-testing should be minimal, our game would likely become more cost-effective with an even wider dissemination and continued use beyond 12 weeks. It stands to reason that a long-term use of our game and the related sustained increases in physical activity would yield additional benefits affecting various diabetes-

related comorbidities and that health care savings would therefore likely exceed the savings that are due to reduced hospitalizations and medication treatment alone. Therefore, with the right dissemination, this type of physical activity-promoting smartphone game can present a successful treatment option from an economic perspective as well.

9.2.2 Selection of Motivational Elements and Game Design

Publication 3 [3] illustrates in detail the motivational elements and behavior change mechanics that were incorporated into the game. It was attempted to combine personal informatics with an elaborate game design and incorporate established behavior change techniques to encourage a sustained increase in daily physical activity through the use of the game. While personal informatics (in our case the tracking of daily physical activity and in-game workouts with an immediate feedback to the user) have been shown to improve self-monitoring and thereby increase daily physical activity in individuals with type 2 diabetes [18], they are not always sufficient on their own to enable inactive and unmotivated individuals to develop enough self-motivation and confidence in the own ability to successfully change physical activity behavior [7]. By integrating personal informatics into an appealing game design, this Ph.D. project's approach circumvents the direct targeting of the behavior of interest (increase in physical activity) and instead uses the motivating character of the game as a mediator that positively affects the frequency of use of the game and thus the daily physical activity behavior. Through the use of the game, the players learn that their regular physical activity is directly responsible for the in-game achievements and thereby develop a feeling of physical activity-related self-competence that is crucial for a sustained enjoyment and a subsequently increased physical activity adherence [19]. Because in-game achievements are not dependent on absolute intensity but rather on the meeting of tailored goals, individual progression, and regularity of physical activity, it was possible for all players, regardless of their fitness level, to experience the same physical activity-related competence that led to the shown increases in intrinsic physical activity motivation [6].

Since extrinsic motivators such as rapid in-game feedback and rewards sometimes carry the risk of actually decreasing intrinsic motivation, for example when players become too focused on in-game rewards so that they adopt alternative (cheating) behaviors to achieve them quickly [7], and because the effectiveness of specific motivational elements may vary from individual to individual [20], a wide array of behavior change techniques [21] was included in this game. By ensuring that the motivational elements incorporated into the game address both internal and external motivational processes and thereby collectively target the same outcome (change in physical activity behavior), the risk of deviations from the intended behavior such as cheating to receive rewards was minimized. While the relationship between the behavior change technique content of an intervention and the resulting health behavior change is not simple [22] and the optimum number or combination of behavior change techniques remains to be conclusively determined [23,24], the choice to include the techniques 'action planning', 'instruction on how to perform the

behavior', 'prompts/cues', 'graded tasks', and 'rewards' in our game design is supported by a recent meta-analysis of 16 studies and 1,069 participants [25], which found these specific techniques to be particularly effective in changing physical activity behavior. The high average duration of in-game training in our study [6] and the effectively changed daily physical activity behavior [5] further underline the successfulness of the included motivational elements and thereby warrant their selection. For future game designs, it could be considered to assess the behavioral profile of the individual at the beginning of play, and then select the motivational game elements based on specific personality traits through a predefined algorithm, similar to the selection of suitable exercises based on the fitness level in our game (see publication 3). This could yield a more tailored and possibly even more successful utilization of the incorporated behavior change mechanics.

The choice of a garden as the main setting was based on the fact that gardening is among the target group's preferred forms of physical activity [26] and that gardening-themed games are quite popular and easily understandable by a wide range of players [27,28]. The engagement in gardening activities and particularly nurturing plants has been shown to be effective in alleviating stress by evoking feelings of curiosity, competence, and enjoyment [29,30], and it was hypothesized that the positive and de-stressing character of this activity would be at least partially transmitted to the player even though the gardening is solely virtual. In addition, the transformation of the garden through regular care stands metaphorically for the transformation of the player's body through regular physical activity and thereby makes the positive effect of the changed behavior visible to the player even if health improvements have not yet become apparent. The humanized animals in the garden have been designed to be very likable and have typical human personality traits that the player can relate to and may perceive at least to some extent as positive social interaction. Contingent on regular in-game physical activity, the animals support the player in taming the Schweinehund, the gamified personification of the own physical activity-related laziness, and thereby help to progress in the storyline. The analysis of the recorded usage data [6] shows that the majority of participants played the game regularly throughout the intervention period. This suggests that they perceived the game's design and storyline as motivating and enjoyable, warranting the design choices that were made based on the results of a previously conducted user study with 12 participants from the target group (see publication 3). One participant disliked the game entirely and ceased to play after three weeks and two participants indicated that while they played the game throughout the intervention period, they would most likely not continue to do so beyond the study. It can be conjectured that a larger scale analysis of the target group's preferred game designs, such as through user analytics that large streaming companies like Netflix use to cater the viewing demands of their customers, would have yielded a game with an even higher acceptance rate. However, considering the likely very different tastes and interests of the participants, the acceptance rate of the game is in fact quite satisfactory and designing a one-size-fits-all game highly unlikely and probably almost presumptuous. The

longer-term acceptance and use of the game have of course yet to be evaluated and a follow-up assessment after an adequate interim period should be considered.

