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MOTIBOT: IL COACH VIRTUALE PER INTERVENTI DI COPING SANO PER ADULTI CON DIABETE MELLITO

MOTIBOT: THE VIRTUAL COACH FOR HEALTHY COPING INTERVENTIONS FOR ADULTS WITH DIABETES MELLITUS

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"Awareness is not the same as thinking. It is a complementary form of intelligence, a way of knowing that is at least as wonderful and as powerful, if not more so, than thinking."

(Jon Kabat-Zinn, 1990)

Contents

Abstract

Diabetes Mellitus (DM) is a self-managed, metabolic disease, in which if the individual is unwilling, unmotivated, or unable to regularly self-manage their DM, the medical and psychosocial outcomes will be poor. Indeed, DM is more than a physical health condition: it has behavioural, physiological, psychological, and social impacts, and demands high levels of motivation in order to follow the clinical recommendations and adopt healthy behaviours. The American Association of Diabetes Educators (AADE) has identified seven self-care behaviours, as necessary for optimal diabetes management: healthy eating, being physically active, monitoring of blood glucose levels—defined as Haemoglobin A1c (HbA1c)—adhering to prescribed medications, adequate problem-solving skills, risk-reduction behaviours and healthy coping. Adults with DM are seen to have difficulty in maintaining these healthy behaviours, thus leading to a negative impact on their psychosocial well-being. To this end, the AADE guidelines introduced the healthy coping construct to identify healthy coping strategies for reducing symptoms of depression, anxiety, stress, and diabetes-related emotional distress while also improving the well-being of adults with DM. These symptoms are common among adults with DM and are associated with sub-optimal self-management, diabetes-related complications, reduced quality of life, and increased health care costs. In this regard, one can assume a *bidirectional* association between psychosocial and medical factors. Indeed, experiencing anxiety, depression and/or stress symptoms cause lower adherence rates and impairment of the well-being of people with DM, thus, involving poor self-care behaviours, reduced health-related quality of life, and poor metabolic outcomes. Moreover, biochemical modifications related to the onset of DM, such as the arousal of the nervous system as the Hypothalamic-Pituitary-Adrenal (HPA) cortex axis, can lead to a greater probability of developing depression, anxiety and/or stress in adults with DM compared to the general population. As such, together with the risk resulting from the above heightened neuro-affective activity, also the psychosocial burden of managing DM can entail the risk of developing stress, depression and/or anxiety symptoms, which in turn can affect the health-related quality of life of adults with DM. In this context, Behavioural Intervention Technology (BIT), an underlying field of electronic health (eHealth) interventions, is aimed at supporting people in changing their behaviours and cognitions associated with mental health, physical health and well-being through the use of digital solutions. For example, BITs via mobile health (mHealth) have largely been deployed for behaviour changes in DM to provide, in particular, regular self-monitoring of

their HbA1c levels and interactions between patients, family members and health care clinicians. Conversational agents—embedded or not in mHealth—can be deployed as means for motivational or behavioural coaching: in this case, a widely used term in the literature is Virtual Coach (VC). VCs have recently become more prevalent in the support and management of common barriers in the context of adherence to healthy behaviours among adults with DM, in particular those regarding medical and physical behaviours. However, few VCs were found to be specifically aimed at providing psychosocial support to adults with DM. The main aim of the present thesis was, indeed, the development and implementation of a VC for the provision of psychosocial support to adults with Type 1 (T1DM) or Type 2 DM (T2DM). More specifically, this VC aimed at motivating adults with DM to reduce depression, anxiety, perceived stress symptoms, diabetes-related emotional distress, and improve their well-being, by encouraging them to acquire and cultivate psychosocial healthy coping strategies. These coping skills referred to the AADE guidelines and thus to practicing meditation; in this study, the Mindfulness-Based Cognitive Therapy has been applied. The VC implemented in the present thesis interacted, firstly with users (i.e., psychology students), and secondly with patients with DM in accordance with the Transtheoretical Model of Change (TTMC) in order to deliver the most appropriate psychoeducational intervention based on the user's/patient's motivation to change their behaviour. The present thesis is articulated according to three studies.

Study 1 aimed at providing meta-analytical evidence on the efficacy of eHealth interventions in supporting the psychosocial and medical well-being of adults with T1DM or T2DM. This study intended to investigate differences in interventions primarily aimed at providing glycaemic control *vs.* those primarily aimed at providing psychosocial support. Intervention acceptability was evaluated by calculating the Odd Ratio of drop-out rates. A total of 13 Randomized Control Trials (RCTs) comprising 1315 adults with T1DM or T2DM were included (M_{age} = 46.18, SD = 9.98). The statistical analyses showed intervention efficacy on HbA1c and depressive symptoms at RCTs endpoint. However, efficacy on HbA1c was not maintained at follow-up and depressive symptoms could not be evaluated at follow-up since no studies assessed these outcomes. Therefore, eHealth interventions that provided medical support were acceptable and effective in promoting glycaemic control and reducing depressive symptoms only in the short-term.

Study 2 aimed at testing the prototype of the simulated VC, namely Wizard of Oz (WOZ), via the WhatsApp messaging platform for 6-week, with two sessions per week. In particular, this study investigated the preliminary acceptability and the User Experience (UX) of the intervention protocol, which will be incorporated into the future VC. Indeed, the design method was two-fold. On the one hand, the WOZ method was applied, in which psychology students believed that they were interacting with a VC, instead they were communicating with a human being. On the other hand, the Obesity-Related Behavioural Intervention Trials (ORBIT) model was used, particularly its early phases, since it favours an iterative approach. The intervention protocol was, indeed, iteratively tested and refined, firstly with experts in BITs and mental health, and, secondly, with 18 psychology students (M_{age} = 23.61; SD =1.975). These psychology students played the role of Standardised Patients (SPs) in simulated evaluation scenarios to ensure the quality of the intervention protocol. Results showed that participants perceived WOZ as supportive, motivating, and able to trigger self-reflection on coping strategies. The analyses of the logged dialogues also revealed that participants accurately played their roles, further confirming the validity and utility of this testing approach in the design and prototype of the intervention protocol regarding a digital solution.

Study 3, following the next phases of the ORBIT model, aimed at assessing the preliminary efficacy of the VC, called Motibot—the abbreviation for Motivational bot—developed through a combination of Natural Language Processing (NLU) and hand-crafted rules. A total of 13 Italian adults with DM (M_{age} = 30.08, SD = 10.61) interacted with Motibot through the Telegram messaging application for 12 sessions, in which the patient planned the appointment according to his/her needs: he/she interacted with Motibot one or two sessions per week. The Patient Health Questionnaire-9 (PHQ-9), the Generalized Anxiety Disorder questionnaire-7 (GAD-7), the Perceived Stress Scale (PSS) were administered at pre-intervention, post-intervention and follow-up to explore the levels of anxiety, stress and depression symptoms. Two other scales were included in order to comprehend if healthy coping strategies had been internalised, such as the Problem Areas in Diabetes Scale-Short Form-5 (PAID-5) and the World Health Organization-5 Well-Being Index (WHO-5), administered only at follow-up. In addition, UX were assessed during the whole interaction and User Engagement (UE) was evaluated only at the end of the study to comprehend the final involvement between patients and Motibot. The statistical analyses showed no significant changes in psychosocial factors at pre-, post-intervention, and follow-up during the 12 sessions. However, most patients showed a decrease of depression and anxiety symptoms during the three time periods—except for perceived stress symptoms, which remained moderate throughout the intervention—indicating, on average, a borderline psychological well-being, which can be seen, overall, as a sufficient psychological well-being and low diabetes-related emotional distress. The text-mining approach revealed that Motibot can support and motivate adults with DM to acquire healthy coping strategies and to reduce anxiety and depression symptoms. Patients further perceived a positive and interesting experience with Motibot for two reasons in particular: on the one hand, the invitation to listen to meditation audios and, thus, for the inclusion of a mindfulness path in the study. On the other hand, the encouragement in self-reflecting on their own emotions. This study allowed the comprehension of the usefulness of VCs, such as Motibot, in supporting and motivating adults with DM to acquire healthier coping strategies, such as practicing mindfulness exercises, and to take action in improving their own well-being. Therefore, Motibot can be a useful tool to provide psychosocial support to adults with DM; as such, it might be prescribed by the diabetologist as a preventive measure for the patient's well-being and/or when the patient presents mild and moderate psychosocial symptoms. It is important to underline that VCs are not developed to substitute the help that professionals in diabetes can provide. In fact, VCs can actually support diabetes professionals and enable them to reach a larger and more diverse population with DM, thereby allowing the patient easier access to psychosocial care and support without overburdening the clinical staff. This user-centred design approach and the concept of bidirectionality between psychosocial and medical factors are key points in the development of a personalised treatment within the digital intervention.

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease consisting of high blood glucose (or blood sugar) levels, which over time, if untreated, leads to serious health complications such as cardiopathy, retinopathy, nephropathy, neuropathy, and vasculopathy [1]. Type 1 DM (T1DM), once referred to as *juvenile diabetes* or *insulin-dependent diabetes mellitus*, is a chronic autoimmune condition in which the pancreas is not able to produce enough insulin due to the loss of beta cells[1] [1]. However, the most common is Type 2 DM (T2DM), once referred to as *adult-onset diabetes* or *non-insulin-dependent diabetes mellitus*, which occurs when the body becomes resistant to insulin, a condition in which cells fail to respond to insulin properly [1]. Over the past three decades, the prevalence of T2DM has increased dramatically in countries of all income levels [2]. DM has a relevant impact on issues associated with clinical, social, and economic factors, as well as on the individual's quality of life, thereby leading to augmented morbidity and mortality [2,3]. The World Health Organization (WHO) estimated that the global prevalence of DM was at 8.5% among adults of 18 years old and above, and 422 million adults were living with DM, compared to 108 million in 1980 [4]. The WHO also reports that deaths from DM increased by 70% worldwide between 2000 and 2019, with mortality rates being greater among males than females, cross-culturally and independently of age [5]. Furthermore, the International Diabetes Federation reports that there are 382 million people worldwide who suffer from DM, and it is expected to reach 592 million people by 2035 [6]. The increasing rates of DM worldwide represent an issue for diabetes specialists, who already, as things stand, do not have enough time to help every patient with physical, medical, and psychosocial problems. In this regard, digital health solutions can further support people with DM by encouraging and motivating them to better manage their health. In the last decades, the high availability of digital health solutions for DM, such as the ones based on Virtual Coaching (VC), has been an important resource to provide widely accessible and low-cost personalised care; subsequently, it ameliorated the communication and monitoring of various biometric information relevant to disease management, and fostered involvement of people towards their self-care [7-10]. In previous studies, VC has been applied for improving healthy coping strategies in college students, demonstrating their beneficial effect of them in

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[1]Beta cells are endocrine cells in the pancreas and located in the area called the islets of Langerhans. Beta cells produce, synthetize, store, and release insulin in a tightly regulated manner, to maintain circulating glucose concentrations within a narrow physiologic range [1].

reducing symptoms of distress [11, 12]. As regards the development of VC in the DM field, studies designed a VC [13] and an interactive diary [14,15]—both embedded in a smartphone application—for improving health-related quality of life among adults with T2DM [13] and with T1DM [14,15]. The health-related quality of life is an important and well-known construct, which underlies the concept of general well-being. However, it should also be noted that anxiety, depression, and stress symptoms interplay with diabetes management, meaning that these outcomes can inhibit an individual's ability to manage DM and maintain an effective glycaemic control; thus, the importance of including these variables when developing program and interventions for adults with DM. Most studies related to the development of digital solutions have investigated physical and medical factors involved in DM management, there seems to be a lack of research on the impact of psychosocial factors in digital health, such as healthy coping. Therefore, the purpose of the current dissertation is to outline the potential application of VC for psychosocial support among adults with DM. Indeed, my present Ph.D. project intended to implement a VC for psychosocial support for adults with T1DM or T2DM, aimed at motivating them to reduce anxiety and depression symptoms, perceived stress, and diabetes-related emotional distress, as well as to improve their well-being by internalising healthy coping skills, such as practicing mindfulness exercises. More specifically, the present dissertation includes three studies in which both qualitative and quantitative methods were applied. The *First* and the *Second Chapter* represent the theoretical overview part. The *First Chapter* outlines the main psychosocial aspects associated with diabetes self-management in adults, the neuro-affective perspectives of the *dynamic interaction* between those psychosocial and medical factors, and, lastly, how to cope with DM. The *Second Chapter* describes and maps the behavioural interventions technologies deployed in DM, with a focus on VC for psychosocial support, in which the user is considered at the centre of the design process, and ultimately, the methodologies used to implement VCs until now. The *Third*, *Fourth* and *Fifth Chapters* relate to the part dedicated to bibliographic and empirical research. This part will cover the discussion on my Ph.D. project based on three studies. The *Third Chapter* refers to a systematic review and meta-analysis aimed at providing evidence gathered from Randomized Control Trials (RCTs) evaluating digital health interventions for adults with T1DM or T2DM, which account for both medical and psychosocial factors. The *Fourth Chapter* describes a pilot study related to the early designing and prototyping of a VC for healthy coping interventions in DM. The *Fifth Chapter* represents the next phase, and, indeed, illustrates a proof-of-concept study regarding the effective development of Motibot (i.e., Motivational bot), a VC for healthy coping intervention in DM. The *Sixth Chapter*, entitled perspectives, is the last part and, thus, represents the summary of the overall results emerging from the above-mentioned three studies, with particular focus on the clinical implications of VC for psychosocial support in people with DM.

PART 1 – THEORETICAL OVERVIEW

CHAPTER 1. THE PSYCHOSOCIAL ASPECTS OF DIABETES MANAGEMENT IN ADULTS

One pivotal aspect associated with the medical, physical and psychosocial well-being of people with Diabetes Mellitus (DM) is successful self-management [16]. Indeed, DM is a largely self-managed disease, in which whether the person is unwilling, unmotivated, or unable to regularly self-manage their DM, the medical and psychosocial outcomes will be poor, no matter how advanced the type of treatment is [17]. DM is more than a physical health condition: it has behavioural, physiological, psychological, and social impacts, and demands high levels of self-efficacy [18] as well as high degrees of motivation. Therefore, poor self-management of DM negatively impacts the emotional well-being and quality of life of patients with this chronic disease [18]. In this regard, emotion-oriented coping strategies are necessary resources for people with DM to ensure the healthy management of their disease and the related psychosocial difficulties that emerge from living with DM. In this context, motivation is a key component in adherence to the diabetes regimen since it is specifically conceptualised for its process rather than for a specific goal [19].

1.1 Psychosocial aspects associated with diabetes self-management

Physical, medical and psychosocial factors significantly contribute to adherence rates to the clinical recommendations in adults with DM, by promoting or inhibiting optimal diabetes self-management [19]. Appropriate diabetes self-management is central to long-term diabetes care, and it encompasses several healthy behaviours, such as monitoring of glycaemic levels, following a healthy diet, physical exercise, taking prescribed medication and/or insulin injections, which in turn have an impact on the general well-being of people with DM. However, diabetes self-management is challenging, and these healthy behaviours are difficult to maintain. Indeed, studies showed that high levels of diabetes-related emotional distress are associated with a worsening of self-care behaviours as well as glycaemic levels [20]. Notably, it is fundamental to understand how psychosocial factors may contribute to self-care adherence in adults with DM. For example, psychosocial barriers, associated with diabetes-related emotional distress and poor diabetes self-management, can be identified with having low self-efficacy [21], low social support and external locus of control [22].

Diabetes distress is the emotional distress emerging from living with DM and the burden of consistent and regular self-management. According to Fisher, Glasgow, Mullan, Skaff and Polonsky (2008) diabetes-related emotional distress is defined as the individual's concerns regarding the self-management of their disease, the perception of social support, the emotional burden, and the accessibility to quality health care [23]. Diabetes-related emotional distress also constitutes a risk factor for the onset of stress, anxiety, and depression symptoms. Indeed, the prevalence rates of *depression* are much higher in people with DM compared to the general population, estimated to be 17% [20]. The literature further suggests that people with DM are two to three times more likely to develop depression [24]. Depression is associated with a worsening of quality of life and glycaemic control, and a decrease in adherence rates [25]. The American Association of Clinical Endocrinologists reports that: "screening for depression should be performed routinely for adults with diabetes because untreated depression can have serious clinical implications for patients with diabetes" [26, p.23]. Continuing along this line, the Canadian Diabetes Association added the construct of anxiety, stating that: "individuals with diabetes should be regularly screened for subclinical psychological distress and psychiatric disorders (e.g., depressive and anxiety disorders) by interview or with a standardized questionnaire" [27, p.S90].

As regards *anxiety* symptoms, studies have found that 14% of adults with DM show generalised anxiety disorder (GAD), a prevalence much higher than the 3-4% rate reported in a community sample [28-30]. Anxiety is associated with unhealthy lifestyle choices, such as higher smoking prevalence, a sedentary lifestyle and the assumption of food high in cholesterol, which can all lead to poor disease management [31]. A study found that female gender, smoking, heavy drinking, unemployment, diabetes complications and insulin use represent risk factors for increased symptoms of anxiety, assessed them using the Hospital Anxiety and Depression Scale (HADS) [32] whilst the type of DM, the educational levels as well as the marital status were not significantly related to anxiety symptoms [33]. Additionally, higher levels of anxiety hinder cognitive capacity, which in turn influences diabetes management and, thus, the ability to fully follow the clinical recommendations [20,31].

Likewise, stress is defined as "the consequence of the failure of an organism–human or animal–to respond appropriately to emotional or physical threats, whether actual or imagined" [34, p.12]. Indeed, the physiological *stress* response is the consequence of a defensive reaction of the organism, which consists in the activation of the Hypothalamic-Pituitary-Adrenal (HPA) cortex axis, from which glucocorticoids are released into the bloodstream: this reaction is defensive and adaptive, called General Adaptation Syndrome (GAS) [35]. Feeling stressed can cause several symptoms, affecting both physical and mental health such as experiencing headaches, muscle tension or pains, chest pains, and stomach issues, as well as difficulties in concentrating, feeling overwhelmed and constantly worrying [35]. In addition, feeling stressed can also affect the individual's behaviour, in which he or she can be irritable, can eat and/or sleep too much or too little, and can drink and/or smoke more than usual [35]. Indeed, feeling stressed has a negative impact on DM since it determines the release of stress hormones, such as cortisol and adrenaline, which prevent insulin from working properly (i.e., insulin resistance), thus, leading to unbalanced glycaemic levels (i.e., not within the optimal range of glycaemic level) [36]. At the same time, people with DM, who feeling stressed can engage in poor health behaviours, which also entail a greater risk for the onset of cardiovascular diseases [37].

Altogether depression, anxiety, and stress are associated with the risk of developing cardiovascular diseases, and the presence of DM further heightens this risk [20,31,36]. These psychological factors provoke lower adherence rates and impairment in the well-being of people with DM, leading to poor psychological and medical outcomes [38]. Therefore, psychological problems, such as diabetes-related emotional distress, depression, anxiety, and stress are common among adults with DM and are associated with sub-optimal self-management, diabetes-related complications, reduced quality of life, and increased health care costs [18]. As reported by Jones, Vallis and Pouwer: "maintaining or achieving good psychological well-being and quality of life is an important outcome of diabetes care in its own right" [39, p.2]. In the 1970s, the definition of quality of life showed similarities with the definition of stress. Since then, definitions have shifted their focus on people's subjective perceptions of the important elements of their life and how they experience them [40]. The way through which individuals interpret and experience the events of their life—in terms of stressful or pleasant—affects how they consider their quality of life. Wenger, Mattson, Furberg, and Elinson (1984) defined quality of life as "an individual's ability to function and derive satisfaction from a variety of roles" [41, p.908], based on their functional capacity, perceptions and symptoms, as well as their consequences. Indeed, the concept of quality of life has become an important key goal of health outcomes and care; however, this term has changed over the past years, assuming different definitions and at the same time other terms—besides the quality of life—such as well-being, satisfaction and health status were and are used interchangeably [40]. According to the recent definition of quality of life reported by the World Health Organization (WHO), it refers to "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [42]. A common consensus regarding the definition of quality of life is still mostly debated and has not yet been reached; however, the majority of researchers refers to the concept of quality of life as a multidimensional construct, including psychological, social and physical well-being and they refer to the individual's subjective consideration of his or her well-being instead of the perception of it by the health care professionals [40]. In addition to the construct of quality of life, the construct of health-related quality of life came into use. Walker and Rosser define the quality of life in the medical setting as "a concept encompassing a broad range of physical and psychological characteristics and limitations, which describe an individual's ability to function and to derive satisfaction from doing so" [43, p.383]. Therefore, the issues associated with the attribution of a common definition of quality of life is often solved using the psychometric approach, thereby operationalising the construct as a single score or a set of factors that emerged in a questionnaire, similar to the definition of the construct of intelligence with a score through the Intelligent Quotient (IQ) test [44]. Taking into consideration the above-mentioned definition, the assessment of the quality of life among people with DM should be developed using self-report questionnaires and should cover the pivotal domains of daily functioning referring to the treatment regimen, physical, mental, and social factors [40]. In the context of DM, relevant domains associated with quality of life may encompass diabetes-related emotional distress, physical and social functioning, psychological state, the perceived burden related to diabetes management, treatment satisfaction and overall perception of well-being [45]. Concerning these above-mentioned definitions, the term health-related quality of life will from now on be used throughout the dissertation.

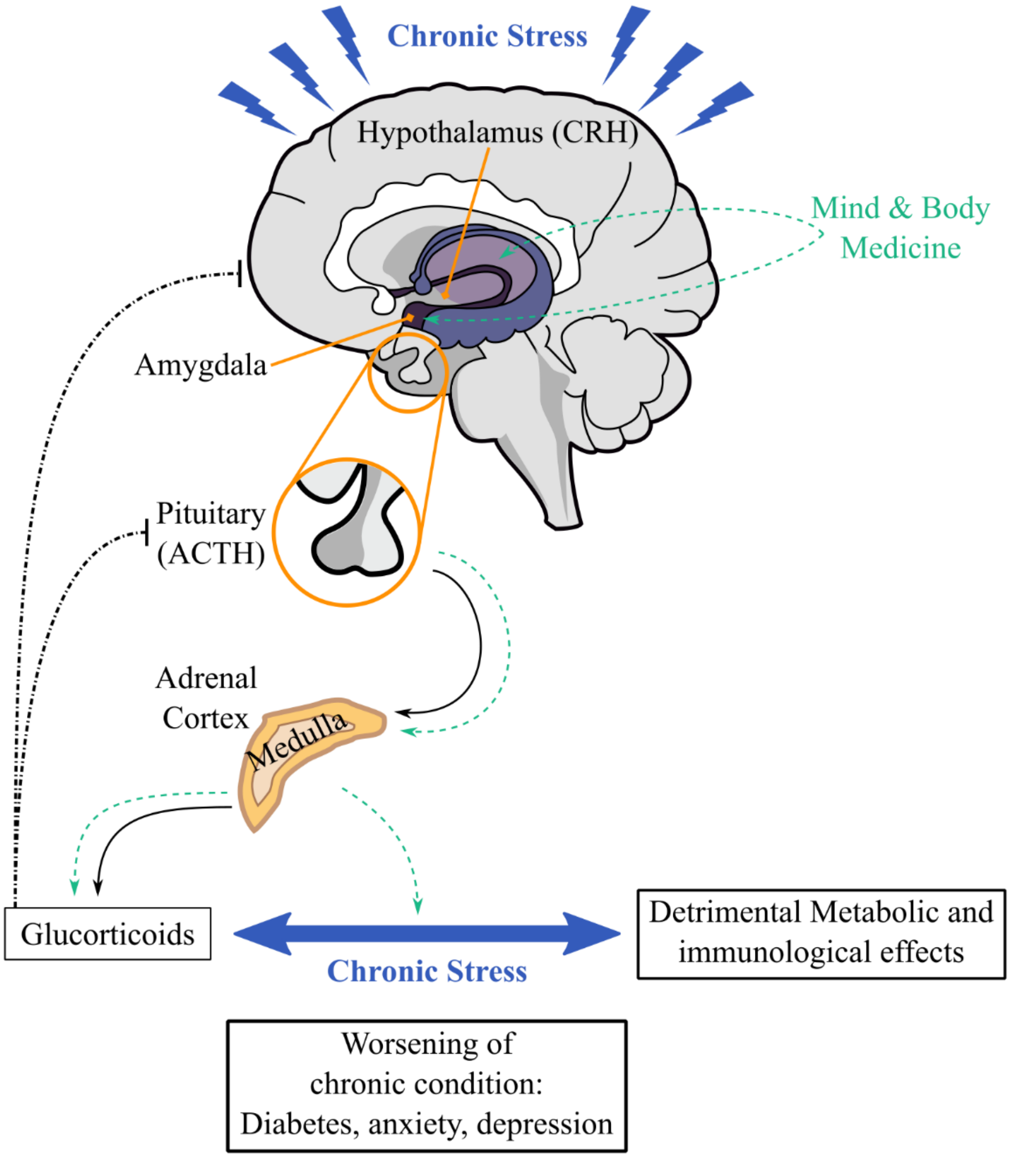
1.2 The *dynamic interaction* between psychosocial symptoms and glycaemic control in diabetes: A neuro-affective perspective

Experiencing anxiety, depression and/or stress symptoms cause lower adherence rates and impairment in the well-being of people with DM, thus, involving poor self-care behaviours, reduced health-related quality of life, and poor metabolic outcomes [46], such as unbalanced glycaemic levels (i.e., not within the optimal range of glycaemic level). DM—

as already stated above—is a metabolic disease, which is associated with dysregulation of several systems within the body, comprising cardiovascular disorders, modified immune system and central nervous system functions [47]. One of these central nervous system dysfunctions includes the activation of the HPA axis in DM. Interestingly, a relatively recent study found that augmented central drive at or above the level of the hypothalamus is responsible for the HPA hyperactivation in DM [47]. The hyperactivity of the HPA axis entails the increase of plasma glucocorticoids levels in people with DM, which can in turn negatively influence the glycaemic control [48] and, thus, the management of the disease itself. In this regard, the stress associated with diabetes management and the related self-care behaviours further activate the HPA axis, thereby leading to excessive stress response [49]; indeed, other authors stated that DM is related to impaired stress responsiveness [47]. The response of the body to stressful situations is usually adaptive since the resulting increases in heart rate, blood flow and respiratory rate enable people to cope with stressful events [50]. Stressors identified via the primary sensory organs create signals, which run through mediating systems found in the amygdala, limbic system, and prefrontal cortex [51]. The function of these regions is to process and examine stress-related information, and in turn, provoke responses via the regulation of the HPA axis [51]. The HPA axis is composed of a set of structures for coping with stress, which stimulates the release of the stress hormones such as adrenaline, noradrenaline, and cortisol from the cortex of the adrenal glands, and through locus coeruleus-norepinephrine (LC-NE) activity and other effector systems. All these hormones cause an augmented level of available energy, in which the first two hormones (i.e., adrenaline and noradrenaline) also stimulating the release of glucose in the muscles [50]. As a reaction to a stressor the hypothalamus releases corticotropin-releasing hormone (CRH), which acts on the pituitary gland, triggering the release of adrenocorticotropin (ACTH) into the bloodstream. Consequently, while experiencing stress, the HPA axis becomes critically engaged through its role in activating the release of glucocorticoids, cortisol in human beings, which are produced by the adrenal cortex [52-54]. The glucocorticoid is a catabolic hormone, whose main role is to increase the energy levels confronted with a stress event, which directly influences the metabolism of carbohydrates and lipids [52,53]. Cortisol has the role of using negative feedback to extinguish the stress response after the perceived threat has passed, affecting the pituitary and hypothalamus activation levels [54]. The hippocampus, which is the “final stop” of cortisol, is the last station of the stress response, responsible for the cessation of the emergency alert [55]. Short-term stresses increase the activity of the immune system, thereby stimulating cells and cellular products, by protecting the body from foreign microorganisms (e.g., bacteria and viruses) [50]. However, human beings usually cope with short-term stress rather than with long-term stress: short-term stress protects the immune system, long-term stress impairs it. Indeed, long-term activation of the stress system increases the risk of heart disease, obesity, and depression: chronic stress can interfere with memory, increase or decrease appetite, cause sleep problems and lead to mood disorders [50]. A chronic increase of cortisol can have deleterious consequences, resulting in, amongst other things, insulin resistance. People with DM already usually experience heightened levels of stress–thus showing an already acute HPA axis–which can cause higher blood sugar levels, which in turn leads to a higher risk of developing diabetes complications and affects their emotional health [47]. The persistent activation of the HPA axis can cause dysregulation in such axis, thereby leading to the onset of depressive symptoms, such as the psychomotor slowdown, already identified in patients with DM [56,57]. Accordingly, studies have found that there are notable similarities between the principal components of depression and the behavioural and neuroendocrine responses to stress. Indeed, depressive episodes usually emerge in the light of significantly stressful life events [58]. In this regard, in cases of depression there is a deficiency in the negative feedback loop, notwithstanding high levels of circulating cortisol, thus involving an excessive activity of the HPA axis [58]. The literature suggests several possible physiological mechanisms to explain the onset of depressive symptoms in DM, which can then interfere with glycaemic levels, such as Haemoglobin A1c (HbA1c). For instance, studies suggest that the effects of insulin deficiency on the metabolism of neurotransmitters may be at the basis of both depression and chronic high glycaemic levels, which in turn have potentially inhibiting effects on the HPA axis [59,60]. A relatively recent longitudinal study also suggested a *"dynamic interaction"* [61, p.952] between depressive symptoms and HbA1c levels, in which depressive symptoms may be risk factors for the increase of HbA1c levels and vice versa [20,61]. Then, experiencing depression predicts together with diabetes-related emotional distress, medication adherence, quality of life, diet as well as physical activity [62]. Considering these findings, one can assume bidirectionality between psychological and medical effects, meaning that they influence one another. A line of research supports the hypothesis that an increased risk of depression is a consequence of the onset of DM [63]. Together with depression, further symptoms often experienced by people with DM–as already stated in the above paragraph–are related to anxiety. Anxiety, indeed, shows the same neurobiological basis of depression: an altered function of the HPA axis has also been identified in people with anxiety [58]. Depression and anxiety are generally considered together since the neural circuits involved can be difficult to distinguish, there is high comorbidity and highly overlapping symptoms such as insomnia, irritability, and difficulty in concentrating and in sleeping [58]. In the context of DM, anxiety and depression can have an impact on how individuals perceive and evaluate their health-related quality of life and influence the course of DM, such as the presence of poor glycaemic control and treatment non-compliance [64]. Anxiety and depression represent relevant domains of the broader construct of health-related quality of life [65]. Therefore, the combination of anxiety and depression symptoms in people with DM is associated with a lower health-related quality of life in comparison to people with DM but without anxiety and depression symptoms [66]. A quite recent longitudinal study investigates the bidirectional association between anxiety, depression symptoms and health-related quality of life among people with DM [66]. The authors pointed out negative bidirectional associations between these above-mentioned variables in people with DM, thereby showing a synchronously evident relationship between changes in anxiety, depression, and health-related quality of life. More specifically, this study highlighted that anxiety and depression symptoms are widely common in people with DM and health-related quality of life is sub-optimal in most of them [66]. Therefore, the authors stated that a pivotal clinical implication is that decreasing anxiety and/or depression symptoms can significantly improve the health-related quality of life in people with DM, similarly, improving the health-related quality of life can prevent the onset of anxiety and depression symptoms while they manage their DM [66].