9.2.3 Selection of Physical Activity Content

To assess the player's strength and endurance-related capabilities and thereby detect a possibly reduced mobility or low exercise capacity at the start of play, it was necessary to incorporate objective exercise tests into the game design. The chosen tests had to meet several requirements to be suitable for their intended purpose. The tests had to provide reproducible results for individuals with a wide range of fitness levels that could be interpreted based on established reference values, to show high correlations with other established exercise capacity tests, and to assess the functional exercise level needed to perform the in-game workouts. The tests further had to be able to be conducted with minimal equipment, to be performed safely without professional supervision, and to be assessed objectively and accurately through the sensors of a smartphone. The 1-min Sit-to-Stand Test (STS) as a measure of the lower body strength endurance [31] and the Six Minute Walk Test (6MWT) [32] as a measure of the submaximal level of functional capacity meet the postulated requirements and were thus incorporated as the in-game baseline tests. For the STS, the phone is placed in the frontal pants pocket and repetitions are counted via the phone's position sensor and predefined threshold values during one minute. For the 6MWT, the phone is held in the hand and the distance walked during the six-minute test period is measured via GPS. The objective and accurate assessment of the performance in established exercise tests through the sensors of a smartphone is an absolute novelty and has the potential to pave the way for a large-scale utilization in various clinical and public health settings due to its easy application.

To be able to use the results from the baseline tests for the selection of suitable entry-level intensities of the in-game exercises, a qualitative user study with 12 participants (see publication 3) was conducted. After conducting the baseline tests, participants were instructed to try out different intensities of the intended in-game strength and walking exercises and rate their perceived exertion and difficulty of performing the exercises. Through an iterative and re-evaluative process, an algorithm was developed linking certain population-based reference values [31,32] from the two tests to suitable intensity and difficulty levels of the different exercises. The algorithm was designed to select entry levels and the rate of intensity progression of the in-game exercises conservatively to avoid physical overload by all means and offer a safe workout option at all times. Because this may yield entry-level exercise intensities that are too low for an effective workout, especially if players initially do not put enough effort into the baseline tests to produce accurate results of their exercise capacity, the baseline tests are repeated periodically during play to set new baselines. In addition, a rating system was incorporated that assesses the perceived exertion after completion of every exercise and directly affects the intensity-level of the same exercise in the next workout.

For the walking exercises, intensity adjustment is achieved via the walking speed and specifically via proposing certain percentages of the maximum walking speed as established during the 6MWT. However, to keep it simple and easily comprehensible for the player, instructions such as 'walk moderately' or 'walk briskly' rather than a specific percentage are given during the workout to meet the intended walking intensity. The combination of objective and subjective measures to control the exercise intensity and training progression proved to be a successful approach that provided unbiased feedback through the repetition of the baseline tests while at the same time keeping the player in control of the game and thereby enabling long-lasting enjoyment and high levels of exercise adherence.

The incorporated multidimensional exercise regimen consisting primarily of strength and endurance exercises as well as some balance and flexibility exercises strictly follows established principles of exercise training regarding, duration, volume, and frequency [33,34]. Strength, balance, and flexibility exercises were designed to be brief bouts of activity, as short as 2-5 minutes, to interrupt prolonged times of sedentary behavior and could be easily integrated into the daily routine. These brief bouts of activity have been shown to yield meaningful improvements in glycemic control in individuals with an impaired glucose regulation that are persistent for up to 22 hours [35,36]. Publication 6 shows that participants made regular use of this physical activity component. To be included in the game, strength, balance, and flexibility exercises had to meet specific requirements. The exercises had to have a high degree of scalability so that they would be feasible for a wide range of fitness levels and at the same time allow a gradual intensity progression through a sufficient number of variations of the same exercise. Further, it was required that execution of the exercises would be easily comprehensible to allow a safe workout even without supervision, that the exercises did not require extensive equipment, and that the exercises would address all large muscle groups. In addition, because it was aimed to objectively measure exercise completion, the exercises had to be trackable via smartphone sensors (camera, accelerometer, gyroscope, and audio sensor) based on predefined threshold values. It was indicated by a few participants that despite an extensive testing phase, not all tracking methods, particularly the camera tracking, worked for all exercises with satisfying precision. While at least two and up to three tracking methods (always including the robust audio tracking) were available for each exercise to ensure the successful tracking of the exercise and thus the progression in the workout, the sometimes-occurring tracking errors partly affected the motivation to perform these exercises [6]. In order to use the camera tracking, the phone had to be placed at a certain distance in front of the player with the phone's display facing the player. In most cases, the noted imprecision was likely due to an incorrect placement of the phone or an incorrect distance from the phone, respectively. This problem could be solved by including more precise instructions of the correct position through clear in-game feedback and by providing a phone stand that puts the phone in the correct position to detect the player's movement more easily. Because the sensor tracking worked well for the majority of exercises and thereby enabled the objective tracking of

the completion of in-game exercises, this innovative approach should be viewed as a major strength of the game that could easily be further improved with some small adjustments.

The game's endurance workouts consist of different in-game walking exercises with continuous and interval character and were designed to be of sufficient intensity and duration to have the potential to improve aerobic fitness [37,38]. Walking is the most popular and most preferred form of exercise among patients with type 2 diabetes [39], and it was hypothesized that implementation of regular walking into the daily routine through the game would therefore have a lower threshold than many other forms of physical activity. In addition, walking-related step counts can be easily and accurately measured via the phone's accelerometer, as shown in publication 4 [4] and therefore be objectively assessed and rewarded in the game. By measuring the number of steps in specific, predefined time intervals, our game further enables the assessment of the walking intensity via the step cadence. The high average duration of in-game walking training [6] along with the shown significant increases in oxygen uptake at the first ventilatory threshold [5] clearly warrant the choice of walking as the primary form of endurance exercise in the game and underline the appropriateness of the chosen walking regimen to improve the aerobic capacity. This easy and objective assessment of the health-beneficial [37] moderate-to-vigorous-intensity walking is groundbreaking as it improves the quality of physical activity assessment distinctly and should be considered in future walking and physical activity-promoting interventions.

9.2.4 Clinical Relevance of the Game-induced Health Effects

The 24-week randomized controlled trial showed that regular use of the innovative smartphone game elicits meaningful increases in daily physical activity that are significantly higher (+3,000 steps) than those following a one-time lifestyle counseling [5]. The found improvement after 24 weeks even exceeds the anticipated increase of 2,500 steps, as postulated for the sample size calculation, and thereby underlines the effectiveness of the game in sustainably motivating a target group that is highly inactive and very unlikely to change their physical activity behavior [40] to meet and adhere to physical activity guidelines. The effectiveness of the game is further highlighted by the very strong correlation (r_s=0.91) between total in-game training and change in daily physical activity [5], which indicates that those who played the game more, in fact, increased their daily physical activity more than those who played the game less. It can, therefore, be emphasized that this Ph.D. project's innovative approach with the combination of personal informatics and an attractive game design following a cognitive-behavioral approach has great potential to successfully promote sustained changes in physical activity behavior even in the least motivated.

The analysis of the usage data that was recorded by the participants' phones [6] shows that the game motivated participants immediately to engage in more physical activity and that the game-related increases in weekly physical activity were stable throughout the intervention period. It

should be noted that the activity wristband-recorded average amount of steps per day after the intervention (9,783 (SD 1,334) [5]) was distinctly higher than the average phone-recorded amount of steps per day during the intervention phase with an average of 6,559 (SD 1,182) steps per day [6]. This can likely be explained by two facts. First, participants may not have always remembered to carry their phones with them, especially when they were at home or at work, which naturally would lead to an underestimation of unknown magnitude of the true number of daily steps. Second, while smartphones have been shown to detect steps accurately during various walking speeds [4], and especially above walking speeds of 3.2 km/h, the accuracy of step detection during slow and very slow walking as well as during intermittent walking, a typical walking profile of incidental everyday activity, has to date not conclusively been confirmed [41,42]. An inaccurate step detection during these incidental activities could therefore likely have led to an underestimation of the true number of steps [42]. However, because of the proven high accuracy of step detection during continuous walking above 3.2 km/h [4], it is likely that the moderate-intensity and thus the primarily health-beneficial steps [43] were recorded accurately as long as the smartphone was carried on the body.

The clinical relevance of the game-related physical activity and particularly of the in-game walking is highlighted by the concomitant significant improvements in aerobic capacity and significant reductions in body fat mass [5] that show the direct health effect of the game-related physical activity content. On average, participants walked 110 minutes (>80%) per week at a cadence of >100 steps per minute during in-game walking [6]. It is likely that particularly this large portion of moderate-to-vigorous-intensity walking contributed to the improvements in aerobic capacity. Applying 3 METs as the lower limit of moderate-intensity activity [44], participants reached an average of 330 MET-minutes during in-game walking per week and thus reached an amount that has been shown to be sufficient to benefit cardiovascular risk factors [45], reduce the risk of premature mortality [46], and improve glycemic control [47]. It is therefore somewhat surprising that while the increase in daily physical activity was associated with significant improvements in aerobic capacity and reductions in body fat mass, no improvements in glycemic control were found. However, this should not be interpreted as a limitation of the game design, especially since a missing association between comparable increases in daily physical activity (+3,200 steps per day) and improvements in glycemic control has been reported before [48]. Instead, as discussed in publication 5, it is possible that the timeframe of 24 weeks was not of sufficient duration to detect improvements in HbA_{1c}, which have been shown to involve a distinct time lag of several months beyond an intervention period to become visible [49]. In addition, the relatively low baseline HbA_{1c} of 6.2% indicates a medically well-controlled diabetes and makes additional improvements through an increased physical activity level more unlikely than would a higher value at baseline. The significant adjusted difference between the two study groups of -0.9 percentage points suggests the superiority of the intervention treatment despite a missing de-facto improvement in HbA_{1c} in the intervention group and underlines the quality and effectiveness of the game-related physical activity promotion.