Overall, one can assume the presence of a complex interplay between these psychosocial and medical factors during diabetes management, meaning that they influence one another. In line with the above, biochemical modifications related to the onset of DM, such as the arousal of the nervous system as the HPA axis, can lead to an increased risk of developing depression, anxiety and/or stress in people with DM compared to the general population [67,68]. As such, together with the risk resulting from the above heightened neuro-affective activity, also the psychosocial burden of managing DM can entail the risk of developing stress, depressive and/or anxiety symptoms [68], which in turn can affect the health-related quality of life. Accordingly, DM demands people to develop and achieve appropriate coping strategies in support of their well-being. For example, Mind and Body Medicine (MBM)—which will be discussed in the next Chapter—focuses on the interaction between brain, mind, body, and behaviour, which in turn influences the well-being [69]. MBM has the role of maintaining stress hormone levels within their normal range, which can also promote the release of CRH and ACTH by helping to relax the mind [69]. This approach encourages self-management, self-care, self-regulation, and self-awareness, by emphasising healthy coping through evidence-based strategies, such as meditation, yoga and relaxation [69]. Figure 1 shows the graphical representation of the HPA axis regulation functionality in the context of chronic stress, which has been adapted from Figure 1 of [69].

Figure 1. Graphical representation of the HPA axis regulation functionality in the context of chronic stress (adapted from Figure 1 of reference 69)



1.3 Coping with diabetes

Beeney, Bakry, and Dunn showed that people experience emotional distress at the time of diagnosis for DM, with a varied range of emotions such as anxiety, shock, anger, guilt, and/or denial [17,61]. People with DM usually deny their diagnosis, and this avoidance can be a risk factor for poor adherence and subsequent long-term complications [17]. Indeed, denial influences their ability to cope with the DM's daily demands such as monitoring their disease, following self-care behaviours and, thus, managing their conditions [70-72]. The non-acceptance of the diagnosis and of those tasks related to the management of DM, such as taking prescribed medications and monitoring blood glucose levels, can lead to poor treatment adherence and diabetes self-management [72]. Accepting life with DM is rather difficult and can take up to a year: indeed, studies indicate that in most people with DM the emotional balance is restored within a period of some months to a year after the diagnosis [17,73], following which they can begin integrating DM into their lifestyle. Furthermore, the possible onset of diabetes complications such as cardiopathy or retinopathy can provoke an in-depth psychological response, which can range from anger and guilty to apathy and depression [17]. In this regard, people with DM are more likely to stop their self-care behaviours [17] and this can entail poor disease outcomes, in medical and psychosocial terms. When clinical recommendations for effective self-care are particularly challenging to maintain, and the associated barriers (i.e., non-adherence and treatment non-compliance) appear to be difficult to untangle, the use of good intentions is not sufficient to support effective diabetes management [46]. Therefore, coping strategies turn out to be difficult to adopt and a person's capacity to self-manage their DM deteriorates. Lazarus and Folkman defined coping as "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" [74; p.141]. In other words, coping allows individuals to use several skills to manage stressful situations and conditions; indeed, coping involves the adoption of various behaviours to prevent, avoid, or manage emotional stress aimed at maintaining psychosocial adaptation when encountering stressful events [75]. Lazarus and Folkman's approach is process-oriented—not trait-oriented—which means that the strategies that people adopt to cope with life events can be modified over time [74]: it, indeed, includes direct coping behaviours. These authors identified two main types of coping: problem-oriented coping and emotion-oriented coping. In problem-oriented coping, the individual has the principal function of solving problems and it is more used when the stressor is perceived as potentially modifiable. In the context of DM, problem-oriented coping strategies is usually used for managing eating problems. While emotion-oriented coping is more useful when the individual perceives the experience of such stressor or situation as impossible to change [74]. These latter strategies can contribute to better medical and psychological outcomes, ameliorating self-care behaviours [75]. Diabetes educators play a relevant role in the identification of persons' motivation to change their behaviours by helping them to set behavioural goals through a careful process and guiding them in confronting their barriers [46]. The American Association of Diabetes Educators (AADE) has identified seven self-care behaviours, critical for effective diabetes management [76], which have been included in the National Standards for Diabetes Self-Management Education. These self-care behaviours refer to the framework of patient-centred diabetes management [5]: healthy eating, being physically active, monitoring of blood glucose levels, adhering to prescribed medications, adequate problem-solving skills, risk-reduction behaviours and healthy coping. Healthy coping is a construct that encompasses several interrelated psychosocial dimensions, namely diabetes-related emotional distress, distress (subsuming depression, anxiety, and stress symptoms) and mental well-being (encompassing health-related quality of life, positive attitudes, and social support) [46]. Psychosocial factors have an impact on health-related quality of life and often influence chronic disease outcomes; for this reason, the healthy coping construct was included, in line with the awareness that psychological distress affects the health-related quality of life of people with DM and, thus, affects their motivation to keep their chronic disease under control [46]. The AADE guidelines introduced the healthy coping construct to identify healthy coping strategies for reducing these symptoms and improving the well-being of adults with DM [76]. More specifically, AADE suggests some strategies to cope with the life stresses and the challenges of managing DM, such as meditating [76]. In this regard, the MBM interconnects features of ancient traditional healing methods—which have since become evidence-based research, such as Mindfulness-Based Interventions (MBIs)—with those modern biomedical models to develop an integrated approach to healthcare [77]. In most studies, researchers stated that the reaction of the mind when encountering, for example, stressful events influence the health of the body. However, this definition is not quite appropriate since mind and body represent a single entity, in which health has an impact on the mind/body as a whole [77]. In line with this, Jung stated that "the separation of psychology from the premises of biology is purely artificial, because the human *psyche* lives in indissoluble union with the body" [78, p.1].

MBM techniques are mainly managed by the individual himself/herself during their treatment care and they are often deployed for treating chronic conditions and psychosocial distress. Tightly linked to the MBM approach are the concepts of self-regulation and self-awareness: indeed, one of the most used techniques is mindfulness practice, which induces the individual to be aware of the present moment and thus of the feelings that mind and body release. Mindfulness-Based Interventions (MBIs) have shown promising results in mental health applications [79,80]. MBI was also applied to chronic conditions such as DM research, and encouragingly, evidence pointed out the psychological beneficial effects of these interventions in people with DM. MBI has a prevention role in DM, in particular for the alleviating of depression and anxiety symptoms, and diabetes-related emotional distress as well as for supporting the health management of their disease [81,82]. Several studies demonstrated the efficacy of mindfulness practices in treating depressive symptoms of people with DM [83,84]. One study that applied MBI showed the effectiveness of these techniques in decreasing stress, anxiety and depression symptoms in people with T1DM [85], and another study highlighted how MBI allows improvements in feelings of worry and thought suppression in people with T1DM and T2DM [86]. In light of this, other studies have been carried out, highlighting that MBI can improve the psychological well-being and thus the health-related quality of life of people with DM [87]. Regular mindfulness practice has been linked to a decrease in chronic stress, which in turn has a beneficial effect on metabolic control [87]. For example, a quite recent study used the 8-week Mindfulness-Based Stress Reduction (MBSR) program—one of the relevant MBIs and most used in clinical and research settings—to investigate the effect of that program on glycaemic control and psychological distress in people with T2DM [88]. More specifically, the authors found lower HbA1c levels as well as lower levels of depression, anxiety and diabetes-related emotional distress; interestingly, these levels were also maintained at follow-up, namely one month after the end of the intervention [88]. A more recent type of MBI is the Mindfulness-Based Cognitive Therapy (MBCT), which has been developed and firstly deployed to people with depression [89]. MBCT represents a summary of MBSR and Cognitive Behaviour Therapy (CBT), and it is now applied to different people with chronic conditions. Studies have found that MBCT was effective in reducing symptoms of distress, depression and anxiety [90]. Indeed, an RCT study showed that after post-intervention the MBCT program allows a significant decrease of anxiety and depression symptoms, and perceived stress in people with both types of DM, with particular benefit to their health-related quality of life [91]. Another RCT study had the aim of evaluating the above-mentioned symptoms in people with T1DM, using the MBCT program [92]. The authors found a decrease of such psychological symptoms and notably these low levels are seen to be sustained for up to six months, without any other interventions. These findings are in line with the few studies that evaluate the long-term effectiveness of the MBCT program in people with T2DM and other medical conditions, such as inflammatory rheumatic joint diseases and asthma [93-95]. Therefore, mindfulness practice—also deployed in digital health applications—ameliorates and improves psychological well-being, the health-related quality of life by diminishing negative thoughts and emotions such as depression, anxiety, stress and emotional distress deriving from the management of chronic disease in favour of promoting awareness in the present moment and engagement in self-care behaviours.

CHAPTER 2: CONVERSATIONAL AGENTS IN DIABETES HEALTHCARE

The term *health* is defined by the World Health Organization (WHO) "as not merely the absence of disease or infirmity but a state of complete physical, mental and social well-being" [96]. Healthcare and how people engage with their health and well-being are going through a period of rapid change. For instance, the Internet allows people to access enormous amounts of information regarding healthcare, medical support, and diseases [99]. Moreover, these changes include the gathering and analysis of new types of data, such as biomarkers, as well as behavioural, environmental, and economic data [100]. These changes further encompass the introduction of novel technologies, such as mobile health, tablets, wearables [100]. In this regard, the European Commission describes eHealth (electronic health) as "...the use of modern information and communication technologies to meet needs of citizens, patients, healthcare professionals, healthcare providers, as well as policymakers" [98]. An underlying field of eHealth, Behavioural Intervention Technologies (BITs), applied via mobile phones or Virtual Coaches (VCs), are now playing a relevant role in the promotion or the decrease of specific behaviours for people with chronic diseases such as with Diabetes Mellitus (DM) [101]. VCs or conversational agents are particularly used for preventing, promoting, and supporting people with DM. Indeed, VCs or conversational agents are mainly applied in healthcare, a domain of the Human-Computer Interaction (HCI) field. The IBM Cloud Education defines conversational agents, also referred to as conversational Artificial Intelligence (AI), as "technologies, like chatbots or virtual agents, which users can talk to. They use large volumes of data, machine learning, and natural language processing to help imitate human interactions, recognising speech and text inputs and translating their meanings across various languages" [97]. It is worth noting that the concept of the *active patient* or the *active user* has become central to the development of these digital health solutions. The user, indeed, is at the centre of the design process: he or she is actively involved in decisions regarding their healthcare and, in this specific case, in their diabetes management.

2.1 Behavioural Intervention Technologies (BITs) for diabetes

BIT, an underlying field of eHealth interventions, is aimed at supporting people in changing their behaviours and cognitions associated with mental health, physical health and well-being using digital solutions [101]. The term BIT is preferred over eHealth since this latter term includes a broader field of medicine and informatics, not primarily addressed to behaviour change interventions [102]. Eysenbach defines eHealth as "...an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve healthcare locally, regionally, and worldwide by using information and communication technology" [103, p.1]. For example, eHealth solutions refer to clinical decision support programs, electronic health records, and informatics to support medical education [104].

BIT, on the other hand, focuses on the development of behavioural and psychological intervention strategies using computers (called Web interventions or Internet interventions), sensors for health monitoring, social media, serious game, virtual reality, and mobile health (also called mHealth interventions) [101,104]. Up to now, BITs have been employed to implement behaviour change strategies, which comprise self-monitoring, self-assessment, goal setting, feedback, problem-oriented, and psychoeducation [104]. In this process, a multidisciplinary approach is requested, and, thus, the design team should include professionals from multiple disciplines, such as psychologists, computer scientists, physicians, software engineers, etc. BITs can overcome many barriers associated with healthcare access, by reaching a wide range of people who otherwise would not have access to care [104,105], in particular through the use of mobile health (mHealth).

2.2 Behavioural Intervention Technologies (BITs): the use of Mobile Health (mHealth) in diabetes

mHealth is a subset of eHealth [106,107] and is particularly suitable to be used in BITs as mobile devices are more familiar and always "at hand". The framework of mHealth will from now on be central in the present discussion, with a specific focus on the DM field. The Global Observatory for eHealth (GOe) of the WHO defined mHealth "as medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices. mHealth involves the use and capitalization on a mobile phone's core utility of voice and short messaging service (SMS) as well as more complex functionalities and applications including general packet radio service (GPRS), third and fourth generation mobile telecommunications (3G and 4G systems), global positioning system (GPS), and Bluetooth technology" [108]. Most mHealth BITs use the SMS system or messages within applications and social media, such as Telegram or WhatsApp. Other mHealth BITs use health diaries and virtual health coaching [107]. Others rely only on voice messages or videos [109], and on automated messaging to deliver tailored information or feedback [104]. In the case of social media communication channels, such as Telegram, WhatsApp or the SMS system [e.g., see 110], their usage is widely common in the general population and, thus, users have already incorporated them in their daily lives. Conversely, as regards mHealth applications, their usage raises more issues. For instance, two-thirds of people who downloaded a mHealth application used it only once [111]. Indeed, the change of habitual behaviour requires an individual to invest a large amount of time and, thus, to benefit from this technology: users should use applications for a sufficiently long period to be able to incorporate them into their daily lives [111]. Furthermore, studies used two types of intervention through the SMS dialogue: the system-initiated dialogue and the patient-initiated dialogue. The time range of messaging varies from once a week to five or more times during the day, and the timing of messages can also be linked to people's work activities or when they are experiencing more difficulties [111]. Lastly, a relevant dimension in mHealth BITs is the concept of personalisation. More specifically, studies have focused on the use of highly personalised messages, tailored to the individual's needs, whilst other works have employed broader suggestions using text messages [104].

BITs via mHealth have largely been deployed for behaviour changes in DM to provide, in particular, regular self-monitoring of their blood glucose levels and interactions between patients, family members and health care clinicians [106]. mHealth could improve hypoglycaemia incidence, could promote and prevent the health-related quality of life, and increase the capacity for diabetes self-management [106]. Self-management regarding their disease and the related tasks has the function of engaging individuals in their long-term care, which augments their self-efficacy, and has the potential to reduce health care costs [106]. As already pointed out in Chapter 1, the behaviour in diabetes management is the cornerstone for the development and maintenance of complex healthy behaviours. mHealth is well-fit for diabetes management since it can provide guidance and support for a healthier diet [106], physical exercise [112], adherence to the prescribed medication [113], and, in particular, self-monitoring of glycaemic control [113]. Four recent meta-analyses evaluated mHealth interventions aimed at supporting specific aspects associated with diabetes management [114-117]. More specifically, one study has evaluated the efficacy of mHealth in improving glycaemic control among adults, children, and adolescents with T1DM [117]. Another study has analysed the efficacy of mHealth interventions for people with T2DM, reporting the beneficial effects on self-efficacy, self-care activities, health-related quality of life and glycaemic control [114]. The other two works have both evaluated the efficacy of mHealth interventions on glycaemic control [115,116]. Ferigerlovà Oussalah, Zuily, and colleagues [116] only involved people with T1DM, while Bonoto, Piassi Godói, Lovato and colleagues [115] included people with T1DM or T2DM and further evaluated health-related quality of life as a secondary outcome. In this last study, the authors found an overall efficacy of these interventions in diminishing HbA1c levels compared to the control group, as well as in increasing the perception of health-related quality of life and self-care behaviours [115]. Notwithstanding these promising results, of 14 mHealth applications deployed for DM, only 6 (i.e., Dexcom Share, Glooko, Accu-Chek Connect, Dario, Livongo, and Telcare) have been regulated and approved by the Food and Drug Administration (FDA) [106]. Overall, these mHealth applications are mainly applied to the Continuous Monitoring of Glucose (CGM). Contrary to these above-mentioned mHealth applications, the BlueStar diabetes coach (powered by WellDoc) is the first application deployed for supporting the behaviour of people with T2DM. BlueStar is prescribed by diabetes clinicians, and, in 2017, the FDA further approved a non-prescription version as mobile prescription therapy (MPT) [118,119]. In particular, the BlueStar application delivers real-time automated messages—in educational, clinical and behavioural forms—when considering the patients' report of several data (e.g., HbA1c levels, medications and lifestyle behaviours) [118]. Additionally, the patient can interact through a Web-based portal with diabetes clinicians in a secure mode; in turn, these answers can be converted into a summary report regarding self-monitored data with treatment guidelines [118]. Another application for T2DM, called Monica, has the function of providing automated patient-specific feedback messages in response to self-reported glucose, blood pressure, weight, and steps, with the inclusion of some alerts for diabetes clinicians [120]. Comparing these two applications mentioned above (i.e., BlueStar and Monica), BlueStar had a larger sample size and involved multiple intervention arms, thus resulting in a larger effect regarding the decreasing of HbA1c between the intervention and the control group, while Monica findings' showed a less clinically significant difference in the diminishing of HbA1c levels between the two groups [118,120]. Another RCT study, that used an SMS-based intervention for people with T1DM or T2DM, was primarily aimed at delivering educational and motivational text messages regarding people's self-management and lifestyle changes, which were personalised based on timing, duration, individuals' goals, and culture/ethnicity, also containing healthy suggestions on how to stop smoking, chiropody, and insulin management [110]. A 2017 qualitative study suggested that mHealth for diabetes self-management augmented the individual awareness of their general condition, thus emphasising feelings of distress and potentially entailing a negative response to intervention [121]. For example, the Dulce Digital application is one of the most relevant RCT studies of the United States, performed among Hispanic adults with T2DM, with low-income and no health insurance [122]. Dulce Digital provides culturally tailored interventions regarding diabetes self-management using the SMS system. The authors found that this type of intervention was effective in improving glycaemic control for six months compared to the usual care group. More specifically, results showed that diabetes-related emotional distress moderates the effect of the Dulce Digital intervention (experimental group) as opposed to the usual care group on changes in glycaemic control over time [122]. Interestingly, the authors found that participants within the Dulce Digital group, who showed moderate and high diabetes-related emotional distress at baseline, manifested a decrease in HbA1c over time compared to those with no or low diabetes-related emotional distress [122]. The authors speculated that excessively high diabetes-related emotional distress levels may inhibit patient engagement, while negligible diabetes-related emotional distress levels may fail to incentivise change [122].

Overall, mHealth BITs are specifically focused on the monitoring of blood glucose levels, diet and physical activity; and few mHealth BITs are developed for increasing health-related quality of life, for diminishing diabetes-related emotional distress symptoms, and for changing maladaptive behaviours into more healthy ones. mHealth BITs' interventions for self-management and psychoeducation generally provide holistic frameworks, such as mindfulness practices, and are developed within Behavioural Change Theories (CBT), such as Social Cognitive Theory [123,124], Theory of Planned Behaviour [125], Information Motivation Behavioural Skills Model [120], motivational interviewing [124], or Transtheoretical Model of Change (TTMC) [126]. This latter theoretical model defines motivation as a continuum rather than as an all-or-nothing construct, in which the individual can move across five stages (i.e., pre-contemplation, contemplation, preparation, action, maintenance), thus moving forward or backward. TTMC has been widely deployed in designing digital health solutions to predict or evaluate behavioural changes in physical activity [127], diet [128], glycaemic control [129] and to ameliorate adherence to medications in adults with risk factors for the development of cardiovascular diseases [130,131]. TTMC is the theoretical framework of the present thesis work, and its stages are summarised in Table 1.

Table 1. Summary of the five stages associated with Transtheoretical Model of Change [132]

Stages	Description	Motivational Tasks
Pre-Contemplation	At this stage, individuals have no intention of changing their behaviour in the foreseeable future; they are unaware, or they present a lack of awareness regarding their problem.	Increase awareness of the problem and possible change (provide information and feedback).
Contemplation	Individuals are aware that a problem exists and are seriously thinking about overcoming it, but they have not yet committed to acting. Serious consideration of problem resolution is the central element of this stage.	Helping to assess costs and benefits, trying to encourage change, sometimes increasing the sense of self-efficacy.
Preparation	The combination of intention and behavioural criteria is pivotal. At this stage, individuals are intending to act in the next month and have unsuccessfully acted in the past year. Individuals who are prepared for action, report some small behavioural changes.	Helping to find the best way to make changes.
Action	Individuals modify their behaviour, experiences, or environment in order to overcome their problems. Individuals are classified as being in the action stage if they have successfully changed their behaviour for a period of between 1 day and 6 months.	Helping to take the necessary steps through behavioural interventions in order to implement the behavioural change.
Mantainance	Individuals are working to prevent relapse and consolidate the gains attained during an action. Stabilising behaviour change and avoiding relapse are the hallmarks of this stage.	Avoid relapses through monitoring the behaviour.

2.3 Virtual Coaching in diabetes healthcare: a user-centred design approach

Conversational agents or chatbots are generally computer programs that simulate conversations with users [133], by mimicking a human being, and they are not necessarily aimed at a specific task. Conversational agents can be deployed as means for motivational or behavioural coaching: in this case, a widely use term in the literature is *Virtual Coach* (VC). VCs are often developed within chat applications, websites, social media, or mHealth applications, and they can interact using text messages, images, audio tracks, and video clips. Virtual Coaching is relatively new to the field of healthcare and is primarily aimed at ameliorating the interaction between patient and digital solutions through the use of a more intuitive and personalised user-systems interaction [134]. The personalisation of communication between the user and the system is fundamental to healthy user engagement and compliance, required to achieve long-standing behavioural changes and adopt a healthier lifestyle [134]. There are several important reasons why the wide use of VCs can be key in healthcare. For example, the ease of the interaction, the intuitiveness of dialogues compared to the use of applications, which could create difficulties for elderly people [135]. While new versions are not provided to regularly update VC content, the VC can be trained ad hoc, based on real user data collected in previous studies [135]. The concept of scalability, which means that the use of VC allows for interaction with a greater number of users at the same time, also decreasing waiting times for assistance to zero, in comparison to the face-to-face intervention [135]. VCs further allow greater user accessibility, a reduced cost to healthcare systems, and relatively quick development of them [135]. VC can engage in real conversation with people, and they can understand an individual's messages and context in order to answer appropriately to the topic of the conversation. VCs can be *rule-based*, which means that a set of predefined options for answers are provided by design [135,136], such as VCs for booking appointments or holidays; while the *smart VCs* are based on more dynamic and free text answers [135,136], which means that users can respond with free text or natural language, that the VC will be able to process and understand by leveraging on previously acquired information and Artificial Intelligence (AI) techniques. These smart VCs are a form of AI since they rely on Machine Learning (ML) algorithms [135,136]. Lastly, VCs are suitable for assisting the individual in behavioural change pathways [135]. Indeed, in the healthcare field, VCs have become pivotal instruments for supporting behavioural change in self-management of people with DM, given the fact that they aim to provide personalised support and improve intervention outcomes [137]. VCs in the field of DM are mainly applied to the monitoring of glycaemic levels, diet, physical activity, such as Wellthy, implemented within a mHealth application [138]. More specifically, a recent systematic review regarding the VCs developed for healthy management of DM has identified two VCs: one designed for DM diagnosis [139] while the other comprised a variety of chronic diseases, including DM but with a specific focus on psoriasis, and its principal goal was the disease monitoring [140]. Indeed, the support to patients' monitoring is the most common feature within VCs for DM [141], as was already highlighted in the previous paragraph regarding mHealth applications. As such, it is worth highlighting the relevance of implementing VCs for supporting people with DM in their healthy coping, and to increase their psychosocial well-being. For example, a study developed a VC for elderly people with T2DM, with the deployment of a voice speech of Google Home, intending to improve healthy coping strategies [142]. The individual can interact with the VC through this voice speech, which can initially screen depression symptoms, administering the Patient Health Questionnaire-9 (PHQ-9) [143], and, subsequently, answer to him or her with appropriate and personalised suggestions concerning the monitoring and the maintenance of their blood glucose levels. Another study developed My Diabetes Coach program, which is a mHealth application with an embodied VC, called Laura, designed to support diabetes self-management in the home setting for 12 months [144]. Laura focuses on several modules, such as the monitoring of blood glucose levels, healthy eating, taking prescribed medications, physical activity, and the importance of foot care. Additionally, although this application includes a scale for assessing the health-related quality of life [144], no behavioural interventions are aimed at improving it. Despite these advances in the healthcare domain, few VCs were aimed at psychosocial support and thus for healthy coping interventions. VC approaches appear to lack the ability of managing the emotional needs of people with DM [145], since the only personalised feedback based on people data is typically related to the insulin dosage suggestions as well as to the CGM [146,147].

In this context, the levels of User Engagement (UE) and User Experience (UX) are pivotal aspects in the development of a personalised VC. UE is a multifaceted construct, which is associated with the quality of the UX, encompassing the individual's time, cognitive, affective, and behavioural investment during the interaction with a digital solution [148]. The UE construct does not cover only the user satisfaction: indeed, the ability to engage and maintain engagement during the interaction with a digital solution shows positive results in e-learning, web searching, and eHealth [148]. Indeed, long-standing engagement is promising in a DM prevention program through the use of a VC [23], engaging 69% of adults for the entire study and resulting in 8.98% weight loss [149]. Furthermore, in two other recent studies, adults with T2DM [150] and young adults with T1DM [151] reported feeling satisfied and engaged with a VC embodied in a mHealth application. In other works, people with DM reported an increased level of satisfaction in the interaction with the VC [152,153]. Indeed, VCs for people with DM help to promote self-care behaviours and behavioural changes [135]. For example, a recent review suggested that VCs for people with DM represent effective interventions for supporting their glycaemic control, also in the co-occurrence of standard care [154]. Therefore, VCs facilitate an overcoming of common barriers associated with adherence by delivering data-driven personalised support in real-time and being available at any time [155], hence allowing scalability.

2.4 User Experience in diabetes technology and its interplay with the user-centred design approach

User Experience (UX) is a crucial element, which intersects with UE. The International Organization for Standardization (ISO) [156] defines UX as the combination of users' engagement, desirability, pleasure, values, perceptions, emotions, beliefs, preferences, physical and psychological responses, accomplishments, and behaviours, which occur before, during, and after the use of a digital solution. The ISO further lists three elements that influence UX: the user's current state and previous experience, the system properties, and the usage context [156]. Therefore, understanding the needs of the users, their working environments, their interactions, and emotional reactions can assist the design process in the development of VCs from the UX perspective: the individual thus becomes an *active user* in this process [156]. Therefore, the ISO definitions necessarily emphasise on a *user*-centred design (UCD) approach, also called human-centred design or patient-centred design approach, which is an iterative paradigm focusing on the users and their needs at each step of the design process [157]. According to the definition proposed by the Interaction Design Foundation "UCD calls for involving users throughout the design process via a variety of research and design techniques to create highly usable and accessible products for them" [157]. This definition emphasises the need to make the interventions as user-friendly and effective as possible [158]. These approaches seek to understand the user's knowledge, skills, behaviours, motivations, cultural background, and organisational context, and they involve users iteratively throughout development [158].

Last but not least, the term UCD refers to those concepts of ethics and respect for personal autonomy in the decisions about their care [158].

As stated above, the user-centred design approach is pivotal in designing self-care technologies since it can also provide relevant information on UX. For instance, O'Kane argued that a good UX is more than just a desirable feature, it is intrinsically related to health outcomes, for instance in people with T1DM [159]. Indeed, studies have reported that higher levels of UX increase the effectiveness of digital health interventions addressing behavioural enhancements regarding T2DM self-management [150], diet [160], and physical activity [161]. Therefore, qualitative and/or quantitative analyses on UX can provide important information about the user's well-being. It is worth noting that the user should be at the centre of each phase of the design process in order to capture this information. Indeed, O'Kane pointed out the importance of the user-centred design approach in the designing of self-care technologies since this is pivotal for both the quality of individuals' health and the quality of individuals' lives [159]. Moreover, Verdozoto and colleagues stated that many systems are developed from the healthcare professional's point of view, thereby not integrating the user perspective regarding his/her health [162]. An interesting example is the use of Design Probes (DP), which is "an unobtrusive way of collecting data" [163; p.277] in order to investigate, identify and comprehend in depth the user's needs, experience, point of view, daily lives, and attitudes regarding self-care practices [163]. The final goal of collecting these data was to inform the design and development of an educational interactive eBook for children with T1DM [163]. Therefore, when developing digital interventions to support self-care, the process of co-design is pivotal for the achievement of both good UX and users' well-being.