The quality of the game design is further emphasized by the fact that the increases in daily physical activity were sustained over 24 weeks as it has been shown that 50% of participants with diabetes drop out of exercise programs within 3 months [50]. In this regard, particularly low self-efficacy (i.e., perceived competence) has been reported to be a decisive predictor of a premature dropout from a physical activity-promoting intervention [51]. Because the game enhanced participants' physical activity-related perceived competence in a dose-dependent manner, as shown by the linear regression model in publication 6, it is quite likely that the game enjoyment markedly contributed to the high adherence rates as well as to the low dropout rate.

The fact that the game enabled participants to increase their physical activity-related perceived competence and subsequently intrinsic motivation, two of the most predictive factors regarding a long-term physical activity adherence [52], gives reason to believe that the change in physical activity behavior may be sustainable beyond the intervention period and even beyond the use of the game. Although to be confirmed in a follow-up assessment in the future, this would further underline the clinical relevance of our game as a successful treatment option and as a stepping-stone towards a long-term change in physical activity behavior in unmotivated and otherwise treatment-resistant individuals.

9.3 Strengths and Limitations

This Ph.D. project has a number of strengths, but also some limitations that should be considered with respect to future studies. A major strength is the novelty of the self-developed smartphone game with its elaborate game design and motivational components as well as with the tailored and guideline-concordant physical activity content. The extensive preparatory work (publications 1 and 2) combined with the successful interdisciplinary cooperation of international experts from the fields of sports medicine, gamification and behavior change research, and game development led to the development of a high-quality exercise tool that motivates inactive individuals with type 2 diabetes to increase their daily physical activity. Because the individualized and structured exercise regimen can be administered remotely via the game, this approach has great potential to set a precedent for future physical activity-promoting interventions in various clinical and public health settings that can save costs compared to conventional physical activity programs given an appropriate dissemination.

A further strength is the 24-week intervention period. Because half of all participants with diabetes drop out of exercise programs within 3 months [50], choosing a study design that exceeds this critical timeframe was important. It has further been shown that after 6 months, usually no further decreases in compliance occur [53]. The fact that the game elicited increases in daily physical activity that were sustained throughout the entire intervention period highlights the motivational quality of the game. Further strengths of the project are that a sample size calculation was performed for the 24-week intervention study and that the primary outcome 'daily physical activity' was measured objectively via instruments of proven validity [4], making this the first

exergame intervention study to do so. In this context, the self-conducted validation of the devices used to measure the primary outcome (publication 4) is a major strength of this Ph.D. project as it underlines its comprehensive and thorough methodology. In addition, the further outcomes 'glycemic control' and 'aerobic capacity' were measured by the respective gold standard methods such as analysis of venous blood and cardiopulmonary exercise testing. By visualizing the direct impact of the questionnaire-assessed increases in intrinsic motivation on the daily physical activity behavior through the illustration of the phone-recorded game usage data, this project further combined subjective and objective instruments and thereby made the meaning of abstract questionnaire scores more tangible. Finally, the fact that participants did not receive instructions on how often and when to use the game and that this project consequently assessed the autonomous effectiveness of the game in a real-life condition, makes the shown improvements in daily physical activity even more relevant.

A limitation of the study design that is due to the smartphone game-based character of the intervention is that there is no adequate placebo condition. A blinding of the study participants as proposed in the CONSORT Statement was therefore not possible [54,55]. By providing the same amount of exercise consultations and follow-up phone calls during the intervention period to participants in both groups, it was ensured that all participants otherwise received the same treatment and amount of personal contact. Combined with the blinding of the outcome assessors, this approach appeared to be the best method to compensate for the inevitable methodological shortcoming of not being able to blind participants. It should be considered for future interventions to use a different control condition, for example, a second smartphone app that administers the same physical activity content, but without the game character. In such a parallel group design, it would be possible to examine the added benefit of the game character over a simple app-based physical activity promotion and it would make it more difficult for participants to know for certain if they had been allocated to the control or intervention group.

Another limitation is the enormous difficulty, even greater than anticipated for the low-motivation target group, which was encountered in recruiting the sufficient sample size. Despite several recruitment measures that were proactively taken to recruit participants as efficiently as possible and in a timely manner, the successful recruitment of the relatively small required sample size of 34 participants took 20 months and therefore longer than estimated (see publication 3). During the recruitment phase, this project was presented and advertised for in eight major hospitals and five clinics in Basel and the cross-border agglomeration. All of these hospitals and clinics focus on diabetes care and ensured their support in the participant recruitment for our study. In addition, flyers and pamphlets were sent out to 26 diabetes clinics and diabetes counseling institutions that ensured their active support in the recruitment. All institutions were regularly contacted to remind of and motivate for further patient recruitment. Additional recruitment measures included articles and advertisements in local and trans-regional newspapers, online advertisement in the job market of the University of Basel, on Facebook and on our department's website as well as

repeated placement of flyers and posters in approximately 60 pharmacies and 50 supermarkets in the Basel cross-border agglomeration.