2.5 Artificial Intelligence in the Virtual Coaching design

In *Artificial Intelligence: A Modern Approach*, Russell and Norvig define AI as "the designing and building of intelligent agents that receive percepts from the environment and take actions that affect that environment" [164]. AI covers several different sub-fields such as of computer vision, speech processing, reasoning, knowledge representation, machine learning, robotics, and natural language understanding [164]. The ML sub-field is aimed at developing, by implementing complex algorithms, expert systems able to forecast or classify new datasets based on datasets containing training examples sets [165].

In the development of a conversational agent based on AI, such as chatbots or VCs, three important concepts should be considered: *topics*, *utterances*, and *exchanges* [166]. Topics refer to the context of a conversation, which can be organised on high levels and divided into several branches. Utterances represent single statements within an exchange and are the elements that compose the whole conversation. Exchanges have the function to communicate information and they consist of two or more utterances. Each communication within an exchange is primarily influenced by both the topic and the previous messages [166]. In this regard, *intents* and *entities* within utterances are necessary for the interpretation of a digital conversation [166]. The intents are actions or purposes behind their utterances, and they generally refer to verbs. The entities, on the other hand, are objectives relevant to the goal of the user, and they generally refer to nouns. The interpretation of these two aspects and, thus, the user's input, allows a VC to obtain the necessary information for generating a proper answer [166]. Conversational AI-based agents leverage AI techniques, which allow them to process, understand and, consequently, craft response naturally [167]. These mentioned techniques come from the fields of Natural Language Processing (NLP) and ML. ML is a sub-field of AI, in which its algorithms increase their performance as long as training example are analysed through their features and (if necessary) supervision. Therefore, as the experience increases, the AI agent becomes better at recognising patterns and using them to make predictions. NLP is a methodology used in conversational AI and aimed at analysing language with the support of ML [167]. The NLP processes flow into a continuous feedback loop with ML processes in order to constantly augment the AI capabilities [167]. Before the ML approach, NLP and the related methodologies have undergone several modifications ranging from linguistics to computational linguistics to statistical natural language processing [168]. More specifically, NLP leverages these steps: input generation, input analysis, output generation

[165]. An input generation represents the action of the user, who provides input—texts or voice messages—through a website or an application. As regards input analysis, in the case of text-based data, conversational AI exploits Natural Language Understanding (NLU) to decode the meaning of the user's input and to derive his or her intention. Conversely, in the case of voice-based input data, conversational AI relies on the joint capabilities of automatic speech recognition and NLU to analyse the data. Output generation represents the action of Natural Language Generation (NLG), a component of NLP that responds to the user's input. Notwithstanding the wide and relevant use of AI methodologies, conversational AI-based agents, still being in its infancy, presents some challenges. A central challenge is the correct decoding of language input, whether text or voice; for example, accents, dialects, and background noise hinder the AI's comprehension of the input stream. However, another crucial challenge is the understanding of emotions, feelings, tone, irony, sarcasm, and thus the interpretation of the intended user meaning [165]. Moreover, a quiet debated issue is related to privacy and security. In particular, it is fundamental that VCs and mHealth applications are developed with high privacy and security standards, including the use of monitoring systems, making the users feel secure in using these digital solutions [165]. ML and NLU represent the techniques used in the development of Motibot, the VC discussed in the present work.

PART 2 – THE RESEARCH

CHAPTER 3. EFFICACY OF DIGITAL HEALTH SOLUTIONS FOR ADULTS WITH DIABETES

The present Chapter outlines the first study of the Ph.D. project: a systematic review and a meta-analysis[2] [169], which was approved and registered on the International Prospective Register of Systematic Reviews in March 2021 (PROSPERO; Registration Number: RD42021238090). This meta-analysis intended to provide relevant information gathered from Randomised Control Trial (RCT) studies regarding the efficacy of eHealth interventions among adults with Diabetes Mellitus (DM), considering both psychosocial and medical factors. Furthermore, the current meta-analysis had the objective of understanding and analysing whether digital treatments are mainly focused on glycaemic control or psychosocial symptoms in order to address future works on the treatments to be developed. In this regard, keeping in mind the advantages of VCs mentioned in section 2.2 of Chapter 2, the mobile health (mHealth) solutions represent valuable resources for delivering interventions to adults with DM in order to support them in their behavioural changes. In the literature, there is a lack of meta-analyses regarding the efficacy of these digital health solutions, which are aimed at supporting and guiding people with DM in achieving a healthier quality of life and in reducing diabetes-related emotional distress as well as symptoms of anxiety, stress, and depression. Altogether these symptoms, together with medical outcomes have a negative impact on DM due to poor adherence and reduced self-care behaviours.

[2]Bassi G, Mancinelli E, Dell'Arciprete G, Rizzi S, Gabrielli S, Salcuni S. Efficacy of eHealth interventions for adults with diabetes: A Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* 2021; 18:8982. doi: 10.3390/ijerph18178982.

Study 1. Efficacy of eHealth interventions for adults with diabetes: A Systematic Review and Meta-analysis

3.1 Aims

Most of the meta-analyses available in the literature are mainly focused on the efficacy of those digital health interventions whose main aim is to improve blood glucose levels, such as HbA1c. Notably, these studies considered psychosocial symptoms as secondary outcomes in the involvement of diabetes management. This consideration raises the need for studies investigating the impact of mHealth and VC solutions on psychosocial and medical factors among people with DM, in order to further ensure appropriate treatments tailored to their needs. Bearing all these aspects in mind, this is the first meta-analysis that provides evidence from RCT studies regarding eHealth interventions for adults with T1DM or T2DM, by considering both psychosocial and medical variables. More specifically, the aim of the present meta-analysis was two-fold. The *primary aim* was to evaluate the efficacy of eHealth interventions in diminishing diabetes-related emotional distress and symptoms of anxiety, stress, and depression, as well as in ameliorating people's health-related quality of life and HbA1c levels. The *secondary aim* was to investigate whether there are differences in the efficacy of eHealth interventions mainly aimed at providing psychosocial guidance *versus* those mainly aimed at improving glycaemic control. In reading this study, it is fundamental to bear in mind one key point: the bidirectionality approach of psychosocial and medical factors.

3.2 Materials and Method

Search Strategy

The present meta-analysis was carried out in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [170] and the Cochrane handbook for systematic reviews recommendations [171]. The search covered articles written solely in English and published in peer-reviewed scientific Journals from 2000 to 2021.

Articles were systematically searched via academic databases, such as Web of Science, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL), using a combination of free-text and Medical Subject Heading (MeSH) terms: *diabetes mellitus, eHealth, Mobile Health, mHealth, Telehealth, serious games, glyc*, glucose, HbA1c, anxiety, stress, distress, depression, quality of life, adults, randomized controlled trial, experimental, clinical*.

A manual search was also deployed to identify any other relevant articles not found through the above-mentioned databases. Each phase of the systematic review and meta-analysis, such as the search process, the full-text reading, the data extraction, and the Risk of Bias assessment was performed by the author of the present thesis together with other members of the research group. More specifically, two authors independently screened titles and abstracts for eligibility and collected potentially relevant articles through a double-blind process. Consequently, the others two reviewers read the abstracts selected in full text using again the double-blind process. Any disagreement regarding both abstract and full-text articles was discussed by consulting a third author until consensus was reached.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were defined together with the aims of the present study, using the PICOS framework (population, intervention, control group or comparison, outcome(s), and study type). The inclusion criteria were: *(a)* adults with T1DM or T2DM aged between 18 and 65 years, *(b)* RCT studies, which compare any eHealth interventions with any control group [e.g., no intervention group, waiting list, treatment as usual (TAU), active conditions], *(c)* psychosocial symptoms such as diabetes-related emotional distress, health-related quality of life, anxiety, stress, and depression, and, lastly, (d) the HbA1c levels.

On the other hand, studies that met any of these criteria were excluded: *(a)* women with gestational diabetes, *(b)* adolescents, children, adults with other medical or psychological disorders different from or comorbid to T2DM or T1DM, and *(c)* adults with prediabetes or at risk of developing DM.

Primary Outcomes

Primary outcomes refer to mean changes in both psychosocial (i.e., diabetes-related emotional distress, depression, anxiety, stress, and health-related quality of life) and medical measures (i.e., HbA1c levels). Time points included in this meta-analysis are endpoints–defined as the end of the eHealth intervention–and follow-up when assessed.

Secondary Outcomes

Secondary outcomes refer to the results of two different sensitivity analyses. One was developed to evaluate the efficacy of eHealth interventions primarily aimed at providing psychosocial support. The other sensitivity analysis was implemented in order to analyse the efficacy of eHealth interventions primarily aimed at improving glycaemic control. Intervention acceptability was assessed by analysing drop-out rates.

Data Extraction

Two reviewers carried out the data extraction, obtained from the full texts of the included studies.

In particular, data regards the first author's name, year of publication, geographical location of the study, population characteristics (i.e., sample size, gender, age, type of DM and its duration), type and length of eHealth interventions (e.g., Internet-based interventions or Web-based interventions, mHealth interventions), type of control condition (i.e., waitlist/no treatment, TAU, active), type of analyses carried out in the included studies [intention-to-treat (ITT) or per-protocol], drop-out rates, primary and secondary outcomes and the related instruments used to assess that specific outcome, means and standard deviations of each outcome measurement at baseline, endpoint and follow-up (when included). Lastly, if reported, the effect size with 95% Confidence Intervals (CIs) for every outcome in both study arms.

Quality Assessment

The quality of the study, namely Risk of Bias (RoB), was independently assessed by two authors considering the included RCTs and using the Cochrane's Risk of Bias tool version 2 (RoB 2.0) [172]. Every single study was judged based on the following domain-level judgments: randomisation process, deviations from the intended interventions (i.e., the effect of *assignment* to intervention, the effect of *adhering* to intervention), missing outcome data, measurement of outcome data and selection of the reported results. Every possible Risk of Bias judgments of the above-mentioned domains was mapped and rated as "low", "some concern" or "high", varying on whether the requirements were adequately fulfilled. A third author was contacted when encountering discrepancies between judgments. Reaching an overall judgment across all domains for a specific outcome occurs when every domain-level judgment has been evaluated, thus providing a synthesis of the whole study's quality assessment.

Data analysis

Statistical analyses were run using Review Manager Version 5 [173] and Comprehensive Meta-Analysis [25]. Primary and secondary outcomes at endpoint and follow-up were meta-analysed when at least three studies provided the necessary information.

Standardised Mean Difference (SMD) with 95% CIs were calculated and heterogeneity was assessed using I^2 statistics to determine whether variations between the included studies were by chance. The value is reported as a percentage of the overall variation across studies, which is defined by heterogeneity rather than by chance. In particular, values were defined as low (25%), moderate (50%) and high (75%), in which values greater than 50% indicates heterogeneity. In this regard, outcomes were analysed using a random effect model when $I^2 > 50\%$, whilst a fixed effect model was deployed when studies showed $I^2 < 50\%$. More specifically, a random effect model assumes that all the included studies allow differences across treatment effects, while a fixed effect model is based on the assumption that all studies are estimating the same treatment effect [174].

Odd Ratio (OR) with 95% CIs was calculated to evaluate intervention acceptability based on drop-out rates. Treatment drop-out might be given by a multitude of reasons beyond the treatment/intervention *per se*. Drop-out rates are, indeed, usually considered as a measure of treatment acceptability [175,176].

Publication bias was assessed by visually examining the funnel plot asymmetry and by using Egger's regression test [177,178]. The "Egger's test is a linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance" [179]. Moreover, publication bias will be identified when the *p*-value is not significant. The fail-sale number [180] was calculated when publication bias emerged and according to the following statement "fail-safe numbers are not necessarily the best way to approach publication bias, but they are a simple first step that can help identify whether more complex approaches are necessary" [181, p.464], the trim and fill procedures [180] were also run, thus further evaluating if the results remained invariant when accounting for publication bias.

Sub-group analyses were carried out based on T1DM *versus* T2DM, control conditions (i.e., waiting list/no treatment, TAU, active), the type of analyses (i.e., ITT *versus* per-protocol), and the type of eHealth intervention (e.g., Internet-based interventions or Web-based interventions, mHealth interventions).

Meta-regression was carried out when at least ten studies provided moderator data, such as participants' age, gender, diabetes duration (assessed in years), and the length of the intervention (assessed in weeks).

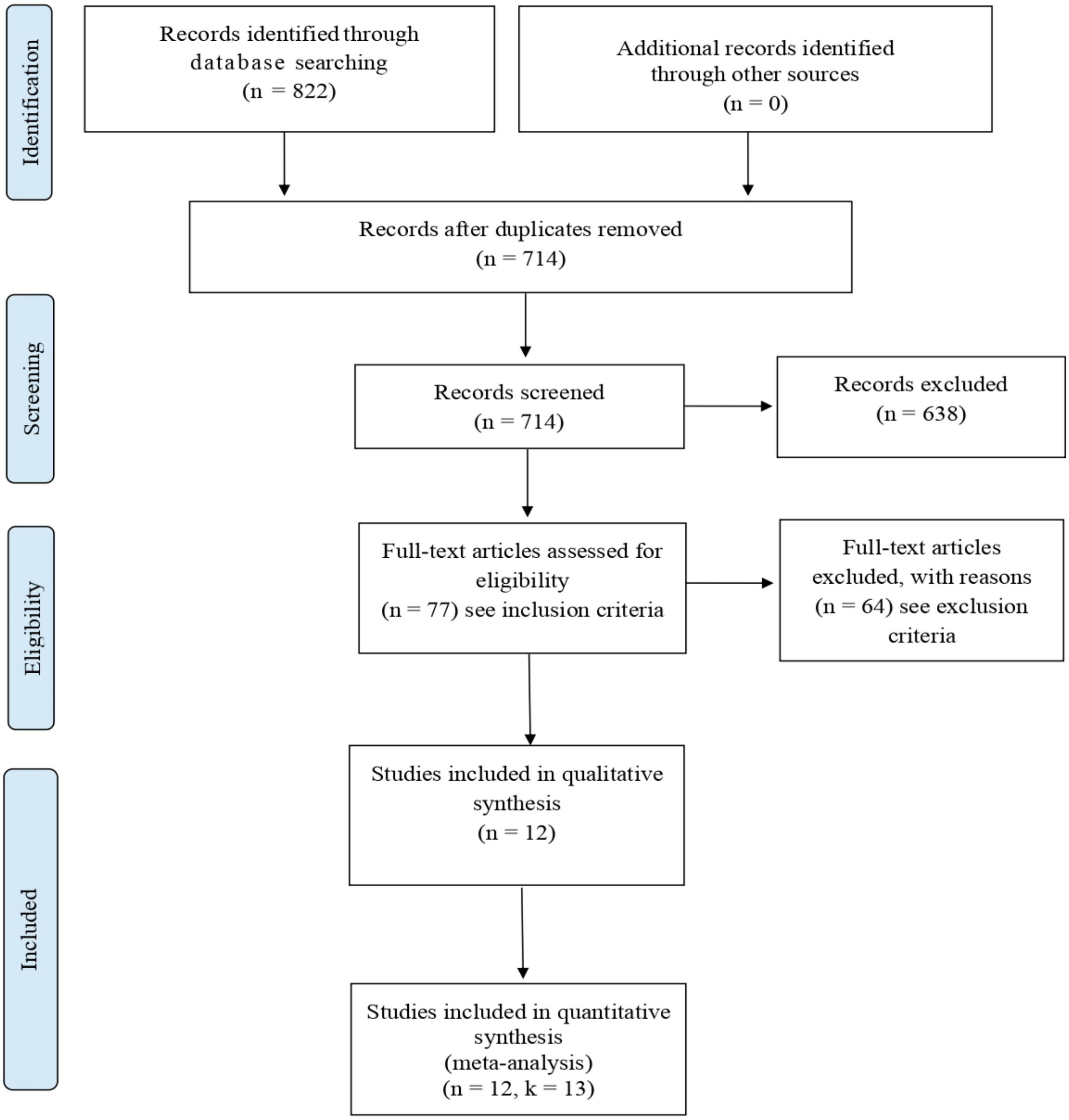
3.3 Results

In this section, the results relating to HbA1c will be described before those relating to psychosocial symptoms since most of the included studies focused on the improvements of HbA1c levels through the deployment of digital health solutions. Therefore, by firstly providing the broader picture referred to all the included studies with the intention to provide the clearest possible data presentation.

Search result

Figure 1 shows the search process, highlighting that the initial search yielded 822 studies. After the removal of duplicates, titles and abstracts of 714 studies were reviewed, gathering 77 studies considered for full-text screening. Based on the exclusion of 64 studies (see, Appendix, Table A1 for the full list of the excluded studies and motives for exclusion), 12 studies reporting data on k = 13 RCTs were finally included and meta-analysed. In this regard, as displayed in Table 2, among the included 12 studies, Trief, Fisher, Sandberg and colleagues [182,183] assessed the efficacy of two independent experimental interventions taking into account different participants' samples. Therefore, Trief and colleagues [182,183] study has been counted as two separate RCTs, thereby resulting in a total of k = 13 RCTs included in the present meta-analysis.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) [170]



Studies Characteristics

Table 1 reports the characteristics of the included RCTs, which shows data from 2006 to 2020 [182-194].

The overall studies comprised N = 1315 adults, of which N = 725 were under the experimental intervention and N = 590 were part of the control group. Overall, 52.09% of adults were females, although one RCT [189] did not report the participants' gender distribution. As such, the percentage is evaluated on the remaining 12 studies. The mean age of participants was 46.18 years (SD = 9.98), and the mean of their diabetes duration was 13.60 years (SD = 8.28). Only one study [192] did not provide adults' diabetes duration.

Moreover, k = 6 RCTs took into consideration adults with T1DM [184-186,189,191,192] and k = 7 with T2DM [182,183,187,188,190]. The overall studies provided data on participants' HbA1c levels evaluated at the intervention endpoint, while k = 6 RCTs also assessed it at follow-up [182-184,187,190,192].

The psychosocial variables relevant for the present meta-analysis and considered in the RCTs were health-related quality of life (k = 7) [183-186,38,191,192], diabetes-related emotional distress (k = 4) [182,190,193] and depressive symptoms (k = 6) [182,183,187,188,193,194]. None of the identified studies provided data on participants' health-related quality of life, diabetes-related emotional distress, or depressive symptoms at follow-up. Notably, anxiety and stress symptoms were neither considered nor assessed in the identified studies.

Lastly, only three of the included studies conducted a preliminary pilot study to assess the intervention feasibility and acceptability [182-185].

Table 1. The characteristics of the included studies

Author, year	Country	Sample	Sample size: Treatment	Sample size: Control	Mean age (years); (SD)	Intervention: Treatment	Intervention: Control	Time points	Outcomes included	Data type	Instruments Used
[182]	USA	T2DM	97 CC	78	57.35 (10.60)	Telephone-based intervention	Active	Endpoint Follow up (16 and 32 weeks)	-HbA1c -Diabetes-related emotional distress -Depression	ITT	-AccuBase A1c Test Kit -DDS-17 -PHQ-8
[183]	USA	T2DM	93 IC	78	56.25 (10.91)	Telephone-based intervention	Active	Endpoint Follow up (16 and 32 weeks)	-HbA1c -Diabetes-related emotional distress -Depression	ITT	-AccuBase A1c Test Kit -DDS-17 -PHQ-8
[184]	Italy	T1DM	67	63	35.70 (9.40)	Mobile-based telemedicine system	TAU	Endpoint Follow-up (12 weeks)	-HbA1c -HRQOL	ITT	-NS -SF-36 -WHO-DTSQ
[185]	Italy	T1DM	63	64	36.90 (10.50)	Mobile-based telemedicine system	TAU	Endpoint	-HbA1c -HRQOL	ITT	-Standard method for HbA1c measurement -DSQL
[186]	France	T1DM	30	30	41.30 (11.30)	Mobile-phone software	Waitlist	Endpoint	-HbA1c -HRQOL	Per-protocol	-HPLC -DQOL

[187]	USA	T2DM	25	25	60.00 (8.81)	Comprehensive telemedicine intervention	TAU	Endpoint Follow-up (13 weeks)	-HbA1c -Depression	ITT	-NS -PHQ-9
[188]	Turkey	T2DM	23	21	52.93 (11.18)	Tele-rehabilitation	TAU	Endpoint	-HbA1c -Depression	Per-protocol	-NS -BDI
[189]	Spain	T1DM	54	64	31.85 (9.57)	Internet-based telemedicine system	TAU	Endpoint	-HbA1c -HRQOL	Per-protocol	-HPLC -EuroQOL -DQOL
[190]	USA	T2DM	93	95	51.50 (9.01)	Interactive web-based tablet, computer-delivered tool	Active	Endpoint	-HbA1c -Diabetes-related emotional distress	Per-protocol	-Bayer DCA 200+ point of care analyser -NS
[191]	Spain	T1DM	19	16	25.00 (8.54)	Telephone-based telecare	TAU	Endpoint Follow-up (26 weeks)	-HbA1c -HRQOL	ITT	-HPLC -SF-12 -DQOL
[192]	Australia	T1DM	36	36	35.20 (10.43)	Smartphone-based app	TAU	Endpoint Follow-up (12 weeks)	-HbA1c -HRQOL	ITT	-Blood Test -SF-36
[193]	USA	T2DM	62	35	54.09 (8.30)	Mobile Health intervention	Active	Endpoint	-HbA1c -Diabetes-related emotional distress -Depression -HRQOL	Per-protocol	- Bayer DCA 200+ point of care analyser -DDS-17 -CEDS -EQ-VAS
[194]	Australia	T2DM	63	63	61.30 (11.10)	Tailored telemonitoring intervention	TAU	Endpoint	-HbA1c -HRQOL -Depression	Per-protocol	-Pathology Blood Test -SF-6D -K10

Note. USA = United States; CC = Couple Calls; IC = Individual Calls; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus; TAU = Treatment as usual; HbA1c = Haemoglobin A1c; HRQOL = Health-related quality of life; ITT = Intention-To-Treat; DDS-17 = Diabetes Distress Scale-17 items; PHQ-8 = Patient Health Questionnaire-8 items; NS = Not Specified; SF-36 = Short Form-36 items Health Survey; WHO-DTSQ = World Health Organization-Diabetes Treatment Satisfaction Questionnaire; DSQOL = Diabetes Specific Quality of Life; HPLC = High Performance Liquid Chromatography; DQOL = Diabetes Quality of Life Questionnaire; PHQ-9 = Patient Health Questionnaire-9 items; BDI = Beck Depression Inventory; EuroQOL = European Quality of Life; SF-12 = Short Form-12 items Health Survey; CEDS = Center for Epidemiological Studies Depression Scale; EQ-VAS = European Quality of Life Visual Analog Scale;SF-6D = Short-Form Six-Dimension Health Survey; K10 = Kessler Psychological Distress Scale.

Characteristics of the eHealth interventions

Table 2 shows the characteristics of the eHealth interventions, which were primarily aimed at improving glycaemic control. Only four RCTs considered and evaluated the efficacy of social support [182,183,193] and health-related quality of life [184,185]. However, none of the included studies had the main purpose of supporting adults with DM from a psychosocial perspective.

The delivery format of the eHealth interventions includes the SMS system (k = 1) [186], phone calls (k = 3) [182,183,187], video calls (k = 1) [37] and web, smartphone, or computer-based applications (k = 8) [182,185,189-194].

The comparison conditions were based on waiting list (k = 1) [35], TAU (k = 8) [184,185,187-189,191,192,194] and active control group (k = 4) [183,189,190,194]. Moreover, k = 7 RCTs included all randomised participants for analysis (ITT) [182-185,187,191,192], while k = 6 encompassed only the observed case (per-protocol) [186,188-190,192,194]. Notably, none of the included studies applied Behaviour Change Theories, except for one study. This research—in both the examined studies—designed the eHealth intervention following the Social Learning Theory and the Interdependence Theory only for the Couple Calls intervention [182,183]. In particular, the authors relied on several behavioural strategies, such as knowledge development, goal setting, self-monitoring, and behavioural contracting [182,183].

Table 2. The characteristics of the eHealth interventions

Author, year	Treatment length (weeks)	eHealth Intervention	Type of digital intervention	Delivery modality	Aim of the eHealth intervention
[182]	16	Telephonic couples or individual behavioural diabetes intervention	Telephone-based intervention	Phone calls	Improve glycaemic control, physical health, and psychological outcomes.
[183]	16	Telephonic couples or individual behavioural diabetes intervention	Telephone-based intervention	Phone calls	Improve glycaemic control, physical health, and psychological outcomes.
[184]	26	Diabetes Interactive Diary (DID) software	Mobile-based telemedicine system	Mobile phone software	Improve metabolic control, quality of life and reduces the risk of hypoglycaemia.
[185]	12	Diabetes Interactive Diary (DID) software	Mobile-based telemedicine system	Mobile phone software	Improve metabolic control while avoiding weight gain and reducing time devoted to education.
[186]	26	GlucoNet system	Mobile phone software	Short Message Service (SMS)	Improve metabolic control through telemonitoring.
[187]	26	Advanced Comprehensive Diabetes Care (ACDC) program	Comprehensive telemedicine intervention	Phone calls	Foster telemedicine-based management of clinic refractory Persistent Poorly Diabetes Mellitus (PPDM).
[188]	6	Tele-rehabilitation (TR) program	Tele-rehabilitation	Video calls	Improve glucose control, exercise capacity, physical fitness, muscle strength, and psychosocial status.
[189]	26	Medical Guard Diabetes (MGD) system	Internet-based telemedicine system	Web-based system	Improve metabolic control.
[190]	12	iDecide program	Web-based personally tailored, interactive diabetes medication decision aid	Tablet computer-delivered tool	Improve key diabetes outcomes by focusing on treatment barriers and diabetes management.

[191]	26	GlucoBeep device	Telephone-based telecare	Telephone device	Improve metabolic control and self-management.
[192]	26	Glucose Buddy app combined with weekly text-message feedback from a Certified Diabetes Educator (CDE)	Diabetes self-management iPhone application	Smartphone application	Improve glycaemic control and other diabetes-related outcomes.
[193]	26	Community-based diabetes self-management education (DSME) plus mobile health (mHealth)-enhanced peer support intervention	Mobile Health intervention	Web application	Foster changes in glycaemic control.
[194]	26	Townsville Broadband Diabetes Telehealth (TBDT) trial	Tailored telemonitoring intervention	Tablet computer-software	Improve glycaemic control and reduce healthcare costs.

Risk of Bias: Quality assessment of the included studies

Figure 2 shows the Risk of Bias assessment whilst Figure 3 represents the Risk of Bias results in an aggregated form for each domain-level judgment.

Overall, the quality of the included studies yielded a high Risk of Bias (k = 11) and only k = 2 RCTs highlighted some concerns.

The main sources of bias were the domain that examines deviation from the intended interventions (84.62% high Risk of Bias, 15.38% some concern), and the selection of reported result domain (100% some concern). As regards the latter domain, all studies were interpreted presenting some concern since most studies did not provide a pre-specified protocol study. However, the studies that show this methodological process did not provide information regarding the planned analyses that they will be carried out. Other sources of bias refer to the randomisation process domain (15.38% high Risk of Bias, 53.85% some concern).

Figure 2. Risk of Bias color-coded

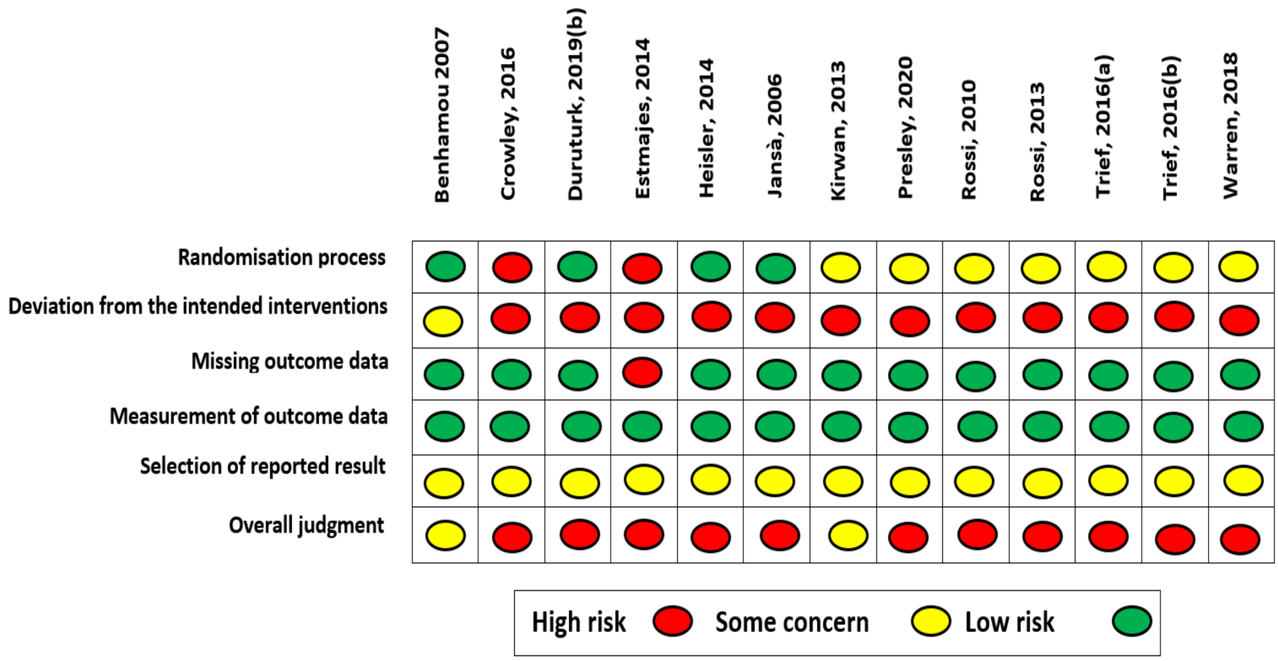
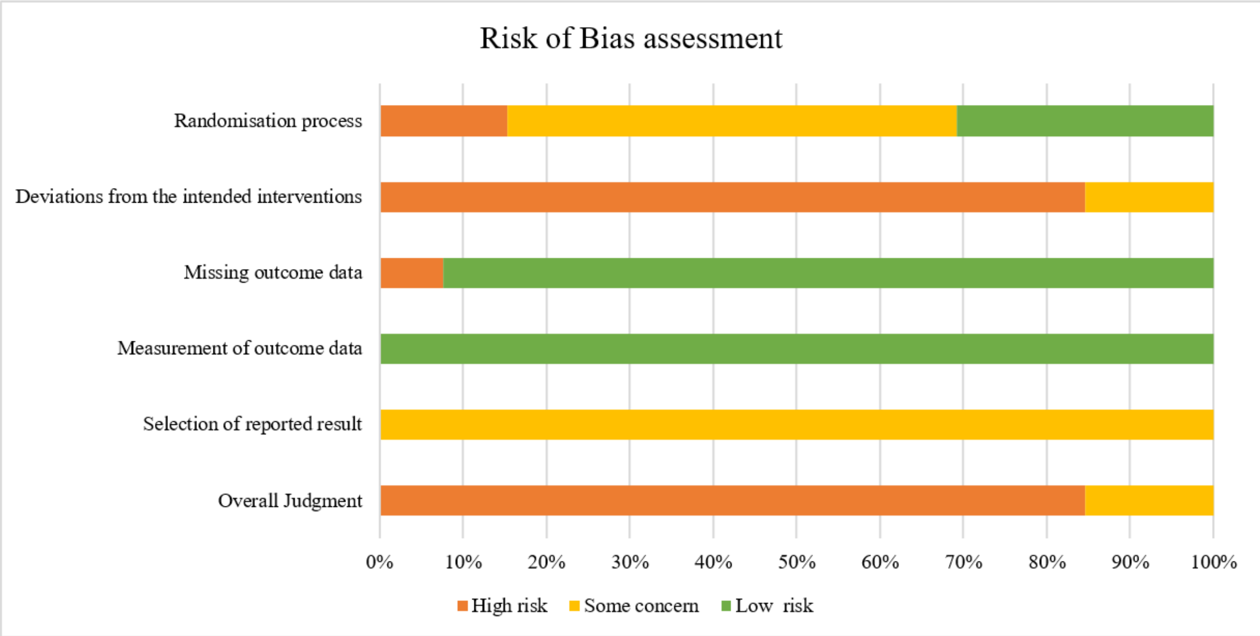


Figure 3. Risk of Bias assessment for each domain-level judgment



The efficacy of eHealth interventions and meta-regression

Haemoglobin 1c (HbA1c)

A random-effect meta-analysis was run to evaluate the efficacy of eHealth interventions in improving the HbA1c levels among adults with DM.

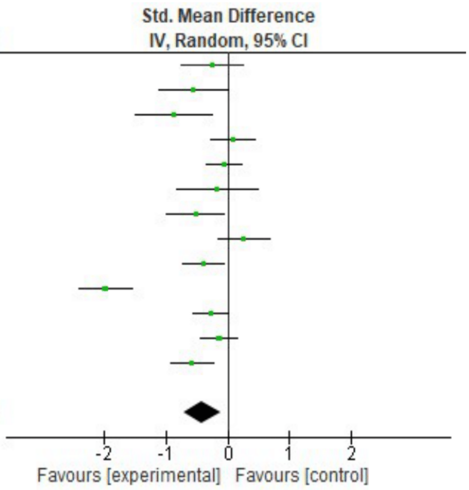
As reported in Figure 3a, results showed a significant effect on HbA1c at intervention endpoint (SMD = -.40; 95% CI = -.70, -.12; I^2 = 85%; k = 13) [182-194], thus providing an ameliorating glycaemic level in the intervention group compared to the higher glycaemic level among the control group.

As shown in Figure 3b, the eHealth interventions were well-accepted (drop-out OR = 1.43; 95% CI = .72, 2.81; I^2 = 74%; k = 10), although the beneficial effect on HbA1c was not maintained at follow-up (SMD = -.13; 95% CI = -.31, .05; I^2 = 67%; k = 6) [182-184,187,190,192].

Figure 3a. HbA1c at endpoint

	Intervention			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Benhamou 2007	8.18	0.59	30	8.34	0.67	30	7.3%	-0.25 [-0.76, 0.26]
Crowley 2016	9.2	1.5	25	10.2	2	25	6.9%	-0.56 [-1.12, 0.01]
Duruturk 2019	5.93	1.46	23	7.92	2.82	21	6.5%	-0.88 [-1.50, -0.26]
Esmatjes 2014	8.7	1.5	54	8.6	0.9	64	8.1%	0.08 [-0.28, 0.44]
Heisler 2014	7.8	1.7	87	7.9	1.9	89	8.5%	-0.06 [-0.35, 0.24]
Jansà 2006	7.5	1.4	19	7.7	0.9	16	6.3%	-0.16 [-0.83, 0.50]
Kirwan 2013	7.97	0.73	36	8.43	1	36	7.5%	-0.52 [-0.99, -0.05]
Presley 2020	9.6	1.9	62	9.1	1.9	35	7.8%	0.26 [-0.16, 0.68]
Rossi 2010	7.7	0.8	67	8	0.7	63	8.2%	-0.40 [-0.74, -0.05]
Rossi 2013	7.9	0.1	63	8.1	0.1	64	7.8%	-1.99 [-2.42, -1.56]
Trief 2016a	8.3	1.4	97	8.7	1.5	78	8.5%	-0.28 [-0.58, 0.02]
Trief 2016b	8.5	1.4	93	8.7	1.5	78	8.5%	-0.14 [-0.44, 0.16]
Warren 2018	7.5	0.96	63	8.1	1.11	63	8.2%	-0.57 [-0.93, -0.22]
Total (95% CI)			**719**			**662**	**100.0%**	**-0.41 [-0.70, -0.12]**

Heterogeneity: Tau² = 0.24; Chi² = 82.00, df = 12 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.76 (P = 0.006)

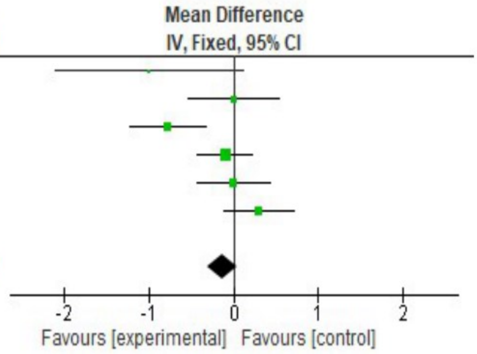


Note. SD = Standard Deviation; Std. Mean Difference = Standardised Mean Difference; 95% CI = 95% Confidence Interval; df = degrees of freedom.

Figure 3b. HbA1c at follow-up

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Crowley 2016	9.2	2	25	10.2	2	25	2.7%	-1.00 [-2.11, 0.11]
Jansà 2006	7.6	0.9	19	7.6	0.7	16	12.0%	0.00 [-0.53, 0.53]
Kirwan 2013	7.8	0.75	36	8.58	1.16	36	16.6%	-0.78 [-1.23, -0.33]
Rossi 2010	7.8	0.9	67	7.9	1	63	31.4%	-0.10 [-0.43, 0.23]
Trief 2016a	8.5	1.5	97	8.5	1.4	78	18.2%	0.00 [-0.43, 0.43]
Trief 2016b	8.8	1.4	93	8.5	1.4	78	19.0%	0.30 [-0.12, 0.72]
Total (95% CI)			**337**			**296**	**100.0%**	**-0.13 [-0.31, 0.05]**

Heterogeneity: Chi² = 14.95, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 1.40 (P = 0.16)



Note. SD = Standard Deviation; Std. Mean Difference = Standardised Mean Difference; 95% CI = 95% Confidence Interval; df = degrees of freedom.

As reported in Table 3, sub-group analysis was consequently carried out, taking into account several variables: the type of DM (i.e., T1DM *versus* T2DM), comparison conditions (i.e., waiting list/no treatment, TAU, active control group), intervention delivery modality (i.e., SMS, phone calls, video calls, mHealth applications) and the type of analysis (i.e., ITT *versus* per-protocol). None of the considered variables showed significant results.

As pointed out in Table 3, the results of the meta-regression analysis showed no significant moderator, namely the participants' age, gender, diabetes duration, and the length of the intervention.

Table 3. Sub-group and meta-regression analyses

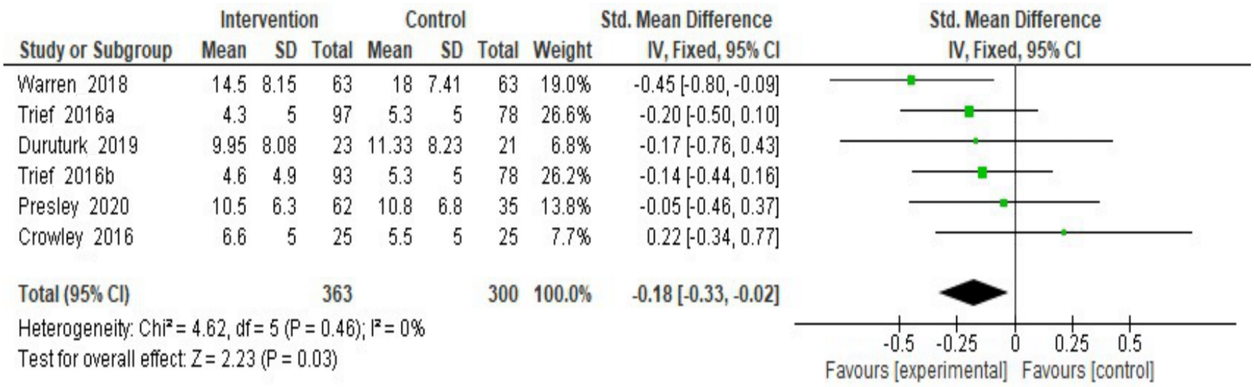
HbA1c					
Sub-group Analysis					
	k	**SMD**	**95% CI**	**I^2**	**p**
Control condition					
Waiting list	1	-.25	-.76, .26	-	
TAU	8	-.63	-1.08, -.17	88%	.10
Active control	4	-.08	-.28, .11	31%	
Diabetes Type					
T1DM	6	-.54	-1.16, .07	91%	.08
T2DM	7	-.27	-.51, -.03	63%	
Intervention delivery format					
SMS	1	-.25	-.76, .26	-	
Phone calls	3	-.25	-.45, -.05	0%	.28
Video calls	1	-.88	-1.5, -.26	-	
Based applications	8	-.42	-.88, .04	91%	
Type of analyses					
ITT	7	-.58	-1.04, -.11	89%	.18
Per-protocol	6	-.20	-.50, .10	85%	
Meta-regression					
	k	β	SE	z	p
Age	13	.02	.02	.97	.33
Female gender	12	.006	.01	.62	.54
Diabetes duration	12	-.02	.04	-.62	.54
Intervention Duration	13	-.007	.03	-.29	.77

Note. HbA1c = Haemoglobin A1c; SMD = Standardised Mean Difference; CI = Confidence Interval; TAU = Treatment as usual; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus; SMS = Short Message Service; ITT = Intention-To-Treat;

Psychosocial outcomes

As displayed in Figure 4, the efficacy of the eHealth interventions on psychosocial outcomes, such as depressive symptoms, health-related quality of life and diabetes-related emotional distress was evaluated. A fixed-effect meta-analysis was only carried out for depressive symptoms since no heterogeneity was detected. Results highlighted a significant effect on adults' depressive symptoms at endpoint (SMD = -.18; 95% CI = -.33, -.02; I^2 = 0%; k = 6) [182,183,187,188,193,194]. Only one RCT [187] provided data on depressive symptoms at follow-up, therefore the efficacy of the interventions for this outcome was not feasible to assess.

Figure 4. Depressive symptoms at the endpoint

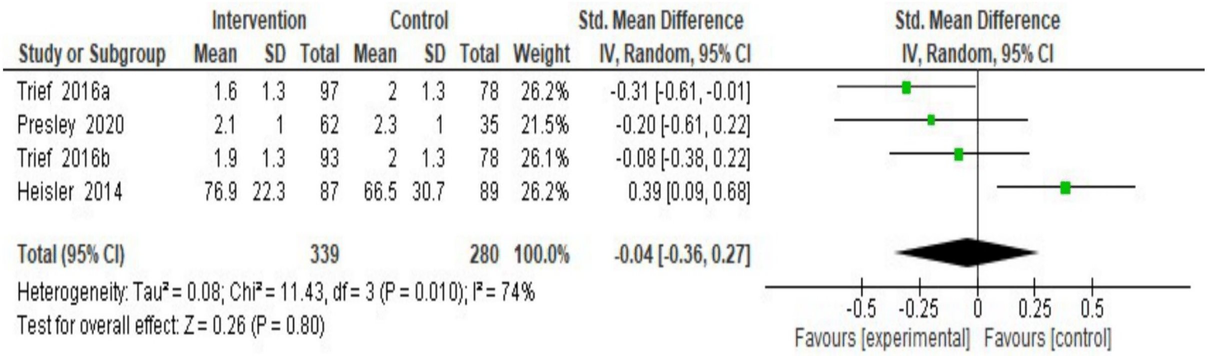


Note. SD = Standard Deviation; Std. Mean Difference = Standardised Mean Difference; 95% CI = 95% Confidence Interval; df = degrees of freedom.

On the other hand, as shown in Figure 5a and Figure 5b, a random-effect meta-analysis was performed to evaluate the efficacy of interventions among adults' health-related quality of life (SMD = -.20; 95% CI= -.72, .32; I^2 = 90%; k = 7) [182,183,190,193] and diabetes-related emotional distress (SMD = -.04; 95% CI = -.36, .27; I^2 = 74%; k = 4) [184-186,189,191,193,194] at interventions' endpoint. Results highlighted no significant effect regarding the above-mentioned psychosocial symptoms. In addition, no data was reported to assess the efficacy of interventions at follow-up for neither health-related quality of life nor diabetes-related emotional distress.

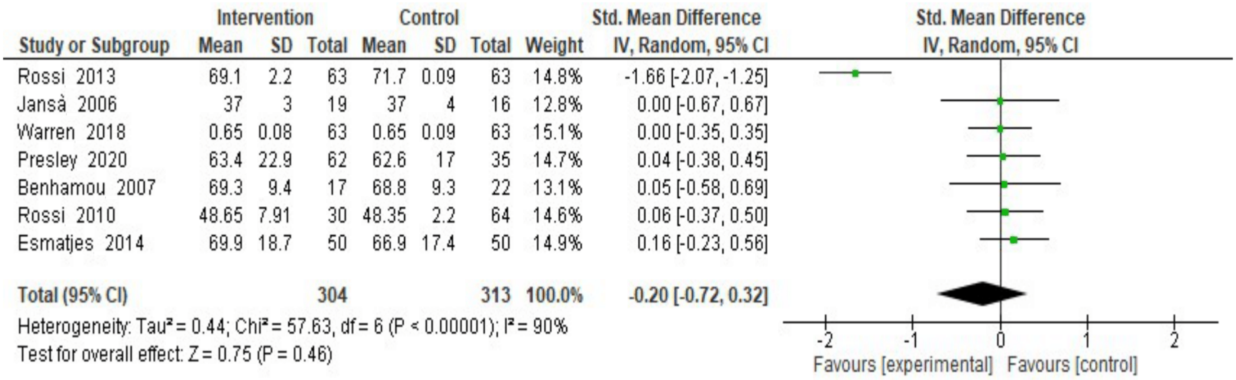
None of the sub-group analyses showed significant differences in the effect size for any of the considered psychosocial outcomes in comparisons with the type of DM (i.e., T1DM *versus* T2DM), control conditions (i.e., waiting list/no treatment, TAU, active control group), intervention delivery modality (i.e., SMS, phone calls, video calls, mHealth applications) and the type of analysis (i.e., ITT *versus* per-protocol). Meta-regression analysis was not feasible to perform since less than 10 studies provided the necessary data.

Figure 5a. Health-related quality of life at endpoint



Note. SD = Standard Deviation; Std. Mean Difference = Standardised Mean Difference; 95% CI = 95% Confidence Interval; df = degrees of freedom.

Figure 5b. Diabetes-related emotional distress at endpoint



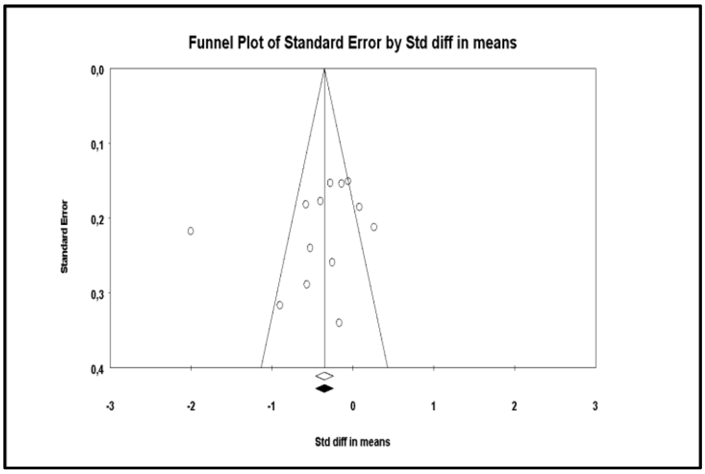
Note. SD = Standard Deviation; Std. Mean Difference = Standardised Mean Difference; 95% CI = 95% Confidence Interval; df = degrees of freedom.

Publication bias

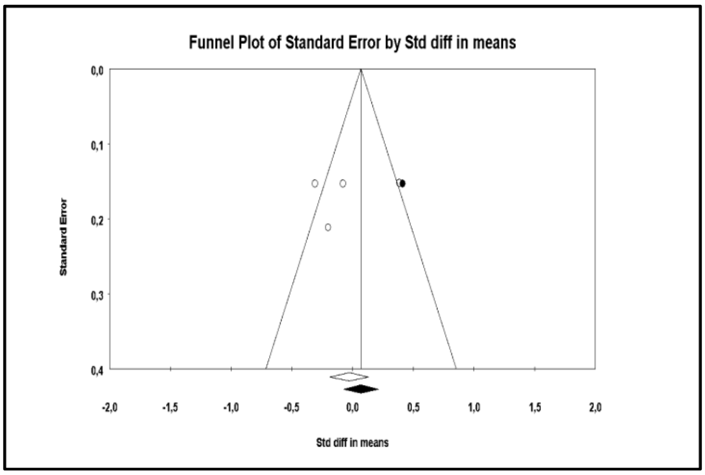
As shown in Figure 6, publication bias was evaluated for all the considered outcomes in the present meta-analysis. The Egger's regression test was further carried out, and no publication bias was identified regarding either HbA1c (β_0 = -2.95; p = .17), health-related quality of life (β_0 = 1.53; p = .41) or diabetes-related emotional distress (β_0 = -3.66; p = .36). However, Egger's regression test revealed the presence of significant publication bias among RCTs investigating depressive symptoms (β_0 = -8.26; p = .02). Therefore, the trim and fill procedures were performed, trimming 2 studies to the left (Point Estimate = -1.31; 95% CI = -1.44, -1.18) and the fail-safe N was equal to 54. These findings revealed that the presence of publication bias did not influence the effect of the interventions on depressive symptoms.

Figure 6. Publication bias Funnel Plots (observed and imputed)

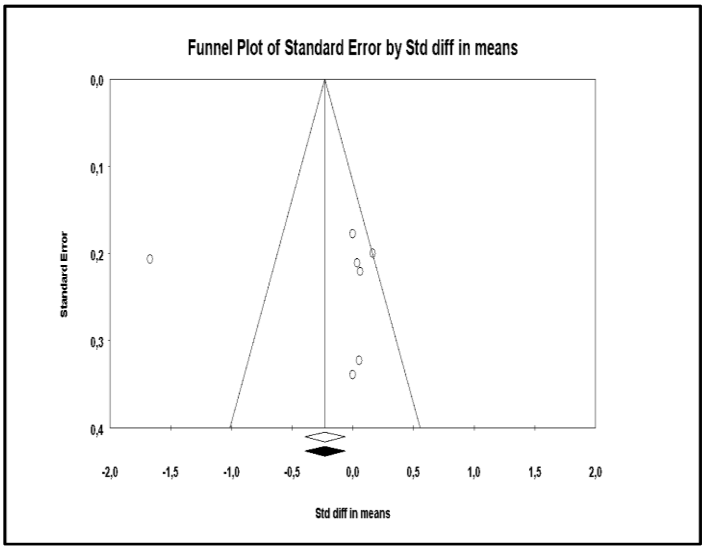
1. HbA1c



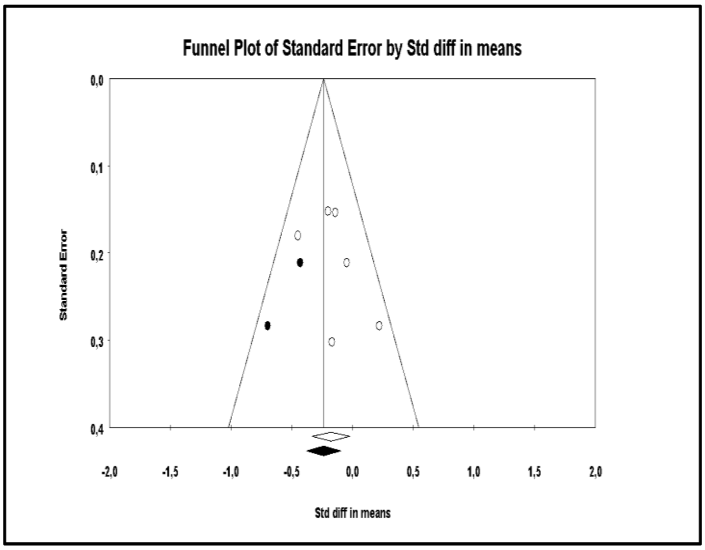
2. Diabetes-related emotional distress



4. Health-related quality of life



5. Depressive Symptoms



3.4 Discussion

After the description of the above results, the *first study* of the Ph.D. project will be now discussed below, with a focus on the pivotal data.

The present meta-analysis analysed data from 13 RCTs of 1315 adults with T1DM or T2DM. All the included studies were designed to enhance glycaemic control and none of them were developed for providing psychosocial support. Therefore, the primary aim of the present meta-analysis, namely the assessment of the eHealth interventions' efficacy in improving psychosocial symptoms, could not be satisfied.

First and foremost, the overall findings proved the efficacy of eHealth interventions among adults with DM, showing acceptable support in controlling HbA1c levels, thus confirming previous studies [114,115]. Indeed, these interventions are mainly deployed in smartphones or tablets-based applications, developed to monitor and improve individuals' metabolic control, physical activity, diabetes self-management, and the risk of hypoglycaemia, as well as to reduce healthcare costs [182-194]. However, the beneficial effects of eHealth interventions on the metabolic control of adults with DM were not maintained at follow-up. This lack of efficacy can be explained by several reasons. Firstly, the lack of generalisability of the enhancements assigned to interventions, which could involve recidivism [195]. Indeed, generalisability is pivotal for the long-term effect of interventions since its assumption refers to the transfer of behavioural change to other areas of an individual's functioning. Furthermore, the difference between the terms efficacy and effectiveness also merits some attention. Efficacy refers to the effect of intervention when assessed in a controlled environment, thus RCT is the preferred design for studies evaluating efficacy [196]. RCTs scrumptiously define the conditions in which the intervention is carried out, attentively monitoring and controlling any potential confounding factor, and, thus, aiming to generalise the data to the whole population [196]. On the other hand, the term effectiveness is related to test effects of the intervention in a more ecological environment, thereby these effects are evaluated in everyday conditions (e.g., not using RCT designs and not systematically excluding confounding variables). Notably, this latter process allows the inter-contextual generalisability of the results [196].

As mentioned above, the eHealth interventions were not designed for psychosocial support, and as expected, no significant results regarding the health-related quality of life and diabetes-related emotional distress have emerged in adults with DM. In addition, no data referred to anxiety and stress symptoms assessed by any of the included RCTs. The fact that psychosocial variables were not pivotal in the development of eHealth interventions among the included studies is by itself a relevant result for the present meta-analysis. Indeed, it is to be noted that considering the healthy coping guidelines proposed by AADE [76] for effective diabetes management, these psychosocial symptoms should be included in the development of treatment among adults with DM. In addition, these findings shed light on the importance of implementing and delivering eHealth interventions suited to providing psychosocial support among people with DM, through an RCT design to test their effectiveness. It is also interesting to note that most studies on eHealth interventions developed to provide psychosocial support are pilot or proof-of-concept studies [197-199]. This aspect underlines the novelty of eHealth interventions aimed at supporting psychosocial factors as well as the potential costs and difficulty in conducting RCT study.

Notwithstanding these shortcomings, results of this meta-analysis gathered encouraging evidence on the efficacy of eHealth interventions in diminishing depressive symptoms [182,183,187,188,193,194], despite these results showed a small effect size. As thoroughly discussed in section 1.2 of Chapter 1, the literature suggests several possible neurobiological mechanisms linked to the effects of insulin deficiency to explain the onset of depressive symptoms, which, in turn, can interfere with the HbA1c levels [59,60]. Therefore, the results of the present meta-analysis confirm and extend those previously emerged, further suggesting a bidirectional association between depression and metabolic control, whereby eHealth interventions aimed at ameliorating HbA1c levels also bring in improvements in depressive symptoms. This bidirectional relationship can expose people with DM to cardiovascular risk factors, encompassing high levels of blood pressure, obesity, hyperglycaemia, hypertriglyceridemia, and reduced high-density lipoprotein (HDL) cholesterol [200]. In this regard, this bidirectionality between psychosocial and biomedical variables is a central aspect, which should be considered to broaden the efficacy of these interventions to an individual’s overall functioning. Furthermore, depression can entail feelings of hopelessness and helplessness [200], which can have a negative impact on the individual’s motivation to adopt and cultivate healthy behaviours, namely doing regularly physical exercise, following healthy nutrition, and taking oral medication and/or insulin injections [200, 201]. Not thoroughly adhering to the clinical recommendations constitutes a risk factor from both a medical and psychosocial perspective, since the non-adherence can entail poor glycaemic control in the short-term, which, can then influence the individual's psychosocial functioning [200].

It is also noteworthy that the results of the included studies showed no significant differences in the efficacy of eHealth interventions when considering the type of DM as a moderator. These findings suggest that these interventions may have been developed around the broader concept of DM, thus focusing on the similarities between people's lifestyles and using self-management of metabolic control as their main focus of treatment. Indeed, in support of this hypothesis, only in one study did eHealth intervention specifically focus on the risk of hypoglycaemia among adults with T1DM [185].

The present meta-analysis showed one principal limitation: most interventions were developed for monitoring and/or improving metabolic control among people with DM. However, in four studies, the authors designed an interactive diary also to motivate the individual to reach a better health-related quality of life [184,185] and to provide social support [182-185]. In addition to this, most studies currently accessible in the literature, which considered the psychosocial factors within the mHealth solutions, are pilot or proof-of-concept studies [197-199]. Therefore, future studies should be directed towards RCT designs to evaluate the effectiveness of eHealth interventions while also taking into consideration the bidirectionality approach between psychosocial and medical factors. It is to be noted that there is also a high risk of bias in the included studies. Notwithstanding the poor RCTs quality, which was for the most part, due to an inadequate investigation into the adherence to the intervention, all studies appropriately evaluated the outcomes of interest and adequately approached missing data. Therefore, the identified RCTs low quality mainly poses concerns on the assessment of the tolerability regarding eHealth interventions, hence not substantially mining the results' reliability.

3.5 Conclusions

The present systematic review and meta-analysis contributed to the growing literature on understanding the efficacy of eHealth interventions for supporting and motivating people with DM in the adoption of healthy goals in order to maintain better management of their disease. In this regard, results highlighted that eHealth interventions aimed at monitoring the metabolic control and enhancing depressive symptoms among people with DM are effective and acceptable in the short-term. However, no evidence was found in the follow-up as to the efficacy of these two latter variables. Future studies should design mHealth solutions or VCs embedded or not in applications following standard guidelines, such as those proposed by AADE [76], thereby, for example, including the healthy coping construct within their intervention protocol. Above all, future works might develop eHealth interventions on multiple levels, including a wide range of psychosocial factors to fully address the users' barriers of non-adherence and non-compliance as well as to foster their well-being by considering both psychosocial and medical factors. Researchers should further develop and design new BIT approaches to support the long-term maintenance of interventions' efficacy associated with metabolic control and depressive symptoms.

CHAPTER 4. DESIGNING AND PROTOTYPING THE INTERVENTION PROTOCOL FOR HEALTHY COPING IN DIABETES: A PRELIMINARY STUDY

The present Chapter describes the *second study*[3] of the Ph.D. project: a preliminary study for designing and prototyping the intervention protocol for healthy coping in DM. In particular, this study aimed at assessing the User Experience (UX) of the conversational agent's intervention for healthy coping in Diabetes Mellitus (DM) by means of an approach using a simulated Virtual Coach (VC), called Wizard of Oz (WOZ).