While the precise reasons for the enormous recruitment challenges are of course conjecture, it is likely that the generally low motivation of our target group to change the physical activity behavior [40] contributed to the overall very low response rate. Only 68 participants were interested in participating in the study, which represents only approximately 1% of all type 2 diabetes patients in the Basel metropolitan area. This underlines the enormous difficulty in motivating the target group to participate in physical activity-promoting interventions, despite the extensive cooperation with various diabetes care specialists. The recruitment was likely made more difficult by our strict inclusion/exclusion criteria. As shown in publications 5 and 6, 28% of all participants that were assessed for eligibility had to be excluded because they did not meet inclusion criteria, mainly due to physical activity levels that exceeded the pre-defined threshold of 150 minutes per week. It is likely that those who are more motivated to engage in increased physical activity look for additional ways to be physically active and therefore show their interest to participate in a physical activity-promoting intervention, whereas those who are unmotivated do not. Further, participants were required to have used a smartphone regularly during the year before the study. While the choice of a target group that is technologically proficient enough to realistically play a smartphone game is justified, this inclusion criterion may have excluded interested individuals from participating. Finally, it is possible that the idea of a physical activity-promoting smartphone game was unappealing to some of the potential participants. While the vast majority of the included participants enjoyed the game, it is possible that a negative connotation towards video games or a general disinterest in smartphone games/ applications kept some of the potential participants from responding to the study ads.

A further limitation is that the effectiveness of the single motivational elements that were incorporated into the game was not assessed and it therefore remains to be determined, which conceptual ideas and behavior change mechanics were particularly successful in increasing daily physical activity. It further remains to be determined how the effectiveness of the different elements differed from player to player or potentially over time in the same player. The identification of individually successful motivational elements would be important knowledge for the design of future game applications and interventions with the potential to tailor the motivational game mechanics to the behavioral profile of the individual player.

Finally, possibly the strongest limitation with regard to the analysis of the physical activity behavior throughout the intervention period is that phone wear and non-wear time was not recorded and that any additional physical activity beyond what was recorded by the phones was not objectively measured. For future studies, it should be considered to measure daily physical activity additionally with an accelerometer of proven wear-time compliance such as an activity

wristband [4] to capture all physical activity throughout the intervention period, preferably in the intervention and the control group.

9.4 Prospects for Future Research

Publication 6 showed that our game was perceived well by the vast majority of our participants and motivated a formerly very inactive target group over 24 weeks to engage in an average of 143 minutes of in-game training per week and thereby adhere to established physical activity recommendations [38] through in-game training alone. The potential of the game to sustainably change the physical activity behavior in the least motivated was therefore effectively demonstrated. To evaluate the effectiveness of the game beyond the intervention period, a one-year follow-up assessment should be considered. It will be interesting to see how many of the study participants are still playing the game and to which extent. Further, it will be insightful to see if the game was able to serve as a stepping-stone towards increased physical activity levels beyond the game particularly in those who ceased to play after the intervention or if participants who quit playing the game after the intervention relapsed into physical inactivity.

In addition, to give more people the opportunity to profit from the game than those that were included in the study, a wider dissemination should be pursued as a next step. It could be envisioned that diabetes care specialists prescribe the game as an enhancement of their standard care and thereby concurrently obtain the opportunity to track their patients' adherence to the recommended physical activity regimen via the game-recorded usage data. Even though the response rate for our study was low, despite the cooperation with diabetes care specialists, it is conceivable that more patients would be willing to try out the game if it were prescribed as an additional treatment opportunity as part of their regular diabetes care consultation rather than in a study setting that may present more of a hurdle. Further, while the game is primarily targeted at type 2 diabetes patients, it is certainly suitable for other inactive target groups with chronic diseases and limited fitness, such as chronic obstructive pulmonary disease or chronic heart failure. The automatic intensity adjustment through the baseline test-based algorithm ensures suitable and safe exercise intensities regardless of the health condition or disease, and the option to manually adjust the game-proposed physical activity regimen enables players to cater to their personal preferences and possible physical limitations. An extended dissemination to other target groups is therefore clearly warranted and should be pursued after making small and target group-specific adjustments in the game content. Through a wider dissemination and based on the promising results from the intervention study [5,6], our game has the potential to contribute to a reduction of physical inactivity in various target groups and thereby positively affect morbidity and premature mortality [56,57].

In a further next step, it should be considered to further extend and refine the game content in the sense of a comprehensive healthy behavior change. It could be envisaged to include nutritional information and the option to track food intake via objective methods such as the Remote Food

Photography Method [58] as integral components of the storyline. The combination of physical activity promotion and dietary advice could further improve health outcomes, particularly in diseases that are in great part attributable to lifestyle-dependent, modifiable risk factors such as overweight and obesity [59]. In addition, based on the specific needs of the target group, medication reminder features could be incorporated to increase medication adherence. The fact that medication non-adherence rates are as high as 50% in patients with chronic diseases and are a major contributor to suboptimal health outcomes and subsequently rising health care costs [60], underlines the importance to increase medication adherence. Although evidence for the effectiveness of medication adherence apps is sparse to date, it has been suggested that patients' medication adherence may be improved if medication reminder functions are incorporated in a well-conceived way and with the inclusion of health care professionals to cater to the specific needs of the individual patient [61]. If the addition of such features is pursued, the continuation of our approach of storing user data locally on the player's phone is highly recommended to ensure data privacy. If data privacy is ensured, no further negative consequences of a sustained use of a physical activity-promoting game with potentially additional features are to be expected.