The protocol specifies the utterances of the conversational agent during communicative interaction (i.e., dialogue) with the user and sets up the rules of this interaction between two or more communicating agents [202]. Indeed, in order to achieve an effective intervention that incorporates the needs and preferences of users in the dialog-based interaction, the development of a natural, robust, and tailored VC is needed [203-207]. For the design of a VC, the typical approach is to first collect primary requirements from users and to rely on, for example, the WOZ methodology. The next step is to refine the intervention protocol with the involvement of users during the interaction, validate it with specific domain experts in the field, and lastly, repeat the procedure until an appropriate and successful intervention protocol has been reached [203-206,208,209]. The WOZ method is based on three pivotal aspects. First, the presence of a script or an intervention protocol, which guides the interaction. Second, the involvement of participants who play the role of the target users, by relying on the role-playing technique. Lastly, a human operator, called Wizard, carries out the VC tasks in simulated scenarios. At the final stage, these tasks will be performed by an automated system [210]. The WOZ method is a process that allows users to engage with a counterpart without knowing that the responses are generated by a human—also called human-controlled—rather than a program. This deceit has the purpose of allowing people to express themselves more freely [210]. As reported above, one of the requirements of the WOZ method is the presence of people that apply the

[3]The present work is under review in the *Journal of Medical Internet Research* (JMIR).

role-playing technique, which can be used in conjunction with the Standardised Patients (SPs) approach. SPs are defined as actors who have been taught to assume the role of a patient and to simulate a problem in a clinically appropriate and realistic manner [211,212]. This approach is effective when an intervention is not yet fully developed and testing the intervention protocol in different simulated scenarios is a faster way than enrolling actual patients, who are more likely to express real vulnerabilities. The goal here is not so much to use a simulation of an SP to replace interaction with an actual patient, but more to enhance it in a standardised and integrative methodology [212,213]. Indeed, in the present study, the SPs interpreted real patients with DM.

Study 2. **The preliminary designing and prototyping of a Virtual Coach for healthy coping interventions in diabetes with Standardised Patients**

Participants who play the role of patients with T2DM will be the focus of this preliminary study. The selection of patient profiles' with T2DM was based on the notion that it should be easier for a person to empathise with this chronic condition since its onset is in adulthood compared to the profile of a patient with T1DM, which is usually developed during childhood, and, thus, more complex to empathise, particularly because they can experience fear of hypoglycaemia.

4.1 Aims

The main aim of the present preliminary study was to assess the acceptability and UX of the intervention protocol, which will be integrated into the future VC. This intervention protocol is based on psychoeducational and counselling approaches aimed at supporting and promoting healthy coping behaviours in people with DM.

The overall findings of this study will be valuable in converting WOZ into a conversational agent, which will be developed using a neural network-based automatic VC. The VC and thus the intervention protocol will be refined for the proof-of-concept study—the last study of the present thesis—by developing a dialog-based interaction as natural and effective as possible for people with DM.

The specific objectives of the present preliminary study are formulated as follows:

1) To design a preliminary intervention protocol for digital psychoeducation delivered by a VC, in which the healthy coping construct in the DM field is its main core.

2) To validate the intervention protocol with experts in Behavioural Intervention Technologies (BITs) and mental health.
3) To test the prototype of the simulated VC, namely WOZ, and thus the intervention protocol with users who interpret a patient with T2DM.
4) To adapt and refine the intervention protocol following the results that emerged in the present study regarding acceptability, usability, and UX through the administered questionnaires and through the logged dialogues.
5) Lastly, to apply clustering algorithms to the logged dialogues between WOZ and users in order to evaluate user engagement and the accuracy of users' role-playing.

4.2 Participants Recruitment

The description of the Participants Recruitment section is consistent with the Study Design section, reported below.

Participants in the Define phase [214] were identified for the designing and development of the intervention protocol. The presence of a team of psychologists was the only criterion for participation.

In the Refine phase, 20 psychology students from the University of Padova (Italy) were involved in the present study. Due to the withdrawal of two participants, the final sample consisted of 18 psychology students (77.8% females), aged between 19 and 28 years (M_{age} = 23.61, SD = 1.98), who played each one out of the six SP roles provided.

The participants were randomly recruited through the university students' mailing list. The study's inclusion criteria were *(a)* to be a psychology student since this implies a potentially greater empathy with the SPs profiles' traits, emotions, and needs; and *(b)* to be familiar with smartphones and the WhatsApp messaging platform.

4.3 Materials and Method

Procedure

WOZ started each interaction at 10:00 a.m.: from that time participants were free to interact with WOZ during the 6-week study. The UX questionnaire, developed ad hoc for the current study, was created in Google Form and sent via as a link to WhatsApp.

The study procedure was performed in accordance with the Declaration of Helsinki (Italian law 196/2003, UE GDPR 679/2016) and it was approved by the Ethical Committee (3518, 1st April 2020) for psychological research of the University of Padova (Italy). Prior to participating in the present study, all participants signed and returned the informed consent agreement, which was also signed and returned when the WOZ identity was revealed at the end of the study.

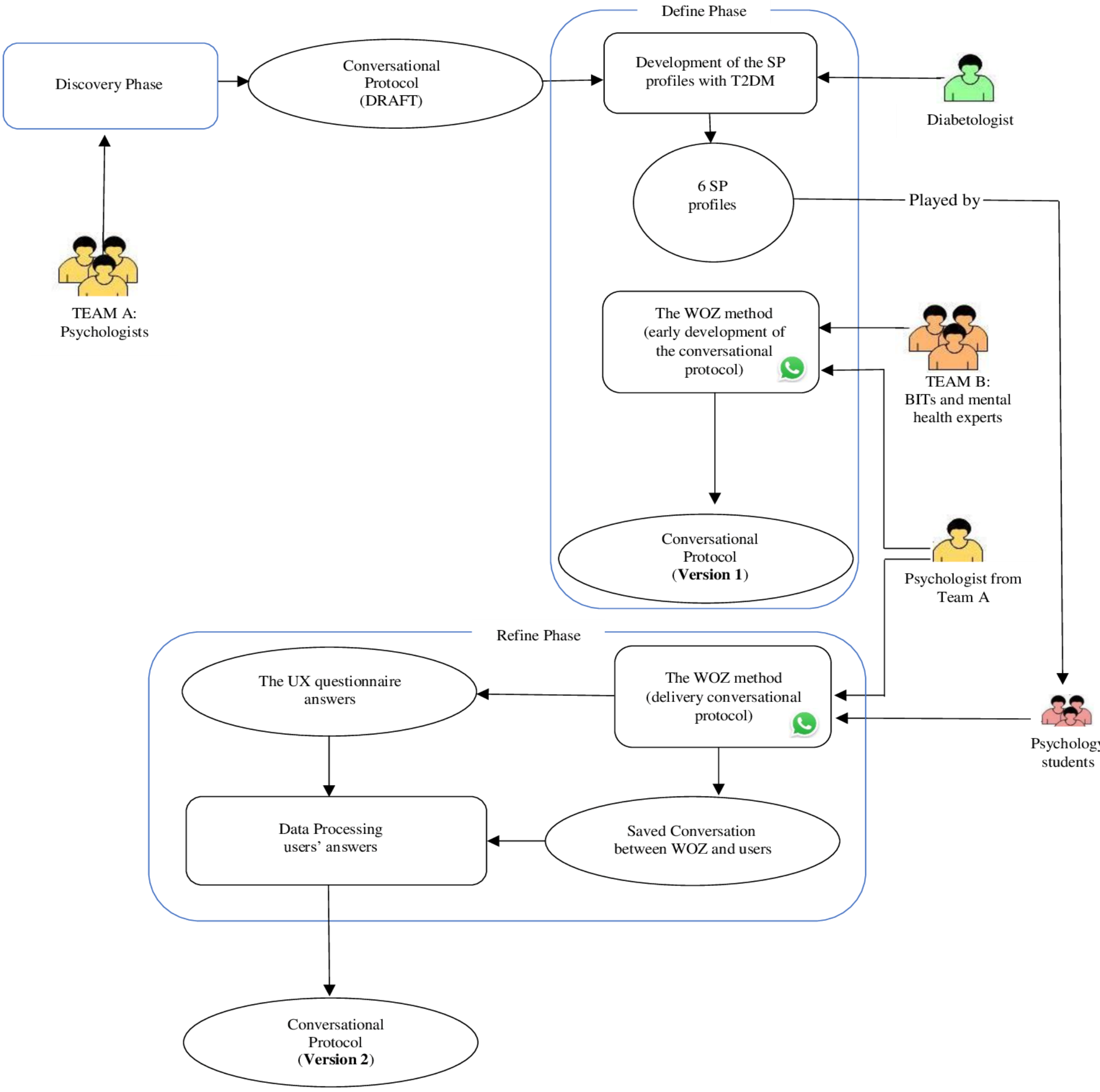
Study Design

The design method of the present preliminary study was two-fold, as shown in Figure 1.

Firstly, the WOZ method was applied, in which users believed they were interacting with a VC but were engaging with a human. This deceit allows the users to use a language that is as natural as possible.

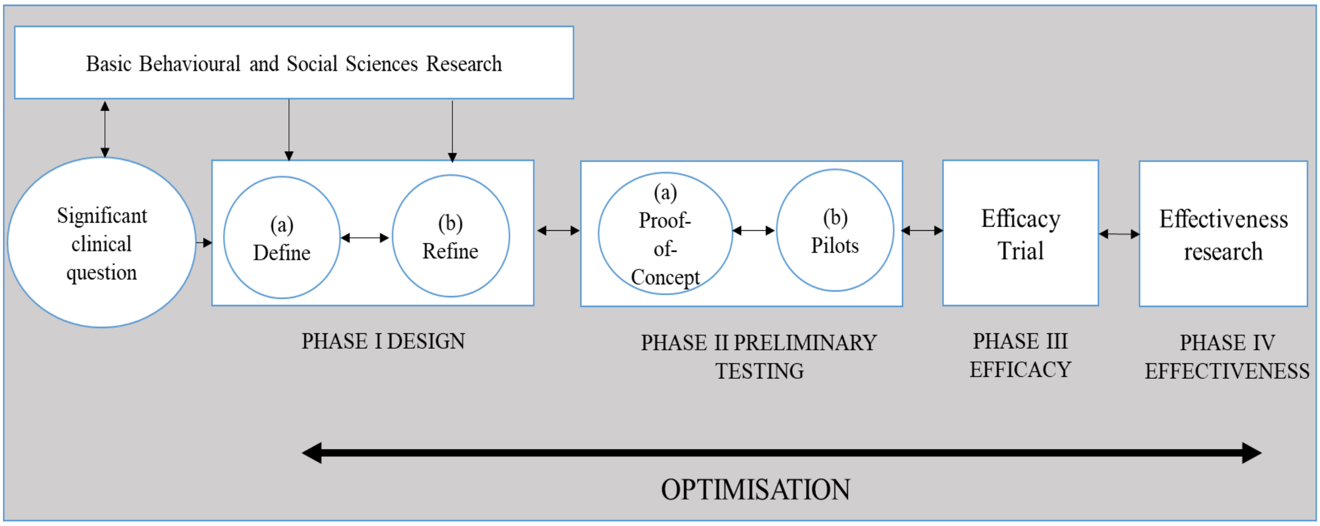
Secondly, the Obesity-Related Behavioural Intervention Trials (ORBIT) model was used to guide the development of the present study. The ORBIT model, as shown in Figure 2, was developed as a behavioural treatment for preventing and managing chronic diseases, such as DM [214,215]. Indeed, ORBIT enables the establishment of healthy coping interventions by defining clear objectives for each phase of the model and by allowing for the revision of prior stages to improve the intervention in light of new data [214]. The first three phases of the ORBIT model were performed as parts of the present preliminary study, outlined below.

Figure 1. The study design architecture of the present preliminary study. Rounded rectangles are the architecture components/performed activities while the ellipsis is the input/output of each activity



Note. SP = Standardised Patient; T2DM = Type 2 Diabetes Mellitus; WOZ = Wizard of Oz; BITs = Behavioural Intervention Technologies; UX = User Experience

Figure 2. Phases of the Obesity-Related Behavioural Intervention Trials (ORBIT) model [213]



Phase 0. Discovery

The development of a preliminary draft of the intervention protocol was the initial phase of the present study design, as shown in Figure 1.

As already stated in the Aims section of the present Chapter, the main purpose of the current study was to develop an intervention protocol, which will be subsequently embedded in a VC—called *Motibot*, which stands for Motivational bot—within a messaging platform, for psychosocial support among adults with DM. Motibot, in particular, encourages people with DM to acquire and cultivate healthy coping skills in order to cope with the stress related to diabetes-related emotional distress.

Therefore, this early phase encompasses various background research in behavioural and cognitive psychology, neuropsychology, health psychology, the pivotal elements of motivational interview, and the field of healthcare related to Human-Computer Interaction (HCI) to develop the intervention protocol. A team of psychologists (Team A) designed the intervention protocol to last 6 weeks with two sessions per week.

The intervention protocol is based on motivational and behavioural interventions in order to improve people's motivation to change their behaviours, by adopting and cultivating healthy coping strategies. In particular, the motivational interventions are dialogues developed for increasing people's awareness of their emotions and for comprehending the costs and benefits of adopting a healthy behaviour, in favour of their health-related quality of life. On the other hand, the behavioural interventions consist of video clips or audio tracks associated with the main elements of the Positive Psychology framework and with the Mindfulness-Based Cognitive Therapy (MBCT) [216]. Furthermore, each day, WOZ supported users in being aware of their emotions asking: *"What are you feeling at this precise moment?"* and indicating the intensity of that precise emotion on a 5-point Likert scale, from 1 (low) to 5 (high).

Bearing all these aspects in mind, it is important to note that the support provided by the VC to the users is not to be understood as a therapy, but rather as psychoeducational support in order to reach, adopt, and cultivate healthy coping to better manage their disease.

Phase Ia. Define

The Define phase was the next step in the architecture design of the present study.

The first draft of the intervention protocol was sent to three mental health and BITs experts (Team B), who interacted with the WOZ through the WhatsApp messaging platform. These experts were aware of who WOZ (from Team A) was and they played three of the six SPs profiles prepared. These profiles were designed in collaboration with a Diabetologist from the Padova Hospital (Italy), and they represented three male and three female profiles of typical patients with T2DM, suited for all ages (i.e., young, adults, and elderly), as they are the target users. Examples of SP profiles are reported in the Appendix (Table A2). The experts contributed to the definition of the intervention protocol—in particular—in relation to the importance of using the BIT frameworks in association with the DM domain, as well as to the selection of the UX tools in order to assess the users' experience with the VC. In this regard, an open-ended question was added to collect additional thematic contents relevant to UX. Therefore, the experts defined and refined the intervention protocol following an iterative procedure, and, thus, developing its Version 1.

Phase Ib. Refine

The term "WOZ" or "simulated VC" will from now on be used interchangeably to allow for a more fluid reading of the study.

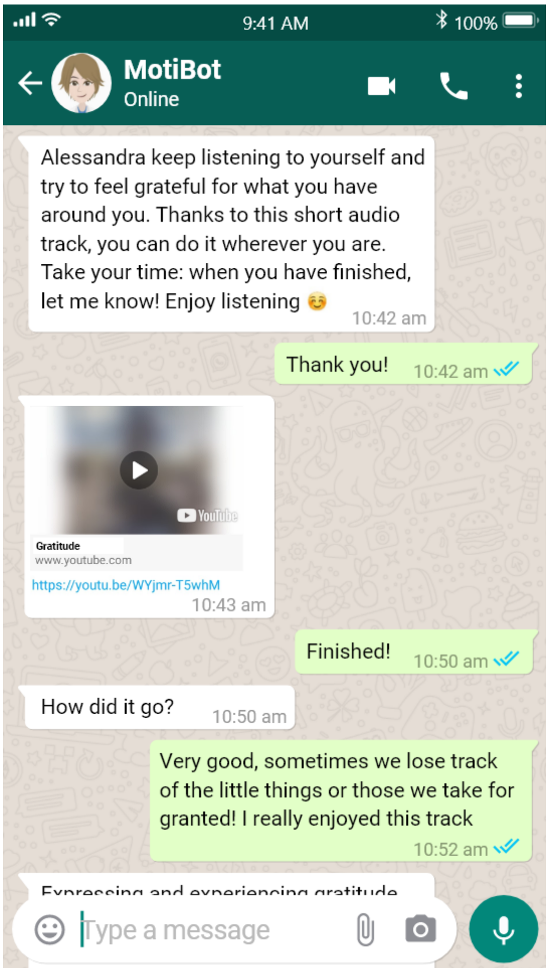
The Refine phase was the preliminary testing of the previously designed protocol.

Firstly, psychology students interpreted and simulated an SP profile with T2DM through the role-playing technique. These SP profiles were assigned to the users at random. Before beginning with the intervention, users read the study information, in which it was underlined that they should have interacted with a VC. However, they were interacting with a human being, namely WOZ (from Team A). Indeed, WOZ delivered the intervention protocol to these users by using the WhatsApp messaging platform. As explained in the above-mentioned Discovery phase, the intervention protocol lasted 6 weeks, comprising two sessions per week. Secondly, WOZ delivered the questionnaire for assessing UX at the end of the 2^{nd}, 4^{th}, and 6^{th} weeks. This questionnaire also enables the collection of qualitative data, as reported by the users' answers to the open-ended question: *"I'm asking you to express your opinions regarding your experience with me..."*.

At the end of the Refine phase, the intervention protocol was refined following users' answers regarding their experience with WOZ, thereby developing its Version 2.

Therefore, the present preliminary study will allow the training of a conversational agent in performing the tasks carried out by WOZ. Figure 3 shows an example of interaction between WOZ and a user via WhatsApp.

Figure 3. An example of interaction between WOZ and a user through WhatsApp



Measures

The User Experience (UX) questionnaire was designed based on the original version of the User Experience Questionnaire (UEQ) [217], including opposite adjectives in compliance with the aims of the present study. In particular, the UX questionnaire consists of 26 adjectives either positive or negative—as displayed in Table 1—to investigate the experience of users in interacting with the simulated VC. Each item was based on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Furthermore, an open-ended qualitative question was included at the end of the questionnaire: *"I'm asking you to express your opinions regarding your experience with me..."*. This qualitative question enables users to express their thoughts with a higher degree of freedom as to their experience with the simulated VC.

Table 1. The User Experience questionnaire: Positive and Negative items

Positive Items	**Negative Items**
Pleasant	Annoying
Profound	Not Reliable
Cordial	Unappealing
Comprehensible Language	Unclear
Empathetic	Complicated
Attentive	Not Efficient
Motivating	Too Much Information
Encouraging	Dissuading
Supportive	Not Stimulating
Trustworthy	Not Engaging
Flexible	Unpredictable
Interesting	Not Reflective
	Conventional
	Rigid

Data Analysis

Statistical analyses were carried out using R, Version 64 [218], SPSS Statistics, Version 24.0 [219], and Python, Version 3.6.6 [220].

The Shapiro-Wilk test was used to determine the normal distribution of the responses to the UX questionnaire items.

The Bartlett's test was also performed to assess homoscedasticity among participants. The key component of linear regression models is the assumption of homoscedasticity, which means the same variance[4] [221].

The first two aims of the present study (i.e., the designing and prototyping of an intervention protocol for healthy coping in DM and its validation with mental health and BITs experts) were carried out in the Discovery and the Define phases, respectively.

The third aim (i.e., the testing of the intervention protocol through the WOZ methodology among psychology students), related to the Refine phase, allowed the achievement of the fourth objective: the evaluation of users' acceptability, usability, and UX. Therefore, the statistical analyses run for reaching this fourth goal were as follows:

[4]The term "homoscedasticity" describes a situation in which the error term—defined as noise or random interference between the independent and the dependent variables—is the same across all the independent variables' total values [221].

Firstly, the main descriptive statistics (i.e., means, standard deviations) were performed regarding:

1. the number of utterances and their length (i.e., the number of their characters) expressed by both the WOZ and users. Each utterance is a user's sentence delivered through WhatsApp. These utterances are saved as a text file using the WhatsApp "Save conversation" feature: each line includes an utterance, its timestamp, and the name of the user's profile. The goal of these descriptive statistics is to highlight the differences between the WOZ and the user messages in order to better understand when and whether the WOZ was too informative or too demanding.
2. The users' response time (assessed in minutes) was also evaluated to investigate the acceptability of the WOZ intervention.
3. The item response distributions among the 26 items of the UX questionnaire were calculated to assess the experience of users with WOZ every fortnight (i.e., 2^{nd}, 4^{th}, and 6^{th} weeks).

Secondly, a series of one-way repeated measures analyses of variance (ANOVAs) were performed to investigate whether there were significant differences on each item's means of the UX questionnaire on a fortnightly basis (i.e., 2^{nd}, 4^{th}, and 6^{th} weeks). A post-hoc test was carried out in which the significant level $\alpha = .05$ has been Bonferroni corrected to $\alpha = .0025$.

Lastly, qualitative analyses have been carried out on the users' answers to the open-ended question provided at the end of the UX questionnaire. In particular, qualitative contents have been analysed using the Thematic Analysis (TA) method [222], by following its six phases. These six phases were performed by the author of the present thesis in collaboration with a member of the research group. Firstly, two authors read and re-read the users' responses to become familiar with the data and thus to find relevant themes. Secondly, these authors analysed and classified the thematic content, assigning labels to each theme that were pertinent to the study's goals. Thirdly, the above-mentioned authors' analysis allowed for the discovery of themes relating to users' quotes that were relevant to the current study's objectives. Fourthly and fifthly, the quality-checking of themes connected to the coded data and the complete dataset was carried out. Lastly, they reviewed the qualitative responses to be incorporated in the final report.

Moreover, the statistical analyses carried out to fulfil this last and fifth objective (i.e., the assessment of users' engagement and the accuracy of the users' role-playing) were:

The Augmented Dickey-Fuller (ADF) test was used to check whether the length (i.e., the number of characters) of the users' utterances and their response times show a trend according to the dialogue steps. Therefore, if the trend is not detected, users are engaged in the interaction with WOZ. A trend, which shows a reduction in the users' response length or an increase in the response time, can be identified as an indicator of disengagement.

Clustering techniques, namely unsupervised learning based on the K-means algorithm, were used to evaluate the accuracy of the users' role-playing. K-means is used on vectors of real numbers derived from the embedding of users' utterances. Natural Language Processing (NLP) techniques, such as sentence embeddings, can translate natural language utterances into vectors of real numbers while maintaining their meaningful distance. As a result, if the meanings of two users' utterances are similar, the Euclidean distance between the corresponding embedding vectors will be relatively small. The embeddings are computed with the Italian version of an off-the-shelf trained neural network, called Universal Sentence Encoder [223]. The Fowlkes-Mallows Index (FMI) was used to calculate the results, with higher values indicating greater similarity between the estimated clusters and the SP assigned to the user. A high degree of similarity indicates that users' utterances are consistent with the provided SP, meaning that they accurately interpreted the role-playing. Therefore, extracted dialogues may be automatically clustered by role, making this a good starting point for training a VC based on neural networks.

4.4 Results

All the answers of users have a non-normal distribution. There was no missing information, and each participant completed all the items referring to the UX questionnaire.

Descriptive Analyses

Wizard of Oz and Users: Utterances and Response time

Table 2 reports the number of the WOZ and users' utterances together with the number of characters per utterance. Furthermore, the users' response times for each of the 18 dialogues were also calculated.

In terms of utterances, WOZ expressed twice as many utterances compared to the users, as indicated by the means and the 50%. Furthermore, the length of the WOZ messages (i.e., the number of characters per utterance) was more than twice that of the users. These results correspond to the initial goal of co-designing a virtual coaching intervention for healthy coping guided by the VC. Moreover, these findings are also consistent with the proactive role of the WOZ in supporting the self-reflection of users on their emotions as well as in their adoption and cultivation of healthy coping strategies.

On the other hand, in terms of users' response time—assessed in minutes—half of the users responded in 15 minutes on average, with some responding in 2.33 minutes and others in 81 minutes. These results pointed out a good acceptance of the WOZ intervention and participation in the present study, as highlighted by the low number of drop-out rates (i.e., 2 users, 10%).

Table 2. Descriptive analyses of the WOZ and users' utterances, and users' response times (in minutes)

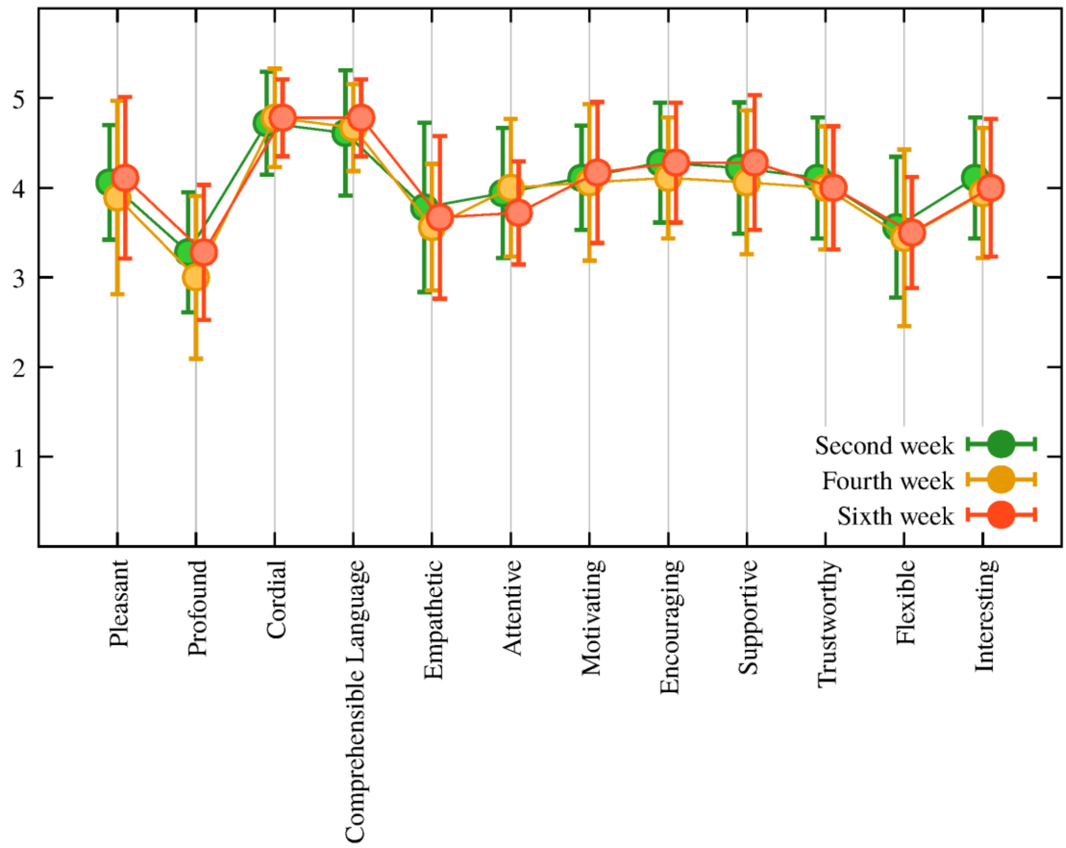
	Number of WOZ utterances	Number of users' utterances	Number of WOZ characters per utterance	Number of users' characters per utterance	Users' response time
Mean	244.39	122.5	86.23	27.98	27.57
SD	19.05	17.7	3.14	9.7	27.20
Minimum	219	95	79.91	13.06	2.23
25%	231.25	111.5	84.4	18.9	5.24
50%	240	120.5	85.96	30.31	15.45
75%	257.25	130	87.74	35.45	48.28
Maximum	283	174	93.61	41.55	81.55

Note. WOZ = Wizard of Oz; SD = Standard Deviation

User Experience questionnaire: positive item response distributions

Overall, the positive items, which refer to the UX questionnaire, indicated a mean greater than 3 on the 5-point Likert scale (M = 4.02, SD = .72), as reported in Figure 3a. In particular, the items Comprehensible Language, Motivating, Encouraging and Supportive slightly augmented every fortnight (2^{nd}, 4^{th}, 6^{th} week). The specific means and standard deviations are shown in the Appendix (Table A3).