As part of the consequent further development of the game, a more tailored selection of behavior change techniques based on the player's previously assessed behavioral profile could yield an even more successful utilization of the incorporated behavior change mechanics. Developing an assessment system that can distinguish those motivational elements that are likely to be successful in an individual from those that may be counterproductive would be extremely beneficial not just for gamified approaches but for all interventions that use technology to promote healthy behavior change. For example, if an individual perceives the reminder function as disturbing and annoying rather than encouraging, it will likely lead the individual to disregard the reminder and subsequently not elicit the intended behavior change. Identification of the negative perception of this specific mechanic would allow its deactivation and thereby eliminate one (additional) factor that is likely to stand in the way of a long-term adherence.

The elaborate exercise tracking and fitness assessment via various smartphone sensors set a precedent for future physical activity-promoting apps with and without gamified content. Because an accurate fitness assessment combined with the objective measurement of patients' training progression and adherence to a proposed exercise regimen is crucial to evaluate the effectiveness of any physical activity-promoting intervention, the demonstrated functionality of our game and its smartphone sensor-based monitoring has important implications for future research in clinical and public health settings. Through its easy smartphone-based application, established exercise tests can be accurately conducted in large cohorts while requiring almost no staff expenses. In addition, the demonstrated feasibility to use a sensor-based verification of the correct execution of an extensive physical activity regimen consisting of endurance, strength, balance, and flexibility exercises improves the effectiveness and safety of remotely-administered physical activity-promoting interventions. Therefore, beyond its immediate results, this Ph.D. project may serve as

pioneer work for a large-scale administration of app-delivered individualized exercise regimens with an objective, sensor-based monitoring of the training progression and adherence.

9.5 Conclusions

In this Ph.D. project and following extensive preparatory research (publication 1 and 2), I collaborated with an international team consisting of sports scientists, gamification researchers, professional game developers, and clinical professionals in developing an innovative smartphone game with the aim to encourage a healthier, more active lifestyle through gamified physical activity in inactive type 2 diabetes patients. The game takes the proven motivational benefits of exergames into consideration and further extends them by integrating established behavior change techniques into an elaborate storyline (publication 3). Noted shortcomings with regard to the suitability and effectiveness of the exercise regimen of current exergames are addressed by offering a fitness level-adjusted training with an individualized rate of intensity progression that is based on the performance in established and in-game-conducted exercise tests. A 24-week randomized controlled trial (publication 5 and 6), the core part of this Ph.D. project, showed that the innovative game motivates persistently inactive type 2 diabetes patients sustainably to engage in regular physical activity. Participants in the intervention group who received the game significantly increased their questionnaire-assessed intrinsic physical activity motivation with a direct impact on the de-facto physical activity behavior that was assessed objectively via smartphones and accelerometer wristbands of proven validity (publication 4). The recorded usage data of the game revealed that participants used the game for an average of 143 minutes of in-game training per week during the intervention, and the objective physical activity assessment post-intervention indicated average step counts of 9,782 steps per day. Both parameters classify this formerly inactive target group as sufficiently active post-intervention and thereby underline the clinical relevance of the game-induced increases in physical activity. The effectiveness of the game is further highlighted by the significant and clinically relevant improvements in aerobic capacity that accompanied the increases in daily physical activity and demonstrate the beneficial impact of the game's high amount of moderate-to-vigorous-intensity training. The shown increases in daily physical activity contributed to the stabilization of a medically well-controlled HbA_{1c} while the significant adjusted difference between the two study groups suggests the superiority of the intervention treatment (game use) over the control condition that consisted of a one-time lifestyle counseling.

In conclusion, a novel smartphone game that incorporates established motivational elements and personalized physical activity recommendations into an elaborate storyline elicits clinically relevant increases in daily physical activity and aerobic capacity in persistently inactive type 2 diabetes patients. Our game is therefore a suitable treatment option to motivate inactive individuals to increase daily physical activity that may be relevant for other inactive target groups with and without chronic diseases.

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http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/

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61. Ahmed I, Ahmad NS, Ali S, Ali S, George A, Danish HS, et al. Medication Adherence Apps: Review and Content Analysis. JMIR MHealth UHealth. 2018;6:e62.

Curriculum Vitae

EDUCATION

Department of Sport, Exercise and Health, University of Basel, Switzerland

Ph.D. in Sports Sciences September 2018

Dissertation: *Mobile Exergaming in Type 2 Diabetes Mellitus – Innovative Ways to Overcome Physical Inactivity and Increase Exercise Adherence*.

Department of Sport, Exercise and Health, University of Basel, Switzerland

Master of Science in Exercise and Health Sciences (magna cum laude) September 2013

Thesis: *Effects of a Structured Lifestyle Intervention on Weight Reduction and Improvement of Vascular Health in Obese Patients.*

Department of Sport, Exercise and Health, University of Basel, Switzerland

Bachelor of Science in Exercise and Health Sciences (magna cum laude) September 2011

ACADEMIC EXPERIENCE

Department of Sport, Exercise and Health, University of Basel, Switzerland

Research Assistant January 2014 – Present

Research Focus: Developing and evaluating new technologies that offer motivating, tailored, intensity-adjusted ways to promote regular physical activity and to increase long-term exercise adherence in sedentary, overweight individuals with chronic diseases such as type 2 diabetes mellitus.

- Design and conduct intervention and exploratory studies and systematic reviews
- Perform examinations with study participants and patients of the department's outpatient clinic including anthropometry, physical exercise testing, (strength and endurance), and vascular diagnostics
- Assist research colleagues with analysis of data, manuscript drafting, and graphic content creation
- Instruct Bachelor's and Master's students on proper scientific practices, use and function of laboratory equipment, and patient care
- Supervise and grade Bachelor's and Masters's theses

TEACHING EXPERIENCE

Department of Sport, Exercise and Health, University of Basel, Switzerland
Measurement & Evaluation / Messmethodik und Anwendung September 2015 – Present

Department of Sport, Exercise and Health, University of Basel, Switzerland
Präsentations- and Kommunikationskompetenz September 2014 – Present

Department of Sport, Exercise and Health, University of Basel, Switzerland
Served as a supervisor for 4 master's and 7 bachelor's theses. October 2015 – Present

NON-ACADEMIC EXPERIENCE

Cardiac Rehabilitation Group Basel, Basel, Switzerland
Exercise Instructor and Administrator January 2016 – Present

Obesity Group Basel, Basel, Switzerland
Exercise Instructor and Administrator July 2012 – December 2015

Idée:Sport (NGO), Basel, Switzerland
Project Manager Midnight Sports October 2011 – May 2016

Department of Sport, Basel, Switzerland
Trainer and Test Administrator May 2012 – June 2015

Department of Sport, Basel, Switzerland
PE Instructor February 2011 – June 2014

PUBLICATIONS

Peer-reviewed Journal Articles

Höchsmann C, Knaier R, Eymann J, Hintermann J, Infanger D, Schmidt-Trucksäss A. Validity of activity trackers, smartphones, and phone applications to measure steps in various walking conditions. Scand J Med Sci Sports. 2018 Jul; 28(7): 1818-1827.

Höchsmann C, Baumann S, Infanger D, Schmidt-Trucksäss A. Oxygen uptake during mini trampoline exercise in normal-weight, endurance-trained adults and in overweight, inactive adults: a proof of concept study. Eur J Sport Sci. 2018 Jun; 18(5): 753-761.

Höchsmann C, Meister S, Gehrig D, Gordon E, Li Y, Nussbaumer M, Rossmeissl A, Schäfer J, Hanssen H, Schmidt-Trucksäss A. Effect of e-bike vs. bike commuting on cardiorespiratory fitness in overweight adults: A four-week randomized pilot study. Clin J Sport Med. 2018 May; 28(3): 255-265.

Keller F, Dhaini S, Briel M, Henrichs S, **Höchsmann C**, Kalbermatten D, Künzli N, Mollet A, Puelacher C, Schmidt-Trucksäss A, von Niederhäusern B, De Geest S. How to conceptualize and implement a PhD program in health sciences – The Basel approach. J Med Educ Curric Dev. 2018 Apr 24; 5: 1-8.

Knaier R, Schäfer J, Rossmeissl A, Klenk C, Hanssen H, **Höchsmann C**, Cajochen C, Schmidt-Trucksäss A. Effects of bright and blue light on acoustic reaction time and maximum handgrip strength in male athletes: a randomized controlled trial. Eur J Appl Physiol. 2017 Aug; 117(8): 1689-1696.

Knaier R, Schäfer J, Rossmeissl A, Klenk C, Hanssen H, **Höchsmann C**, Cajochen C, Schmidt-Trucksäss A. Prime time light exposures do not seem to improve maximal physical performance in male elite athletes but enhance end-spurt performance. Front Physiol. 2017 May 1; 8: 264.

Höchsmann C, Walz S, Schäfer J, Holopainen J, Hanssen H, Schmidt-Trucksäss A. Mobile exergaming for health - Effects of a serious game application for smartphones on physical activity and exercise adherence in type 2 diabetes mellitus – study protocol of a randomized controlled trial. Trials. 2017 Mar 6; 18(1): 103.

Höchsmann C, Zürcher N, Stamm A, Schmidt-Trucksäss A. Cardiorespiratory exertion while playing video game exercises in elderly individuals with type 2 diabetes. Clin J Sport Med. 2016 Jul; 26(4): 326-31.

Höchsmann C, Schüpbach M, Schmidt-Trucksäss A. Effects of exergaming on physical activity in overweight individuals. Sports Med. 2016 Jun; 46(6): 845-60.

Working Papers

Knaier R, **Höchsmann C**, Infanger D, Hinrichs T, Schmidt-Trucksäss A. Automatic wear-time detection of wrist-worn and hip-worn ActiGraph GT3X+ - Validity in a free-living setting. J Phys Act Health [under review].

Höchsmann C, Müller O, Ambühl M, Klenk C, Königstein K, Infanger D, Walz SP, Schmidt-Trucksäss, A. Behavior change technique-based smartphone game sustainably increases daily physical activity in type 2 diabetes patients – a randomized controlled trial. Diabetes Care [submitted].