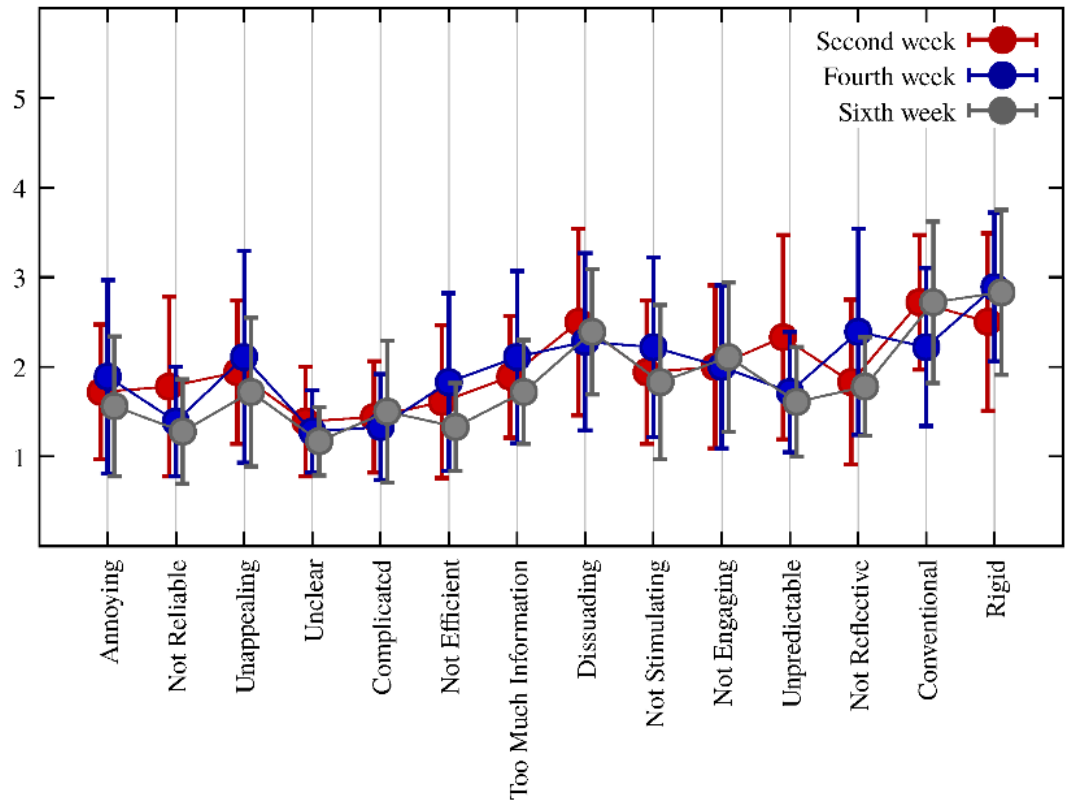
Figure 3a. The plot of the positive items every fortnight week (2^{nd}, 4^{th}, 6^{th} week). Means and standard deviations are represented by circle dots and error bars, respectively (N = 18)



User Experience Questionnaire: negative item response distributions

As displayed in Figure 3b, overall, the mean of the negative items related to the UX questionnaire trends in the expected direction (M = 1.92, SD = .81). Indeed, all items decreased each fortnight. Of particular interest is the item Not Reflective, which decreased in week 6 compared to weeks 2 and 4. Furthermore, the item Unpredictable presented a downward trend each fortnight while the item Conventional showed an upward trend. Lastly, the item Rigid slightly increased in week 4 and slightly decreased in week 6. Again, the specific means and standard deviations are shown in the Appendix (Table A4).

Figure 3b. The plot of the negative items every fortnight week (2nd, 4th, 6th week). Means and standard deviations are represented by circle dots and error bars, respectively (N = 18)



ANOVA repeated measure: Differences in the answers of the UX questionnaire

A series of one-way repeated measure ANOVAs with Bonferroni corrections were carried out, in order to explore potential significant differences on each item's means of the UX questionnaire, administered every fortnight (2^{nd}, 4^{th} and 6^{th} week). The only significant differences were identified for two negative items: each fortnight, Not Efficient [$F(1.652) = 3.752$, $p = .030$], and Too Much Information [$F(1.906) = 3.974$, $p = .025$] presented a reduction in their means. Post-hoc analyses revealed that these differences were significant.

Qualitative Perspective: users' open-ended answers to the UX questionnaire

Table 3 reports the qualitative data gathered from users' free text answers at the UX questionnaire, delivered at the end of the 2^{nd}, 4^{th}, and 6^{th} weeks. This process allowed the understanding of users' interaction with WOZ, and thus their UX. Two pivotal categories were detected by the above-mentioned two judges, yielding (a) *Insights themes* including the subcategories of Pleasant, Natural, Supportive, Stimulating, and Self-Reflective whilst (b) *Challenges themes* comprising the subcategories of Repetitiveness and Restrictive.

Table 3. Users' quotes to the open-ended question provided at the end of the UX questionnaire every fortnight (2^{nd}, 4^{th}, 6^{th} week)

Weeks	Users' Quotes	Insights Themes	Challenges Themes
2	I think it is a pleasant and useful reminder to think about your mood and emotional aspects. (Participant 3)	Self-reflective	
	I find the experience stimulating. (Participant 4)	Stimulating	
	I find this new approach very interesting because without being intrusive, it enables you to have the right support during the day and proposes stimulating activities. (Participant 7)	Supportive	
	The messages stimulate a lot of self-reflection in the present moment. The responses to the messages seem very much in line with what I wrote. (Participant 14)	Natural	
4	I am enjoying the interaction. It is not too forced and often the exchange is pleasant. (Participant 7)	Pleasant	
	I found it to make very stimulating proposals and always try to stimulate a person even when they are not so inclined to undertake a certain activity. (Participant 9)	Stimulating	
	Interesting but sometimes a little repetitive in the advice and suggestions. (Participant 10)		Repetitiveness
	It seems to respond adequately to my answers. When I answer more articulately its answer is often in line with what I wrote. (Participant 14)	Natural	
	I think this is a good way to support. If you follow the suggestions consistently, I think it can be very helpful. (Participant 15)	Supportive	
6	Motibot offers many interesting and not trivial ideas on how to cultivate your well-being. I think it can be very useful, especially for those who do not know this area. Moreover, beyond the content of the messages, I think that having a regular appointment during which you have to stop for 10/15 minutes and think, can have many positive implications. The only criticism, which comes to my mind, and which is perhaps intrinsically linked to the origin of Motibot, is that its "sensitivity" to the answers of the writer could be improved because sometimes one gets the impression that it has not "understood". Despite this, however, since it is a virtual entity, I believe that it performs its function correctly. (Participant 1)		Restrictive
	This path with Motibot has been very positive and useful to take an optimistic, comprehensive, and effective perspective; besides listening to me more, managing my emotions better and taking care of myself as well as others. As a result, I understood how to achieve greater well-being, paying attention to the present moment, and getting in tune with the world. (Participant 6)	Self-reflective	
	I found the proposed activities very interesting and useful to practice; I think it is good to support as it can motivate and encourage. Maybe sometimes I found some proposals and related explanations a bit repetitive among them, but overall, the interaction was very pleasant. (Participant 10)		Repetitiveness

	It was very stimulating. (Participant 12)	Stimulating	
	This bot can help, and support people diagnosed with diabetes. The answers are very much in line with what I wrote. If you write a long and articulate message, the bot will understand if that message is positive or negative and will respond accordingly. Only a few times, it happened that the answers seemed a little out of place. The exercises that are proposed to you are easy to understand and do not require too much time. In my opinion, this allows the person not to interrupt the path, and to follow the advice without too many problems in their working day and not. (Participant 14)	Natural	
	It was a positive experience, gradually I felt more and more involved and motivated to listen to the tracks and the proactive suggestions. (Participant 17)	Supportive	

The Augmented Dickey-Fuller (ADF) test for assessing the user engagement

Table 4 shows the results of the ADF test for each user.

Number of characters per user utterances

A very low-test result suggests that the average number of characters in users' utterances (i.e., second column) or response times (i.e., fourth column) did not change significantly as the dialogues progress. Users' utterances did not tend to be shorter, and their response times did not increase, indicating that user engagement remained consistent. These statistics reveal that all but one of the users were actively engaged in the interaction with WOZ.

Most of the users had a low average number of characters per user utterance as shown by the ADF test, except for user 14. This user presented a lower critical value of -3.49 at 1%; indeed, this user used longer sentences in the last utterances with WOZ, implying a higher level of engagement.

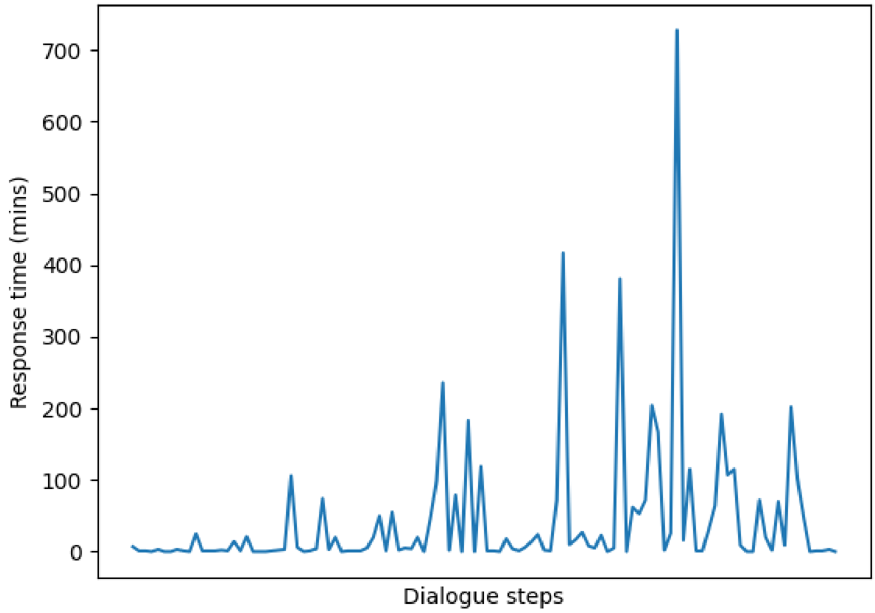
Response time per user

Except for users 5, 11, 15, the test provides good results in terms of average response time per user (critical value of -3.5 at 1% for all). Users 11 and 15 experienced longer behavioural interventions (i.e., audio tracks, video clips), during the last interactions with WOZ, requiring more time to comprehend the content and, subsequently, to react to it. Therefore, even if there is a modest increase in response time in these cases, they cannot be appropriated to disengagement. In these cases, users may require additional time to ponder and respond to WOZ. Furthermore, their test statistics were quite close to the critical criterion, with a p-value lower than .05. User 5 responded with a longer time at the end of the study, showing as the user with the longest reaction time. This trend can be easily confirmed by looking at the plot of the response times, as shown in Figure 4. Notable was the upward trend that began in the central part of the dialogue. Therefore, all users—except for one—were more likely to respond with a non-increasing response time. The goal is not to have a fast response time, but to understand if there is a response time with a non-increasing trend.

Table 4. The statistical test and corresponding p-values for the Augmented Dickey-Fuller (ADF) test regarding the average number of characters and the average response time per user

User	Test Statistics (Mean number characters)	P-value (Mean number characters)	Test Statistics (Mean response time)	P-value (Mean response time)
1	-8.63	5.96*10-14	-9.55	2.65*10-16
2	-9.42	5.57*10-16	-10.22	5.30*10-18
3	-10.12	9.68*10-18	-9.57	2.25*10-16
4	-9.44	4.89*10-16	-11.04	5.50*10-20
5	-8.97	7.85*10-15	-1.94	0.314
6	-11.18	2.52*10-20	-10.8	2.01*10-19
7	-11.66	1.89*10-21	-10.77	2.40*10-19
8	-10.22	5.35*10-18	-11.63	2.23E-21
9	-10.31	3.22*10-18	-10.28	3.78E-18
10	-9.81	5.68*10-17	-12.33	6.40E-23
11	-10.6	6.26*10-19	-3.36	0.012
12	-6.77	2.71*10-09	-9.49	3.59*10-16
13	-7.12	3.84*10-10	-12.1	1.99*10-22
14	-3.24	0.018	-10.88	1.30*10-19
15	-5.76	5.63*10-07	-3.36	0.012
16	-5.55	1.64*10-06	-10.07	1.30*10-17
17	-9.82	5.36*10-17	-10.5	1.07*10-18
18	-5.65	9.98*10-07	-9.73	9.18*10-17

Figure 4. The response times for user 5 according to the progress of the dialogue



Clustering techniques for evaluating the accuracy of users' role-playing

Table 5 reports the cluster results with the K-means algorithm, in which three of the six SP profiles provided to the users are presented. Table 5 does not show three SP profiles because two users with these profiles dropped out from the study and, thus, their data had not been analysed while the third profile, namely Mirta, will be discussed below.

More specifically, the second column highlights the true user-role ID assignment, from now on called the gold standard. On the other hand, the third column shows the clustering run by the algorithm. The names of the SP profiles were deleted from the dialogues to avoid biases when the neural network carried out the embedding.

Below are the results of the clustering of users' roles:

- All users who played role A were clustered, except users 0 and 4.
- Users who interpreted role C are split since user 6 played a different role; indeed, user 7 is clustered with user 6.
- Users who played role E are grouped correctly.

FMI is described as a metric in which higher values indicate better performance. In the present study, FMI equal to .32 indicated a somewhat low performance. However, removing the users who played the SP profile of "Mirta"[5], resulting in an FMI of .72, indicating a high level of similarity between the cluster and the gold standard. These findings showed that the users that role-played Mirta's profile did not interpret it accurately. The remaining users, on the other hand, performed their roles accurately.

[5]Mirta is a woman of 70 years with T2DM (see the whole description in Appendix, Table A2).

Table 5. The k-mean results (third column) compared to the true user-role ID assignment (second column) for each user in the first column

User ID	Gold standard role ID (name)	Predicted role ID
0	A (Alessandra)	cluster_0
1	A (Alessandra)	cluster_1
2	A (Alessandra)	cluster_1
3	A (Alessandra)	cluster_1
4	B (Alessandra)	cluster_2
5	C (Federico)	cluster_3
6	C (Federico)	cluster_4
7	D (Federico)	cluster_4
13	E (Simona)	cluster_3
14	E (Simona)	cluster_3
15	E (Simona)	cluster_3
16	E (Simona)	cluster_3
17	E (Simona)	cluster_3

4.5 Discussion

This preliminary study deployed an original approach to the process of designing and prototyping an intervention protocol. The use of the WOZ method combined with the SP approach represents a valuable resource in designing an intervention protocol since it informs the design of a more natural dialogue flow. A recent study showed that the application of the WOZ method in the development of a VC intervention to detect stress among older people emphasised users' needs, further allowing greater freedom within the dialogue process [224].

Acceptability and User Experience

As a preliminary test, this study highlighted how the ratio between the number of WOZ utterances over the number of users' utterances provided useful information regarding the WOZ's potential support in fostering self-reflection. Indeed, a ratio close to one implies an under-informative VC and, as a result, a low self-reflection role, while a high ratio shows an over-informative VC, provoking undue stress for users. In this regard, the dialogues delivered by WOZ were twice as long as the answers given by the users: as consistent with the design of the intervention protocol. Indeed, WOZ did not require a large amount of text input and information from users, as highlighted by the low mean of the number of characters used in users' utterances. WOZ demonstrated adequate support to the user without being too intrusive or delivering too much information, emerging from the analysis of ANOVA repeated measure. Moreover, all these above-mentioned results are in line with the aim of the VC protocol to encourage users to reflect on their emotions by teaching them healthy coping strategies, such as mindfulness exercises, for improved chronic disease management. Furthermore, each day the users were asked to reflect on and express their emotions so that they could become more aware of them and, in turn, modulate them with the additional support of mindfulness exercises. In other words, WOZ is perceived as less demanding while remaining sufficiently engaging for users. Altogether these provide evidence of a minimal standard deviation in the WOZ utterances, which is a valuable input for its improvement. The advantage of the WOZ method, and thus the virtual coaching, in terms of user reaction time, is that it allows users to think and reflect on the suggested motivation and behavioural interventions: some users require more time to respond than others. Furthermore, the positive items' average was higher than the median value of 3, while the negative items' average was lower than 3. These findings showed that users had a positive perception of interaction with the VC (simulated). In line with these findings, the analyses that emerged from the UX questionnaire revealed that the digital healthy coping intervention was perceived as supportive, encouraging, motivating, and able to trigger self-reflection on their emotions. Moreover, users found the simulated VC as predictable and conventional as each fortnight progressed: one can assume that users understood the flow of the dialogues, thus feeling more confident and secure in interacting with the simulated VC.

Users' qualitative contents

Qualitative analyses confirmed the above-mentioned quantitative data and allow a thorough understanding of the users' perception regarding the interaction with the simulated VC. Users perceived the simulated VC as supportive, enabling them to self-reflect on their emotions and doing mindfulness exercises; they also found it natural and pleasant in its interaction. On the other hand, it was considered slightly restrictive in its VC intervention and sometimes repetitive in its suggestions. However, users perceived WOZ as effective in stimulating their thoughts and in supporting their use of healthy and new coping strategies.

Users' engagement and accuracy in their role-playing technique

The clustering algorithm highlighted that most users interpreted the provided role accurately, even when they personalised it. Indeed, users used the same words for the same role and a high level of accuracy emerged in clustering users according to their roles. Once the dialogues were collected, they were organised into clusters according to their roles to provide an initial dataset for training a VC using neural networks. Therefore, these neural networks enabled users to respond more precisely throughout the intervention. These encouraging results of the clustering analysis applying neural networks suggest that these algorithms can distinguish between the various SP's roles. Therefore, they may be able to respond with personalised interventions in accordance with the SP profiles. For example, Cohen, Kitai, David, and Ziv suggested that the SP approach represents the most effective method for training primary care physicians and reduces the number of patients with uncontrolled asthma by 27%, allowing them to better manage their condition [225]. Even though most of the users played their role accurately, those who interpreted Mirta's profile experienced some difficulties. This finding may be due to the age differences between the SP and users. Indeed, as previously mentioned, Mirta is a woman aged 70 years, and, on the other hand, users present a mean age equal to 23.61 years. Lastly, all but one user was actively engaged with WOZ: they did not shorten their answers to the VC or increase response times as a result of repetitive or uninteresting interaction, thus confirming a stable and positive engagement level with WOZ.

Bearing all these findings in mind, it is important to note that several refinements on the intervention protocol were carried out.

As regards the motivational content, new healthy coping strategies were added that enable people with DM to adopt a positive attitude towards their diabetes management. For example: *Thinking about a positive episode related to their DM, describing it, and expressing the associated emotion*. Moreover, the intervention protocol was also updated, including the Frequently Asked Questions (FAQs) gathered from the users' conversations, as well as potential responses, such as: *"What did you mean with gratitude?", "Aren't you going to send me a video or a recording today?"*, *"How can I improve my motivation?"*, *"What strategies will you teach me to be more mindful?"*. Based on these FAQs emerging from users, others were added in the prediction of other potential FAQs from the users, such as: *"What is this test for?"* (Aim) *"How will the collected data be processed?"* (Data collection), *"How long is the test?"*(Length), and *"How long does it take to complete it?"* (Duration).

The present preliminary study presented some limitations. The choice of involving psychology students instead of real patients with DM could be considered suboptimal, however it is derived from the need to improve the intervention protocol from the perspective of the users' experience without comprising the overall well-being of vulnerable users, such as patients. The adoption of the WOZ method and the SP approach allows the iterative refinement of the intervention protocol, before delivering it to real patients. This iterative procedure, which involved both mental health and BITs experts as well as psychology students with their SP roles, enabled the collection of several interesting insights to improve the protocol and, thus, an implementation of a more effective intervention.

4.6 Conclusions

The preliminary results of the present study are encouraging: the VC intervention tested was well-accepted. Indeed, users found WOZ as supportive in triggering self-reflection on their emotions, as well as encouraging the adoption of healthy coping strategies through motivational and behavioural interventions. Furthermore, the WOZ method combined with the SP approach enabled an effective and real-time refinement of the intervention protocol. In this context, the application of clustering techniques for investigating the accuracy of users' role-playing is an original contribution provided by this study. Indeed, the dataset of dialogues collected—the quality of which has been verified—provide a useful source for training an algorithm to substitute the role of a human coach. As a consequence, this preliminary study enables the collection of key insights from users, which are potentially useful in designing future versions of the VC prototype and intervention.

CHAPTER 5. THE DEVELOPMENT OF MOTIBOT FOR HEALTHY COPING INTERVENTION IN ADULTS WITH DIABETES: A PROOF-OF-CONCEPT STUDY

The present Chapter is dedicated to the *third study*[6] of the Ph.D. project, which represents the evolution of the previous work [226]. The current proof-of-concept study assessed the preliminary efficacy of a Virtual Coach (VC) intervention, called Motibot—the abbreviation for Motivational bot—aimed at providing psychosocial support to adults with Diabetes Mellitus (DM). More specifically, the Motibot intervention has the purpose of reducing symptoms of anxiety, depression, perceived stress, and diabetes-related emotional distress as well as of improving their well-being, by motivating them to acquire and cultivate healthy coping strategies, such as mindfulness practice. This study also attempted to assess the User Experience (UX) and the User Engagement (UE) encounter from both qualitative and quantitative standpoint regarding the interaction with Motibot.

***Study 3.* Motibot: A Virtual Coach for Healthy Coping Intervention in adults with diabetes, a Proof-of-Concept study**

In the present study, Motibot was implemented and interacted with adults with T1DM or T2DM. The decision to also include adults with T1DM was based on the results of previous studies (i.e., study 1 and study 2). In particular, according to the results of the meta-analysis (i.e., study 1), the type of DM, which was considered as a moderator in the efficacy of digital interventions, was not statistically significant [169]. Therefore, these results suggested that these authors referred to the broader concept of DM while they were designing the digital intervention, implying that their lifestyles are similar [169]. On the

[6]Bassi G, Giuliano C, Perinelli A, Forti S, Gabrielli S, Salcuni S. Motibot—The Virtual Coach for Healthy Coping Intervention among adults with diabetes: A Proof-of-Concept study. *JMIR Human Factors*, 2021. doi: 10.2196/32211

other hand, based on the results of the previous study (i.e., study 2), the intervention protocol was shown to be transversal, namely suitable for people with T1DM and T2DM.

In this proof-of-concept study, Motibot was accessible through personal smartphones within the Telegram messaging platform. It is worth noting to give a brief mention regarding the main features of the Telegram messaging application. A quite recent study showed that Telegram provides better back-up and security features compared to WhatsApp [227]. For example, all messages in Telegram are secured via client-server/server-client encryption. Indeed, for the above-mentioned reasons, these authors suggested that Telegram is preferable to WhatsApp, and is also suitable for the development of VC [227]. The ability to execute commands in a Telegram chat, which then trigger activities or request information, is a key feature of a Telegram VC [228]. For example, the command "/help" can be sent to the VC, which will then output all the commands available to this VC as text feedback in the conversation [228]. Furthermore, Telegram VCs are usually public, all people can find and use them; however, Telegram VCs can be also accessible to specific people if a separate communication channel with the VC is established [228]. This channel is a private group, comprising three people: the individual who develop the VC, the user, and the VC itself [228]. The process of creating a VC is usually straightforward. The virtual user "*Botfather*", which is the central development tool for Telegram VC, is there to support the individual who has the goal of creating a VC [225].

5.1 Aims

As mentioned above, Motibot—via Telegram—intends to support adults with T1DM or T2DM in reducing symptoms of depression, anxiety, perceived stress, and diabetes-related emotional distress as well as in improving their well-being, by motivating them to adopt and cultivate healthy coping strategies, which should be flexible to the users' needs, according to the American Association of Diabetes Educators (AADE) guidelines [76].

More specifically, this proof-of-concept study had three objectives:

1. To investigate the preliminary efficacy of Motibot intervention as relates to symptoms of depression, anxiety, perceived stress at pre-, post-intervention and follow-up, as well as diabetes-related emotional distress and well-being, evaluated only at follow-up.
2. To explore UX and UE during the interaction with Motibot.

3. To assess semi-structured interviews on both UX and how patients felt during the interaction with Motibot through the text mining approach, as explained in the Data Analysis section.

5.2 Participants Recruitment

In this study 18 voluntary Italian adults with T1DM or T2DM were recruited through Social Network Sites (i.e., Facebook groups) using snowball sampling. Due to the withdrawal from the study of 5 adults for personal and medical reasons, the final sample consisted of 13 adults aged from 18 to 51 years (M_{age} = 30.08, SD = 10.61), with 77% (N = 10) being females.

Participants reported an overall mean diabetes duration of 10 years, in which 61.5% (N = 8) of adults had T1DM and 38.5% (N = 5) had T2DM. One participant did not fill in the questionnaires regarding the psychological measures administered at post-intervention, and thus, was excluded from the analyses.

The following eligibility criteria required were: *(a)* having been diagnosed with T1DM or T2DM and *(b)* owning a smartphone with a Telegram account. On the other hand, the exclusion criteria were: *(a)* women with gestational DM, *(b)* adults with prediabetes or at risk of DM, and *(c)* children and adolescents with T1DM or T2DM.

The term “patients” will from now on be used in order differentiate the participants of this study from those of the previously described study.

5.3 Materials and Method

Procedure

The proof-of-concept is the fourth phase of the Obesity-Related Behavioural Intervention Trials (ORBIT) framework [215], which provides guidance during the entire process. To optimise successive iterations of the intervention, the ORBIT model emphasises the significance of adopting an empirical, evidence-based approach, in which the patient is at the centre of the design process [215].

Moreover, the author of the present thesis was monitoring each chat between Motibot and the patient, in order to support him/her with any issues that might arise during the interaction.

The study procedure was carried out in accordance with the Declaration of Helsinki (Italian law 196/2003, UE GDPR 679/2016). The Interdepartmental Ethical Committee of Psychology of the University of Padova (Italy) approved the project (number 3968, 3rd February 2021).

Patients agreed to participate in the study as well as to a semi-structured interview one month after the end of the study, by signing a written informed consent form delivered via mail. In this latter form was underlined that their data would be confidential, that they could omit any information they did not want to share, and that they could leave the study at any time without giving any explanation.

Intervention Description: Motibot design

Motibot was developed using Rasa, and, subsequently, was deployed via the Telegram messaging platform. In particular, Rasa is an open-source and robust framework designed for the development and training of VCs [229]. The framework provided by Rasa is based on Machine Learning (ML) libraries and pre-trained embeddings from language models, thus enabling the creation of a VC for specific languages by linking ML frameworks and rule-based dialogue.

Natural Language Understanding (NLU) [168], which is a ML technique, allows Motibot to interpret patients' messages, as shown in Figure 1. NLU—together with the conversational history and a set of predefined rules—defines the transition from one dialogue exchange to the next. As a result, the NLU system was trained using a dataset that includes 6899 examples of patient utterances, distinguished in intents and annotated with entities. Examples of intents were as follows: *affirm, deny, say your name, say what you feel, schedule the next meeting and express the level of motivation*. Examples of entities were as follows: *the user's name, the emotion felt, the date and time of the next meeting* and *the level of motivation.* NLU was used for the interpretation of intents and entities. In the present study, 54 intents and 6 entities were identified. Intents and entities were gathered from patients' messages in interaction with Motibot and, subsequently, categorised using the Dual Intent and Entity Transformer (DIET), a trained multi-task transformer architecture [230].

As mentioned in Chapter 4, the intervention protocol was designed to last 6 weeks. These 6 weeks comprise 12 sessions of 10-20 minutes each. In the present study, each session was scheduled by the patient himself/herself to better suit him/her needs; therefore, the term "session(s)" will from now on be used. Furthermore, patients could answer Motibot by entering text or touching a button on their smartphone screen.

As displayed in Figure 2, the intervention protocol was designed using the Transtheoretical Model of Change (TTMC) approach [132], which enables Motibot to assess what motivational state the patient is in and consequently send the most appropriate type of psychoeducational intervention, which is based on the patient's motivation to change their behaviour. In particular, the intervention protocol relied on evidence-based frameworks linked to the healthy coping construct [76] and to Mindfulness-Based Cognitive Therapy [216] for supporting and motivating the development and/or improvement of their coping strategies.

More specifically, at the beginning of the first session, Motibot asked the patient to introduce himself/herself. After that, Motibot sent a video presentation of itself, its functionality, and its main features, in order to involve the patient in the interaction. Thereupon, Motibot delivered three questionnaires to assess the levels of depression, anxiety, and perceived stress symptoms. These three questionnaires were also sent at post-intervention and at follow-up. In addition, two psychosocial scales were added to investigate diabetes-related emotional distress and well-being, which were evaluated only at follow-up, namely two months after the end of the study. These two scales were included to understand if coping strategies had been internalised, therefore assuming a greater well-being. Furthermore, Motibot sent two other questionnaires: one for evaluating UX (i.e., an adapted version of the User Experience Questionnaire) during the whole interaction and the other (i.e., User Engagement Scale-Short Form) for understanding the patients' overall and ultimate involvement. Semi-structured interviews were performed one month after the end of the study to further understand UX and how patients felt when interacting with Motibot. Altogether these questionnaires will be described below in the Measure section.

Every day, Motibot asks the patient what emotion he/she is experiencing at that time, as well as the intensity of that emotion, in order to support him/her in becoming more aware of his/her own emotions and in self-reflecting on them. Following this question, Motibot asks patients *"How much do you want to improve your well-being on a scale from 1 (not at all) to 10 (very much)?"* to understand their motivation to keep their DM under control, according to the TTMC framework and following the state of change ruler (i.e., pre-contemplation state, contemplation, preparation, action, maintenance) [132]. More specifically, as reported in Figure 2, when patients are in the *pre-contemplation state*, thus Motibot tries to explore why they were feeling this way and then tries to support them in becoming emotionally aware by guiding them through self-reflection on their emotions and the importance of taking care of both their body and mind. Motibot provides motivational interventions when patients are in the *contemplation state*, focusing attention on the costs and benefits of adopting a healthier behaviour to promote psychosocial well-being. Finally, when patients are in the *action state*, Motibot sends audio tracks or video clips relevant to mindfulness practices as behavioural interventions.

Figure 1. Motibot: A Virtual Coach for psychosocial support

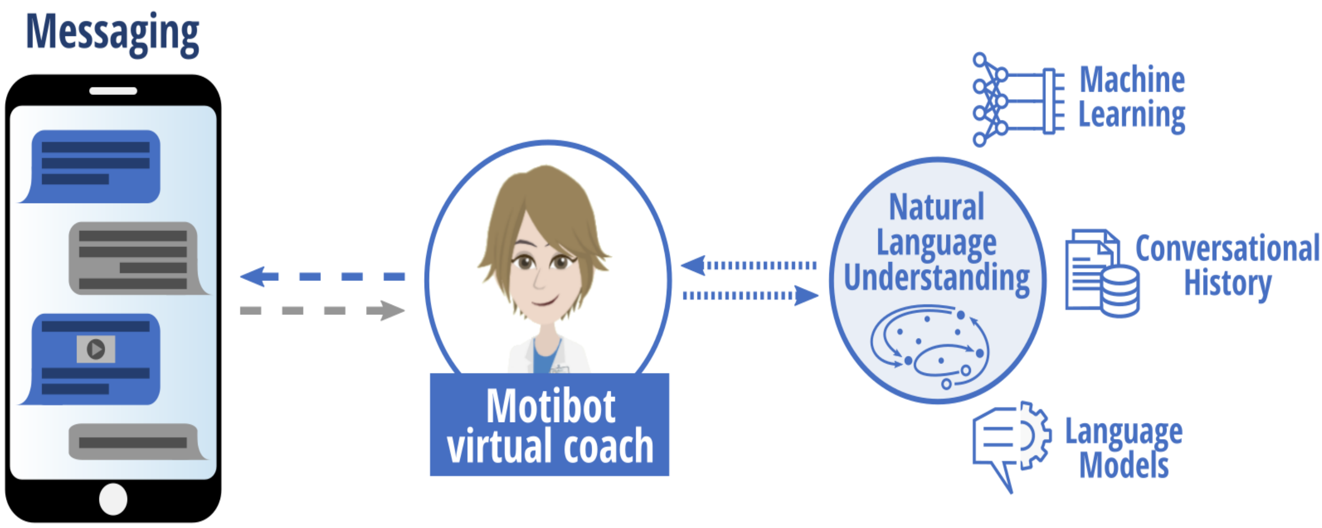
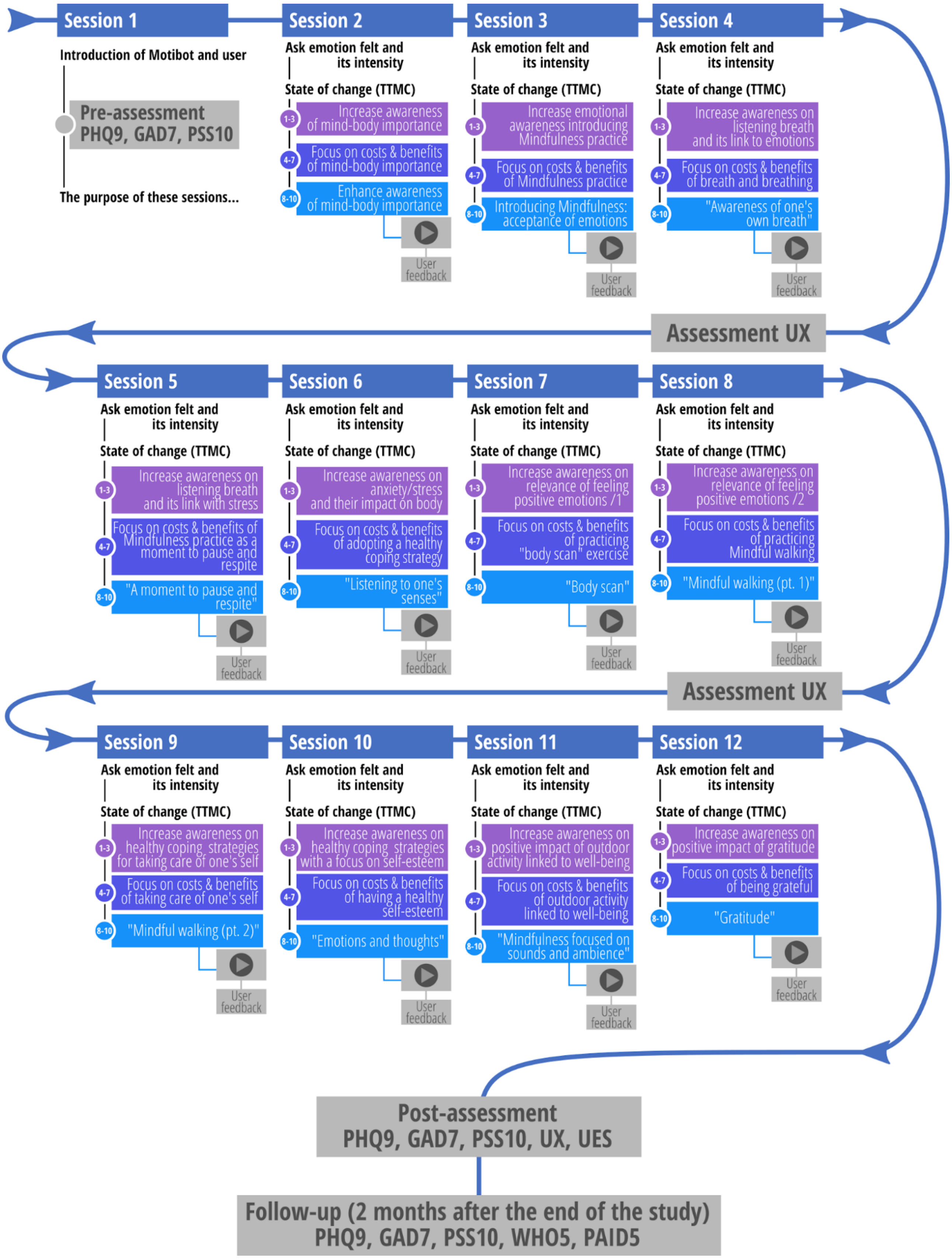


Figure 2. Graphical representation of the intervention protocol delivered to patients as well as its chronological structure



Measures

As reported in Table 1, the psychosocial questionnaires were administered at pre-, post-intervention, and follow-up. Moreover, semi-structured interviews were conducted one month after the end of the study.

Table 1. Overview of questionnaires administered and of their administration timing

Pre-Intervention	At second, eighth and twelfth session	Post-Intervention	1 month after the end of the study	At follow-up (2 months after the end of the study)
PHQ-9 (Depression)	UX (User experience)	PHQ-9	Semi-structured Interviews	PHQ-9
GAD-7 (Anxiety)		GAD-7		GAD-7
PSS-10 (Perceived stress)		PSS-10		PSS-10
		UES-SF (User engagement)		WHO-5 (Well-being)
				PAID-SF-5 (Diabetes-related emotional distress)

Note. PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; PSS-10 = Perceived Stress Scale-10; UX = User Experience; UES-SF = User Engagement Scale-Short Form; WHO-5 = World Health Organization-5 Well-Being Index; PAID-SF-5 = Problem Areas in Diabetes Scale-Short Form-5.

The Patient Health Questionnaire-9 (PHQ-9) [143] is a brief self-reported unidimensional measure developed to evaluate and monitor the severity of depression symptoms within the previous two weeks. The questionnaire consisted of 9 items based on a 4-point Likert scale from 0 (never) to 3 (almost every day). PHQ-9, which integrates the DSM-IV-TR criteria, has a total score ranging from 0 to 27, with a score of 10 indicating the optimal cut-off for detecting clinically significant depression. The PHQ-9 questionnaire encompasses five categories of severity: *(1)* absent (scores 0-4); *(2)* subthreshold depression (scores 5-9); *(3)* mild depression (scores 10-14); *(4)* moderate depression (scores 15-19) and *(5)* major depression (scores 20-27). The following is an example of item 2: *"During the previous two weeks, have you felt down, depressed, hopeless?"*. PHQ-9 has demonstrated good psychometric properties [143].

The Generalized Anxiety Disorder-7 (GAD-7) [231] is a brief self-reported unidimensional measure designed to screen potential cases of GAD and to evaluate the severity of symptoms in the previous two weeks. The questionnaire includes 7 items rated on a 4-point Likert scale from 0 (never) to 3 (almost every day). GAD-7, which integrates the DSM-IV-TR criteria, has a total score ranging from 0 to 21, with a score of 10 highlighting the cut-off for this disorder. The questionnaire includes three categories of severity: *(1)* mild anxiety symptoms (score ≥ 5), *(2)* moderate anxiety symptoms (score ≥ 10), and *(3)* severe anxiety symptoms (score ≥ 15). The following is an example of item 2: *"During the previous two weeks, how often did each of the following problems bother you? Not being able to stop worrying or keep worries under control"*. GAD-7 has shown to have good validity and reliability [231].

The Perceived Stress Scale-10 (PSS-10) [232] is a brief self-reported unidimensional measure, developed to investigate individuals' perception of stress in the previous month. The PSS scale is a measure of how each event in one's life is considered as stressful; indeed, the items are designed to assess how people perceived their lives as unpredictable, uncontrollable, or overloaded. The scale further includes questions regarding the current levels of perceived stress. PSS encompasses 10 items rated on a 4-point Likert scale from 0 (never) to 5 (very often). The total score of PSS ranges between 0 and 40, in which high scores highlight an increased level of perceived stress. Furthermore, PSS consisted of three categories of severity: *(1)* low perception of stress (scores 0-13), *(2)* moderate perception of stress (scores 14-26), and *(3)* high perception of stress (scores 27-40). The following is an example of item 2: *"In the previous month, how often did you feel that you were not* *able to have control over the important things in your life?"*. PSS-10 indicated good psychometric properties regarding reliability and validity [232].

The Problem Areas in Diabetes Scale-Short Form-5 (PAID-SF-5) [233] is a self-reported unidimensional measure designed to investigate diabetes-related emotional distress. The questionnaire includes 5 items rated on a 5-point Likert scale from 0 (not a problem) to 4 (serious problem). PAID-SF-5 presents a total score, which range between 0 and 100, with higher scores (i.e., ≥ 40) suggesting greater diabetes-related emotional distress. PAID-SF-5 has been shown good psychometric properties [233].

The World Health Organization-5 Well-Being Index (WHO-5) [234] is a self-reported unidimensional measure, which assesses the psychological well-being, a key component of quality of life. The questionnaire comprises 5 items rated on a 6-point Likert scale from 0 (never) to 5 (always). The total score was recomputed in order to present a range from 0 to 100, in which a score ≤50 indicating poor psychological well-being and a score ≤28 likely suggesting depression. The scale has been demonstrated good psychometric properties [234].

The User Engagement Scale–Short Form (UES-SF) [235] is a brief self-reported questionnaire designed to evaluate the user engagement in interaction with a digital solution. UES-SF consisted of 12 items rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). UES-SF includes four factors: *(1)* Focused Attention refers to the feeling of being completely absorbed in the interaction (e.g., *"I lost myself in this experience"*), *(2)* Perceived Usability[7], which is the negative impact of the interaction and the time spent on it (e.g., *"I felt frustrated while using Motibot"*), *(3)* Aesthetic Appeal refers to the graphical and visual attractiveness of a digital solution (e.g., *"Motibot was aesthetically appealing"*), and *(4)* the Reward factor (e.g., *"Using Motibot was worthwhile"*). This latter factor is a single set of three factors from the original UES questionnaire [233], such as *endurability*, which assesses the overall success of the interaction, *novelty*, which explores the overall interest in interacting with a digital solution, and finally, *felt involvement*, which investigates the overall enjoyment of the interaction. The overall scale has proved to be reliable [235].

[7]This factor is the only one in which scores were reversed.

The User Experience (UX) questionnaire is a modified version of the original UEQ [236] in order to align the bipolar adjectives with the aims of the current study. In particular, the questionnaire included 28 adjectives either positive or negative—as shown in Table 2—designed to evaluate the experience of interacting with Motibot. In this questionnaire, two items were added to the previously described study, such as *"Effective"* and *"Not Effective"*, in order to investigate the preliminary efficacy of this proof-of-concept study. Each item was rated on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree).

Table 2. The User Experience questionnaire: Positive and Negative items

Positive Items	**Negative Items**
Pleasant	Annoying
Profound	Not Reliable
Cordial	Unappealing
Comprehensible Language	Unclear
Empathetic	Complicated
Attentive	Not Efficient
Motivating	Too Much Information
Encouraging	Dissuading
	Not Stimulating
Supportive	Not Engaging
Trustworthy	Unpredictable
Flexible	Not Reflective
Interesting	Conventional
Effective	Not Effective
	Rigid

Semi-structured interviews were performed by the author of the present thesis with all participants who concluded the interaction with Motibot. The semi-structured interview was based on 11 ad hoc questions that were asked a month after the end of the study and lasted around 10 minutes. Each interview began with a question regarding the patients' purpose for participating in the present study and ended with a question regarding whether or not they would recommend Motibot to other people with the same chronic illness, along with an explanation of why. As shown in Table 3, the remaining 9 questions were divided into two sections. The first consisted of 5 questions regarding the patients' experience with Motibot; thus, the purpose was to evaluate UX. The second section, on the other hand, comprised 4 questions regarding how patients felt throughout their interaction with Motibot.

Table 3. Questions asked to patients during semi-structured interviews

User Experience	How patients felt during the interaction
What motivated you to participate in the study?	
What were your expectations with regard to Motibot?	Motibot proposed several audio tracks regarding mindfulness. How was this mindfulness experience for you?
With regard to Motibot, which aspect did you like the most?	Did you find Motibot useful to find a mindful moment for yourself?
With regard to Motibot, which aspect did you dislike the most?	Did Motibot help you to soothe any anxiety, stress and/or depression symptoms?
With regard to Motibot, how was your user experience?	Did you listen to Motibot mindfulness audio tracks again at the end of the study?
Would you be interested in using a complete virtual coach in the future?	
Would you suggest Motibot to someone with Diabetes Mellitus? Why?	

Data Analysis

Statistical analyses were carried out through R, version 4.0.0 (The R Foundation) [218], and SPSS Statistics, version 24.0 (IBM Corp) [219].

The Shapiro-Wilk test was performed in order to assess the normality of the sample distributions referring to the considered variables in the current study.

Descriptive analysis was run regarding psychological dimensions: depression, anxiety, and perceived stress, at pre-, post-intervention and follow-up; the same analysis was performed on diabetes-related emotional distress and well-being, at follow-up only. These data are shown through plots.

Means and standard deviations were also calculated regarding the UX questionnaire, which was administered at 4^{th}, 8^{th}, and 12^{th} session, as well as regarding the UE scale, which was delivered at the end of the study. The data regarding the UX questionnaire are shown through plots.

Kruskal-Wallis non-parametric test was applied to assess differences in symptoms of depression, anxiety, and perceived stress. A post-hoc Wilcoxon non-parametric test was then used to compare the differences in the psychosocial outcomes at pre-, post-intervention, and follow-up, in order to investigate if the psychoeducational intervention was beneficial.

A text mining approach [237,238] was used in order to gather data from the semi-structured interviews on UX and on how patients felt during the interaction with Motibot. This analysis was carried out using the R package "Quanteda" [239] and custom shell scripting language in a Linux environment. The analyses were conducted on the written interview transcripts (Italian) as per the following explanation: the transcripts were first cleaned by substituting uppercase letters with lowercase letters and deleting numbers, punctuation, and stopwords; subsequently, patient's answers were clustered into groups, in which each group comprised all answers to one among the interview questions. In particular, two phases of analysis were carried out: *(1)* extraction of three sets of responses (i.e., yes/no/maybe) from some of the questions in the semi-structured interviews; *(2)* extraction of concepts that recur (i.e., word stems) and their associations in terms of di-grams (i.e., pairs of word stems) from the remaining questions. A word stem was considered recurrent if it appeared at least 3 times across interviews, and di-grams were classified recurrent if they appeared at least

2 times across interviews. According to the following rule-of-thumb, the threshold for including a stem was set at 3 occurrences: stems were considered significant if they belong to the 5% most frequently occurring. However, since occurrence is measured as an integer number, this percentile criterion can only be applied roughly. Setting the minimum occurrences requirement to 3 yielded the extraction of between 3.8% and 7.9% most recurrent stems (average 6.2%) for the different questions, which is within reasonable compliance with the 5% threshold specified above. Furthermore, the average stem occurrence for a given question was 1.35, thus, a threshold of 3 occurrences is equal to a stem recurring more than twice as frequently as the average.

5.4 Results

A non-normal distribution emerged regarding the variables considered in the present study. As noted in the Participant section, only one patient did not complete the entire post-intervention questionnaire and was thus excluded from the analysis of the psychosocial variables.

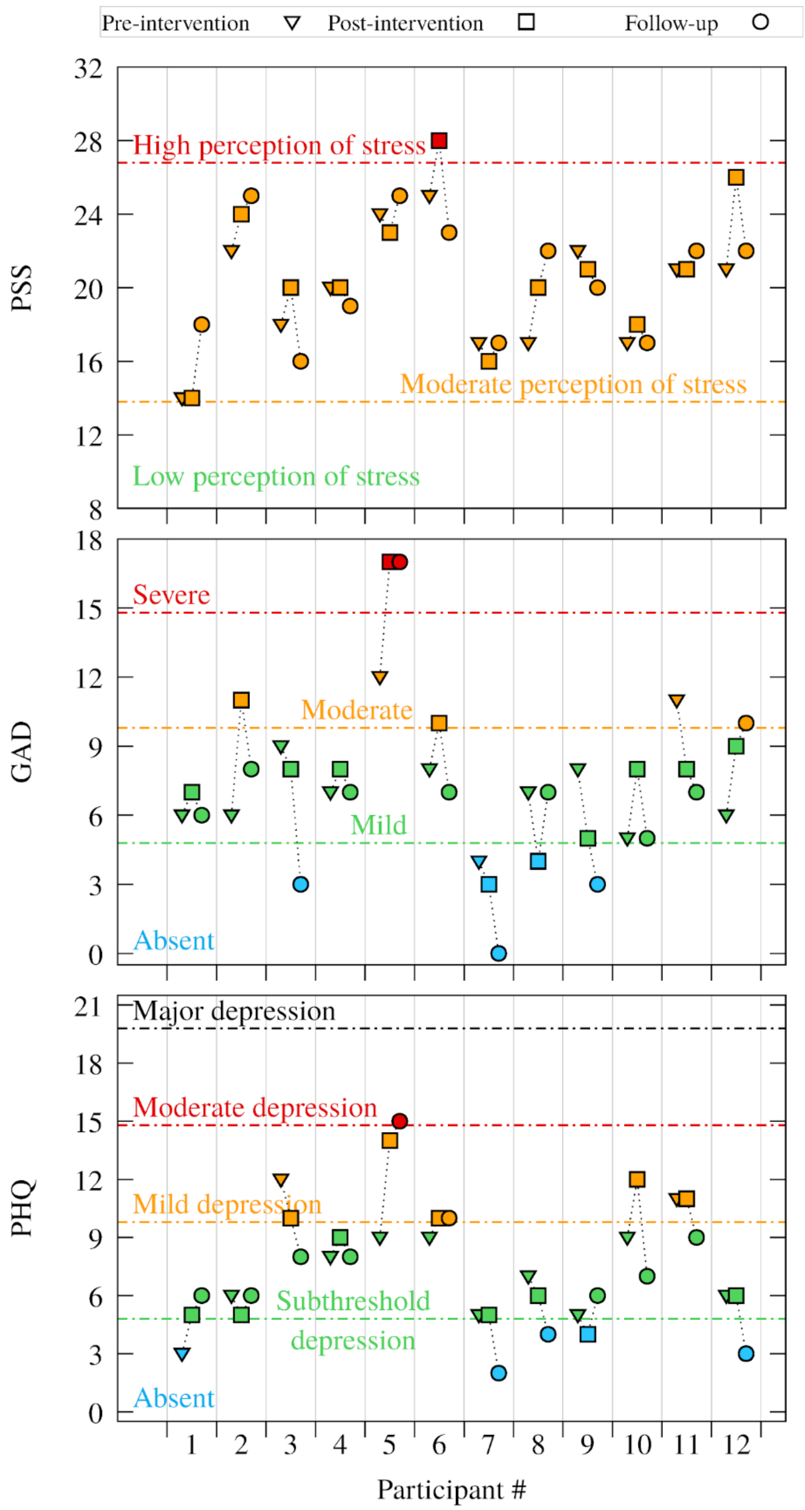
Descriptive Analyses

Perceived Stress, Anxiety and Depression Symptoms assessed at pre-, post-intervention and follow-up

As shown in Figure 3, all patients highlighted moderate symptoms related to perceived stress (evaluated through PSS-10). At post-intervention, only patient 6 showed a high perception of stress; however, at follow-up, the level of perceived stress has decreased.

Except for patient 5, who had severe symptoms at each period, thus resulting in an outlier, the remaining users showed increased symptoms of anxiety and depression (assessed through GAD-7 and PHQ-9, respectively) at post-intervention and a reduction at follow-up.

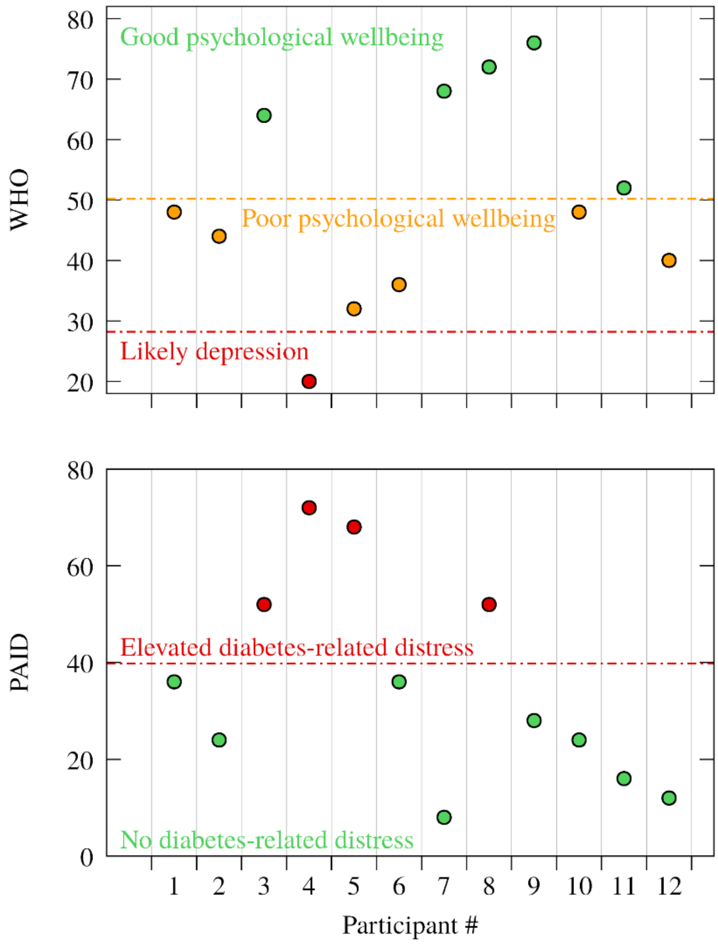
Figure 3. Plots regarding symptoms of perceived stress, anxiety, and depression, assessed through PSS-10, GAD-7, and PHQ-9, respectively, at pre-intervention, post-intervention, and follow-up (N = 12)



Well-being and diabetes-related emotional distress assessed at follow-up

As displayed in Figure 4, when considering the presence of the outlier, patients showed a range between poor and good psychological well-being (assessed through WHO-5), with an overall mean of 50.00 (SD = 17.18), which suggests poor psychological well-being. However, if the outlier is removed the overall mean is equal to 51.64 (SD = 17.01), which indicates, on average, a borderline psychological well-being. In terms of diabetes-related emotional distress (as measured by PAID-5), the majority of patients showed a moderately high diabetes-related emotional distress; indeed, the total mean is 35.67 (SD = 21.20). If the method applied above is used and, therefore, if the outlier is removed, the overall mean is equal to 32.73 (SD = 19.50), which is an even smaller value, indicates low levels of diabetes-related emotional distress.

Figure 4. Plots regarding well-being and diabetes-related emotional distress, assessed through WHO-5 and PAID-SF-5, respectively, at follow-up (N = 12)[8]

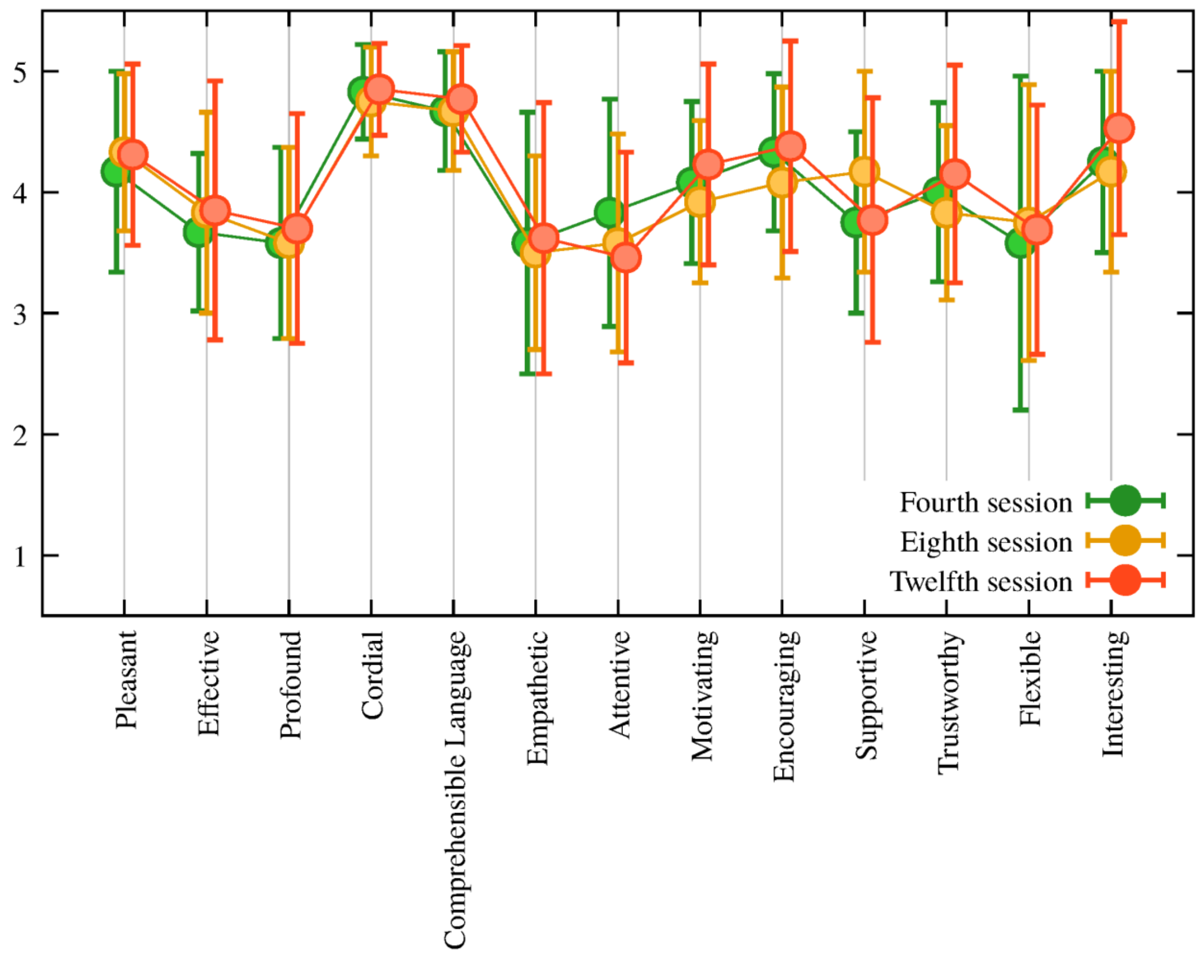


[8]In this Figure the outlier was not removed.

User Experience questionnaire: positive item response distributions

As reported in Figure 4a, analyses of the positive items (evaluated through the UX questionnaire) showed a mean greater than 3 on the 5-point Likert scale (M = 4.04, SD = 0.22). More specifically, the items Comprehensible Language, Empathetic, Motivating, Encouraging, and Interesting showed an upward trend from the 2nd to the 12th session, while the item Supportive showed a downward trend from the 2nd to the 12th session. The precise means and standard deviations are reported in the Appendix (Table A5).

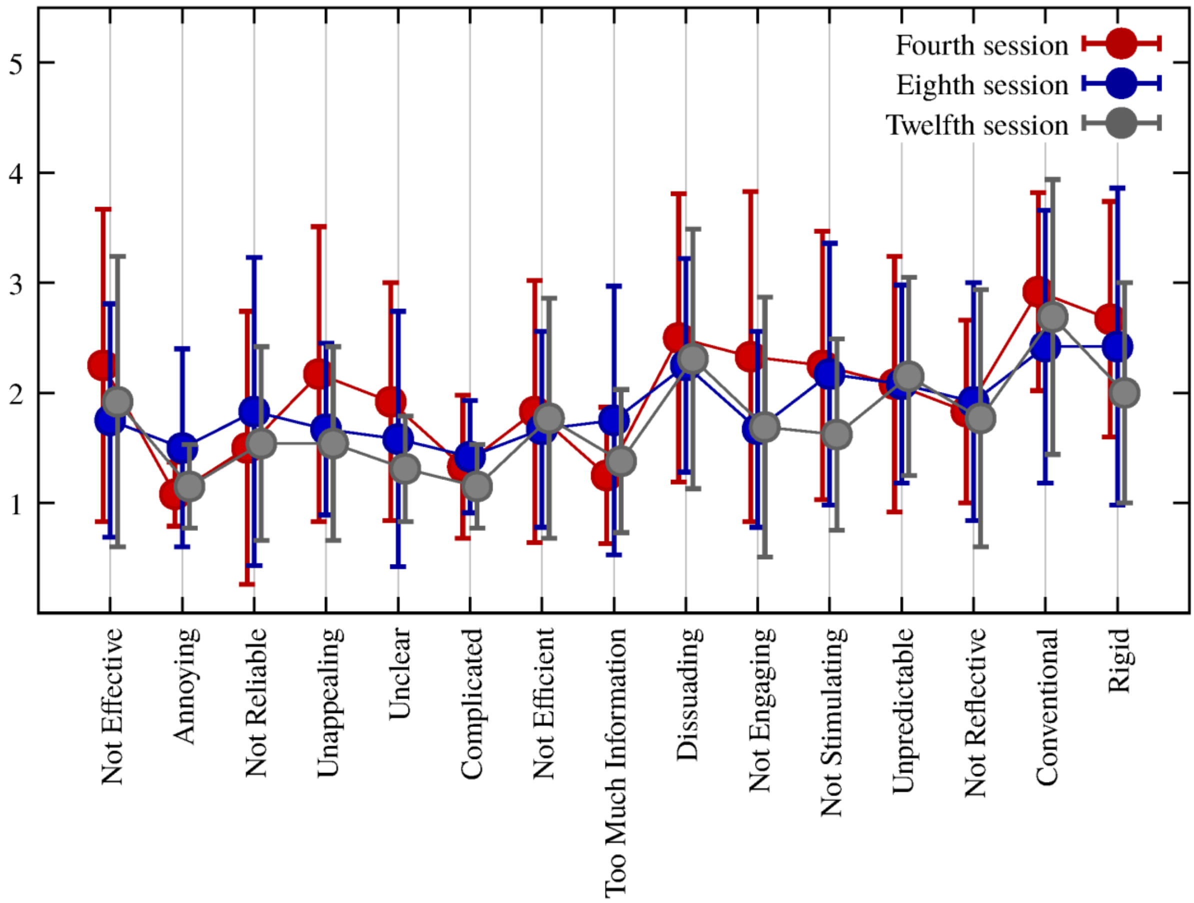
Figure 4a. Plot of the positive items of the UX questionnaire. Means and standard deviations are represented by circle dots and error bars, respectively (N = 13)



User Experience questionnaire: negative item response distributions

As displayed in Figure 4b, analyses of the negative items (assessed through the UX questionnaire) showed a mean lower than 2 on the 5-point Likert scale (M = 1.86, SD = 0.30), thus indicating that patients disagreed with the overall items. More specifically, the items Not Stimulating, Not Engaging, and Rigid showed a downward trend from the 2nd to the 12th session. Again, the precise means and standard deviations are presented in the Appendix (Table A6).