Höchsmann C, Infanger D, Klenk C, Königstein K, Walz SP, Schmidt-Trucksäss, A. Effectiveness of a behavior change technique-based smartphone game to improve intrinsic motivation and physical activity adherence in type 2 diabetes patients: a randomized controlled trial. J Med Internet Res [submitted].

Höchsmann C, Knaier R, Fischer J, Infanger D, Schmidt-Trucksäss, A. Validity of smartphones and activity trackers to measure steps in a free-living setting during three consecutive days [in progress].

PRESENTATIONS

Conference Presentations

Step count accuracy of smartphones during various walking conditions when worn at different wearing positions. Presented at the 23rd Annual Congress of the European College of Sport Science in Dublin, Ireland (July 4-7, 2018).

Mobile Exergaming in Type 2 Diabetes. Presented at the Symposium of the German Society of Sports Medicine and Prevention in Hamburg, Germany (May 24, 2018).

Rebounding - an alternative and effective low-impact form of cardiorespiratory exercise. Presented at the 10th annual conference of the Swiss Society of Sports Sciences in Magglingen, Switzerland (February 8/9, 2018).

Accuracy of smartphones to measure steps during various walking conditions. Presented at the 10th annual conference of the Swiss Society of Sports Sciences in Magglingen, Switzerland (February 8/9, 2018).

Effect of E-Bike vs. Bike Commuting on Cardiorespiratory Fitness in Overweight Adults: A Four-Week Randomized Pilot Study. Presented at the 9th annual conference of the Swiss Society of Sports Sciences in Zurich, Switzerland (February 9/10, 2017).

Effects of exergaming on physical activity in overweight individuals – a systematic review. Presented at the 8th annual conference of the Swiss Society of Sports Sciences in Berne, Switzerland (February 18/19, 2016).

Invited Presentations

Mit Aktivitäts-Daten spielend die Gesundheit verbessern – ein Anwendungsbeispiel bei Typ 2 Diabetes. Presented at the BIG DATA Symposium in Zurich, Switzerland (March 3, 2017).

Exergaming and self-tracking in the treatment of obesity and type 2 diabetes – improving exercise adherence. Presented at the Symposium of the Swiss Society of Public Health in Berne, Switzerland (October 26, 2016).

GRANTS / STIPENDS

PhD Program for Health Sciences (PPHS), University of Basel, Switzerland May 2018

Extension Stipend to fund additional research related to the main PhD project (15,000 CHF).

PROFESSIONAL SERVICE

Invited Reviewer

- BMJ Open Sport & Exercise Medicine
- Perceptual and Motor Skills
- Games for Health Journal
- Atherosclerosis

ACADEMIC ASSOCIATIONS

European College of Sport Science (ECSS) 2018 – Present

American College of Sports Medicine (ACSM) 2017 – Present

PhD Program for Health Sciences (PPHS), University of Basel, Switzerland 2014 – Present

- PPHS Steering Committee (October 2016 – Present)

PERSONAL DEVELOPMENT

Course	ECTS
SSPH+ Summer School 2014 Measurement of Physical Activity , Arno Schmidt-Trucksäss	2
Writing to be Published – Academic Writing Conventions and Style, Sprachenzentrum der Universität Basel, Paul Skandera	0

Peer Review – From submission to Retraction, University of Basel, Transferrable Skills Program, Markus Geisler	1
Good Clinical Practice Basiskurs, Clinical Trial Unit, University Hospital Basel, Barbara Peters	0
Self-branding and self-promotion, University of Basel, Transferrable Skills Program, Petra Wüst	0
Fundraising and Proposal Writing for PhDs, University of Basel, Transferrable Skills Program, Andrea Degen	1
Research Integrity: Zitat oder Plagiat? University of Basel, Transferrable Skills Program, Klaus-Peter Rippe	1
Self-Management: Become More Efficient & Enhance Your Success, University of Basel, Transferrable Skills Program, Alice Cossy Ganter	1
Creating the job hunting package, University of Basel, Transferrable Skills Program, Verity Elston	1
Academic Writing in the Health Sciences, University of Basel, PhD Program Health Sciences, Annegret Mündermann	1
Conflict Management and Better Communication, University of Basel, Transferrable Skills Program, Hermionie Blake	1
Presentation Training + Video Support, University of Basel, Transferrable Skills Program, Sibylle Sommerer	1
Make the Most Out Of Your Science – Patenting and Spin-Off Workshop, University of Basel, Transferrable Skills Program, Peter Eckard	1
Good Scientific Practice, University of Basel, Transferrable Skills Program, Helga Nolte	1
How to Improve Your Negotiation Skills, University of Basel, Transferrable Skills Program, Melissa Davies	1
Essentials in Health Research Methodology (“Randomized Controlled Trials, Systematic Reviews and Meta-Analysis” and “Observational Studies and Analysis of Observational Datasets”, University of Basel, PhD Program Health Sciences, Matthias Briel	1
Summer School CardioLung 2017 - Updates in Cardiovascular-Pulmonary Pathophysiology, University of Pisa, Italy, Carlo Palombo	6
Get Your Video Abstract – Your Research in a Film, University of Basel, Transferrable Skills Program, Judith König & Tilman Hassenstein	1