Figure 4b. Plot of the negative items of the UX questionnaire. Means and standard deviations are represented by circled dots and error bars, respectively (N = 13)



User Engagement Scale

As shown in Table 4, the overall score regarding the UE scale revealed that patients were engaged with Motibot. The Reward Factor, which refers to the patients' worthwhile and absorbing experience with a digital solution, showed a maximum value of 5. Perceived Usability and Focused Attention presented the same pattern. As mentioned in the Measure section, the Perceived Usability is the factor in which scores were reversed, thereby suggesting a good and positive experience with Motibot.

Table 4. Descriptive statistics regarding the user engagement (assessed through UES), (N = 13)

	Minimum	Maximum	Mean (SD)
Total Scale	3.25	4.83	4.14(0.49)
Perceived Usability	4	5	4.82(0.32)
Focused Attention	2.33	5	3.62(0.83)
Aesthetic Appeal	2.67	4.67	3.79(0.55)
Reward Factor	3	5	4.33(0.58)

Note. SD = Standard Deviation.

Kruskal-Wallis test for assessing differences between psychosocial outcomes

The Kruskal-Wallis test, performed to evaluate differences between symptoms of depression, anxiety, and perceived stress, did not show any significant result at each period; however, Figure 3, reported above, showed a downward trend regarding anxiety and depression symptoms over the three-time periods (i.e., pre-intervention, post-intervention, and follow-up).

Text Mining Approach for evaluating semi-structured interviews

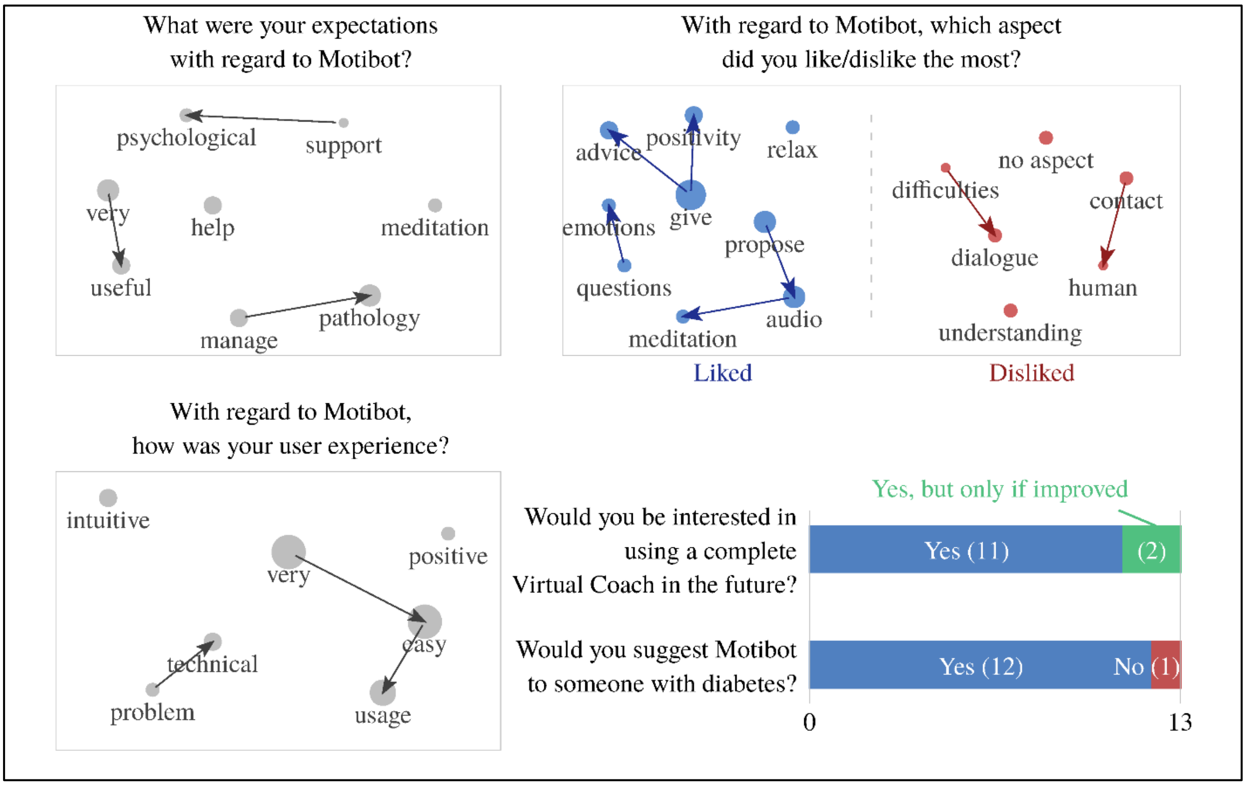
Overall, the mean length of the 13 semi-structured interviews was 9.04 minutes. The transcripts of interview answers included, on average, 562 words.

Figure 6a and Figure 6b showed the results of the text mining approach carried out on the patients' answers of the semi-structured interviews, regarding both UX and how patients felt during the interaction with Motibot. In both figures, bar plots highlight the distribution of three types of answers (i.e., yes/no/maybe), whereas scatter plots report the most frequent concepts, namely word stems appearing at least 3 times during the interviews. Within scatter plots, arrows represent recurrent di-grams, namely sequences of two-word stems appearing at least 2 times during the interviews. It is important to note that the inverted word-order of some di-grams (e.g., "support → psychological") is due to the analysis performed on Italian texts, in which the order of words is different from English. In this regard, stems were translated at the end of the analysis, taking into consideration potential nuances between the two languages. The number of occurrences of each stem is proportional to the circle radius.

Text Mining: Patients' experience with Motibot

As displayed in Figure 5a, 85% of the patients would be interested in using Motibot for psychosocial support and 92% would recommend it to other people with DM. Overall, patients reported having a positive experience with Motibot. Moreover, patients largely reported positive aspects in the interaction with Motibot, with the exception of some technical problems, as shown in the upper-right panel, in which stems graphed in blue and red refer to "liked" and "disliked" aspects, respectively. It is worth noting that 3 patients reported that there were no features that they disliked.

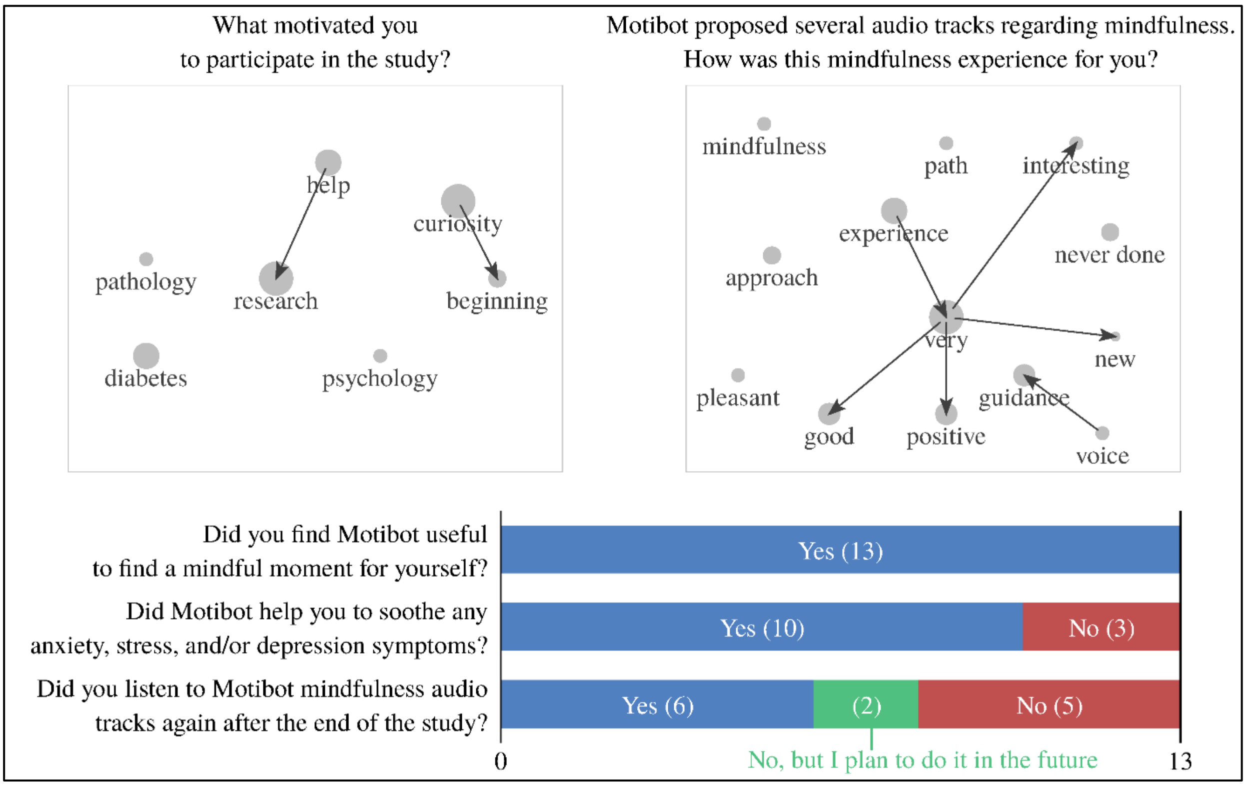
Figure 5a. Answers to the semi-structured interviews regarding User Experience with Motibot



Text Mining: How patients felt during the interaction with Motibot

As shown in Figure 5b, patients described mindfulness audio tracks as a very good, positive, interesting, and a new experience; they also perceived the voice of the audio tracks as a guide to the mindfulness path. Indeed, 62% of the patients listened to the mindfulness audio again after the end of the study or planned to do so in the future in order to achieve another mindful moment. Finally, 77% of patients reported that Motibot helped them to diminish symptoms of anxiety, depression, and/or stress.

Figure 5b. Answers to the semi-structured interviews regarding how patients felt during the interaction with Motibot



5.5 Discussion

Psychosocial Symptoms

The present proof-of-concept study showed that the use of a VC, such as Motibot, can lead to improvements in symptoms of anxiety and depression, as highlighted from the downward trend of the relevant variables analysed at pre-intervention, post-intervention and follow-up, although these were not significant. It is worth noting that following the exclusion of one outlier, patients showed an increase in anxiety and depression symptoms at post-intervention and a subsequent decrease throughout follow-up. Moreover, following the same mentioned process, patients reported, on average, a borderline psychological well-being, which can be seen, overall, as a sufficient psychological well-being and a low diabetes-related emotional distress. These findings highlighted how the psychoeducational intervention was maintained over time, thus resulting in the patients' internalisation of healthy coping strategies and active awareness of their emotions. Furthermore, during the semi-structured interviews most patients reported a perceived reduction in anxiety, depression and/or stress symptoms, indicating the usefulness of Motibot in supporting and motivating them to find a mindful moment for themselves. However, patients also showed moderate symptoms of perceived stress, which were consistent throughout the intervention, including follow-up; however, patients reported low diabetes-related emotional distress[9]. These results shed light on the potential stressful events that underline the perceived stress, such as the impact of contingent events: these findings appeared to be not associated with the burden of managing DM. It is worth noting that the current study was conducted in 2021, during the Covid-19 pandemic, which had a substantial impact on the psychological well-being of the general population [240]. In particular, during the Covid-19 lockdown, previous studies showed that adults with T1DM or T2DM reported increased levels in stress symptoms, emotional distress and anxiety [241,242]: one can assume that these symptoms may have persisted after the lockdown.

User Experience and User Engagement

Patients felt involved and engaged with Motibot: they reported a worthwhile and absorbing experience and a positive perception of Motibot, indicating that it was *very easy to use*. Moreover, patients came across some technical issues during the interaction with Motibot,

[9]After the exclusion of the outlier.

in particular when planning the next session. However, these problems were solved during the course of the study. Nevertheless, patients welcomed the psychoeducational intervention, in particular for the invitation to listen to meditation audios and, thus, for the inclusion of a mindfulness path in the study. To this extent, patients reported having a very good, positive, interesting, and new experience: most patients listened to the audio tracks long after the study ended in order to reclaim a mindful moment for themselves. Indeed, mindfulness-based interventions have recently become more relevant in DM care, as they have been linked to a reduction in negative emotions, improvement in an individual's attitude and the enhancement of coping strategies [56]. Patients also reported having a positive and interesting experience with Motibot since it asked them what emotion they were experiencing at that time. The goal of asking patients to express their emotions is to encourage them to become more aware of their feelings and to reflect on them: one can assume that the more one is aware of his/her own emotions, the better he/she can regulate them. Patients perceived Motibot as empathetic and stimulating in its dialogic interaction, even if slightly less supportive from the second to the twelfth session. This latter result could imply that patients were familiar with Motibot throughout the sessions and thus they did not perceive any further support, although feeling engaged and absorbed in the interaction. Moreover, patients also perceived Motibot as motivating since it encouraged them to acquire healthy coping skills; indeed, patients expressed their appreciation of Motibot's *positive advice*. Notwithstanding these encouraging findings, few patients expressed a desire for human contact in order to gain psychological support. This data was identified for those who showed high symptoms of anxiety, depression, and/or perceived stress. As a result, VCs might be used to effectively assist and motivate people with mild to moderate psychological symptoms, whereas those with more severe symptoms would benefit more from psychotherapy support in face-to-face, human settings.

The current study presented two main limitations. Firstly, the small sample size was typical and compliant with the preliminary testing phases of the ORBIT framework [215]; however, this sample size did not allow for data generalisation. Secondly, a more sophisticated analysis regarding text mining on the semi-structured interviews, such as supervised/unsupervised learning was not feasible to apply due to the small sample size, as well as to the short length of comments collected during these interviews (i.e., between approximately 200 and 1000 words each regarding the patients' answers). Bearing all these aspects in mind, during the implementation and evaluation of future VCs for digital health interventions, it would be recommended to monitor also other medical factors, such as glycaemic levels, along with the major symptoms experienced by adults with DM.

5.6 Conclusions

Motibot was developed by using a combination of NLU and rule-based dialogue techniques, with the goal of providing a psychoeducational intervention for adults with T1DM or T2DM, allowing them to interact using both free text and pre-set response options. The main finding derived from this evaluation study was a positive user experience and involvement with Motibot. Moreover, even though results on changes in psychosocial symptoms were not statistically significant, patients reported the usefulness of using a VC aimed at decreasing symptoms of anxiety and depression and diabetes-related emotional distress while also improving their well-being. In particular, patients perceived Motibot as motivating in supporting them to acquire healthy coping strategies, such as mindfulness exercises, not just during the study, but also at the end of the delivered intervention. It is worth noting that VCs provide the potential advantage of scalability, allowing greater accessibility to valuable support for adults with DM who are experiencing mild and moderate psychosocial symptoms, thereby ensuring them much needed assistance.

PART 3 – PERSPECTIVES

CHAPTER 6. CONCLUSIONS

The present work addressed three main studies applying different methodologies, to reach the final goal: the preliminary evaluation of a Virtual Coach (VC) efficacy aimed at providing psychosocial support to adults with Diabetes Mellitus (DM), called Motibot, the abbreviation for Motivational bot.

In the *first study*, a meta-analysis was conducted in order to understand the efficacy of digital interventions regarding both glycaemic control and psychological support in adults with DM [169]. Following the results of this meta-analysis, the *second study* was carried out, whose aim was to explore and assess the acceptability, usability and thus the user experience regarding the intervention protocol, before the digital intervention was delivered to real patients with DM. In this study, on the one hand, the Wizard of Oz (WOZ) method–the simulated VC–was used in the interaction with psychology students who interpreted a patient with Type 2 DM (T2DM) by referring to the Standardised Patients (SPs) approach. On the other hand, the Obesity-Related Behavioural Intervention Trial (ORBIT) model [215] was employed as guidance for the study. The results of this study allowed the subsequent work to be conducted: the *third* and, thus, the *final study*, in which the next phases of the ORBIT model were implemented to evaluate the preliminary efficacy of the VC intervention [226]. More specifically, Motibot was developed using a combination of Natural Language Understanding (NLU) and hand-crafted rules and was then deployed through the Telegram messaging application. In this study, Motibot interacted with adults with T1DM or T2DM to be able to support them in reducing symptoms of anxiety, depression, stress as well as diabetes-related emotional distress while also improving their quality of life, by motivating them to adopt and cultivate healthy coping strategies. On the one hand, Motibot relied on the Transtheoretical Model of Change (TTMC) [132] to understand what motivational stage the person was at, to provide the most appropriate psychoeducational intervention, in which motivation is a key component as it enables the adult to adhere to clinical recommendations. On the other hand, Motibot followed the American Association of Diabetes Educators (AADE) guidelines [76], in which it is reported the healthy coping construct for the identification of healthy coping strategies, such as practicing meditation. Indeed, Motibot motivated adults to acquire healthy coping strategies, which were mainly focused on mindfulness practices since they have also proven their effectiveness in the context of DM [79-87].

6.1 Summary of results

The main results that emerged from the present thesis work are summarised as follows:

- As regards the *first study*, 13 Randomised Control Trials (RCTs) involving 1315 adults with T1DM or T2DM (52.09% females; M_{age} = 46.18, SD = 9.98) were included in the meta-analysis. Statistical analysis revealed that the eHealth interventions were welcomed by participants (OR = 1.43; 95% CI = 0.72, 2.81; k = 10). Moreover, results showed that these digital interventions were effective in reducing Haemoglobin A1c (HbA1c) levels (SMD = -0.40; 95% CI = -0.70, -0.12; k = 13) and depressive symptoms (SMD = -0.18; 95% CI = -0.33, -0.02; k = 6) at RCTs endpoint. Nevertheless, efficacy on HbA1c was not maintained at follow-up (SMD = -0.13; 95% CI = -0.31, 0.05; k = 6). Furthermore, only one RCT [187] included data on depressive symptoms at follow-up, thus the efficacy of the digital interventions regarding this outcome was not feasible to evaluate. It is also noteworthy that the results of the included studies highlighted no significant differences in the efficacy of digital interventions when taking into consideration the type of DM as a moderator. These findings imply that these interventions may have been developed around the broader concept of DM, thus focusing on the similarities between people's lifestyles and using self-management of metabolic control as their central focus of treatment. It is also interesting to note that most of the digital interventions that were aimed at providing psychosocial support were mainly pilot or proof-of-concept studies [197-199], thus none of the RCT studies were developed for providing psychosocial support. Indeed, the primary aim of the meta-analysis study, namely the assessment of the eHealth interventions' efficacy in improving psychosocial symptoms, could not be satisfied.
- As regards the *second study*, the designing and prototyping of the digital healthy coping intervention were well-accepted by 18 psychology students (77% females; M_{age} = 23.61, SD = 1.98). Indeed, both quantitative and qualitative analyses showed that the intervention protocol and thus the simulated VC was perceived as motivating, supportive, encouraging, and capable of triggering self-reflection on healthy coping strategies, as well as natural and pleasant in its interaction. Indeed, these results suggest the emotional supportive role of the simulated VC, thereby representing a good starting point for the final study with adults with DM. Furthermore, analyses of the logged dialogues demonstrated that the majority of

psychology students interpreted their randomly assigned SPs' profiles accurately. These findings established the validity and utility of using the WOZ method in conjunction with the SP approach, thereby highlighting an original approach in the preliminary evaluations of behavioural digital interventions and protocols.

- As regards the *third study*, Motibot interacted with 13 adults with T1DM or T2DM (77% females; $M_{age} = 30.08$, $SD = 10.61$). Statistical analyses revealed that no significant changes emerged at pre-, post-intervention, and follow-up regarding the psychosocial variables during the 12 sessions of the Motibot intervention. However, most participants showed a downward trend over the three time periods in depression and anxiety symptoms—except for perceived stress symptoms, which remained moderate for the whole intervention, including follow-up—thereby highlighting, on average, a borderline psychological well-being, which can be seen, overall, as sufficient psychological well-being, and low diabetes-related emotional distress[10]. Furthermore, participants felt motivated, engaged, encouraged, emotionally understood, and stimulated by Motibot during the whole interaction. Indeed, text-mining analyses of interviews highlighted that Motibot was able to support and motivate adults with DM in their acquisition and cultivation of healthy coping strategies. In addition, these last analyses showed that participants perceived a reduction of anxiety, depression, and/or stress symptoms during the Motibot intervention. Participants further reported having a very good, positive, interesting, and new experience with Motibot, particularly regarding the mindfulness audio tracks and the encouragement for self-reflection on their own emotions. Indeed, most participants continue to listen to the audio tracks long after the study ended or planned to do so in the future in order to reclaim a mindful moment for themselves. Overall, these findings highlighted how the psychoeducational intervention was maintained over time, thus resulting in the patients' internalisation of healthy coping strategies and active awareness of their emotions.

[10]After the exclusion of an outlier.

6.2 Conclusions: What is the message to be conveyed?

The overall thesis work will be now discussed to provide a comprehensive perspective and to summarise the main key points resulting from the three studies, and thus from these three years of the Ph.D. journey.

Overall, these three years have given rise to important reflections. One of these reflections regards the concept of *bidirectionality* between medical and psychosocial aspects, which emerges once again, as explained in Chapter 1. The concept of bidirectionality represents a key focal point in the development of digital (and non-digital) interventions to support the individual's adoption of healthy behaviours through the healthy management of his/her disease. In this regard, it is important to consider the individual as a whole comprising both medical and psychosocial factors and their *dynamic interaction* when implementing both digital and traditional treatments. Achieving better management of adults' chronic illnesses, indeed, represents the cornerstone of optimal disease outcomes. The second reflection regards the concept of *novelty*, which is related to the concept of *bidirectionality* even if it refers to the development of VCs deployable among adults with DM to provide them with psychosocial support. In other words, available studies showed that there are clinically significant benefits that can be obtained from digital interventions beyond glycaemic control [113]: medication adherence [113], enhanced physical activity [112], sustained weight loss [149], and reduced symptoms of depression, as emerged in the meta-analysis carried out in the present thesis work [169]. Nevertheless, the results concerning the reduction of depression symptoms emerged from the evaluation of the psychological questionnaires, despite the digital intervention primarily having a medical purpose, namely the monitoring of blood glucose levels.

With this in mind, the development of Motibot represents, for many reasons, a valuable resource to provide regular support to the psychosocial aspects among adults with DM. First of all, the Motibot intervention was well-accepted by patients with DM. Indeed, they had largely reported a very positive experience of interacting with Motibot. Secondly, they also gave more importance to the capacity of self-reflection as regards their own emotions, both in answering the question *"what emotion are you feeling right now?"* and in being able to pause and practice mindfulness using the audios tracks that Motibot sent to them as guidance. Indeed, to stop and think about one's own emotions is a precious coping strategy to develop emotional awareness and, in turn, to regulate emotions. Moreover, Motibot allowed patients to be free to plan their next appointment, usually once or twice a week, according to their own needs and without any schedule being imposed by the VC. In this way, from a clinical perspective, Motibot was enabling the patients to exercise a certain degree of flexibility regarding the appointments scheduling, thus allowing them to give more importance to their needs. This is important, in particular among patients with chronic diseases who need, on the one hand, constant support and, on the other hand, to be free to interact when they need to. Therefore, the usefulness of Motibot in supporting and motivating people with DM to acquire healthier coping strategies, and to take action in improving their well-being, represents an important achievement in the psychological and HCI fields.

Motibot can be prescribed by the diabetologist as a preventive measure for the patient's well-being and/or when the patient presents mild and moderate psychosocial symptoms. For example, the diabetologist could prescribe Motibot to perform a screening of the patient's psychosocial symptoms, which would subsequently produce a clinical report, to be sent back to the said specialist, enabling them to understand the patient's symptom levels. If the patient might present mild or moderate symptoms, the psychoeducational intervention, as proposed by Motibot, becomes a relevant resource in promoting their well-being. However, should the patient show severe psychological symptoms, he/she could not be supported by Motibot but would instead need face-to-face psychological assistance in a traditional setting. It is important to underline that Motibot is not developed to substitute the help that professionals in diabetes can provide. Motibot functions as a support for diabetes professionals enabling them to reach a larger and more diverse population with DM, thereby allowing the patient easier access to psychosocial care and support without overburdening the clinical staff. Ultimately, this is expected to result in better disease outcomes. Moreover, Motibot can be advantageous and a valuable resource for people with DM, who might have difficulty in attending appointments or who need constant attention, which cannot be provided during a single follow-up. Motibot does not only appear to be a promising resource in providing comprehensive support to the patient with DM, but also a valuable tool in terms of assisting the referral diabetologist in terms of reducing healthcare costs and decreasing waiting times for assistance to zero. Therefore, here too, the importance of the concept of bidirectionality emerges, as it is not only relevant to the association between psychosocial and medical factors but also as regards the collaboration between clinical professionals and patients, indeed fundamental for better disease outcomes when planning both traditional and/or digital treatments.

6.3 Limitations and Future Directions

The precise limitations of the three studies have already been explained in the above Chapters. Here, however, limitations purely associated with Motibot and thus with its future development will be emphasised. More specifically, Motibot also supports adults with DM in becoming more aware of their emotions, according to the concept that if one is aware of one's own emotions, in turn, one is also able to regulate them; however, this aspect has not been investigated through specific questionnaires. Moreover, another limitation of Motibot is the non-monitoring of blood glucose levels, such as HbA1c. Therefore, referring to the ORBIT model, the next experimental phase is an RCT study to verify the efficacy of Motibot intervention, where, on one hand, a questionnaire aimed at investigating emotional awareness and emotional regulation will be added, and, on the other hand, also the monitoring of glycaemic levels will be included to obtain a comprehensive view of the individual as a whole. For instance, future studies should design VCs solutions following standard guidelines about DM, such as those proposed by AADE [76], whereby the healthy coping construct is included in the intervention protocol. In this regard, more research is needed, firstly, to identify the long-term and widespread impacts of virtual coaching from the biopsychosocial perspective. Secondly, future works should explore how to maintain long-term engagement with VCs, as well as how patients prefer to communicate with their diabetologists and VCs, thereby placing particular importance on a user-centred design approach. To conclude, future works might develop VCs on multiple levels, including a wide range of psychosocial factors to fully address the patients' barriers of non-adherence and non-compliance as well as to improve their well-being by considering both psychosocial and medical factors.

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Abbreviations

AADE	American Association of Diabetes Educators
ACHT	Adrenocorticotropin
ADF	Augmented Dickey-Fuller
AI	Artificial Intelligence
ANOVAs	one-way repeated measures analyses of variance
BDI	Beck Depression Inventory
BITs	Behavioural Intervention Technologies
CBT	Cognitive Behaviour Therapy
CC	Couple Calls
CEDS	Center for Epidemiological Studies Depression Scale
CENTRAL	Cochrane Central Register of Controlled Trials
CGM	Continuous Monitoring of Glucose
CIs	Confidence Intervals
CRH	Corticotropin-Releasing Hormone
DDS-17	Diabetes Distress Scale-17 items
df	Degrees of freedom
DIET	Dual Intent and Entity Transformer
DM	Diabetes Mellitus
DQOL	Diabetes Quality of Life Questionnaire
DSQOL	Diabetes Specific Quality of Life
eHealth	electronic Health
EQ-VAS	European Quality of Life Visual Analog Scale
EuroQOL	European Quality of Life
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FMI	Fowlkes-Mallows Index
GAD	Generalised Anxiety Disorder
GAS	General Adaptation Syndrome
Goe	Global Observatory for eHealth
GPRS	General Packet Radio Service
GPS	Global Positioning System
HADS	Hospital Anxiety and Depression Scale
HbA1c	Haemoglobin A1c
HCI	Human-Computer Interaction
HDL	high-density lipoprotein
HPA	Hypothalamic-Pituitary-Adrenal
HPLC	High Performance Liquid Chromatography
HPLC	High Performance Liquid Chromatography
HRQOL	Health-related quality of life
IC	Individual Calls
IQ	Intelligent Quotient
ISO	International Organization for Standardization
ITT	intention-to-treat
K10	Kessler Psychological Distress Scale

MBCT	Mindfulness-Based Cognitive Therapy
MBIs	Mindfulness-Based Interventions
MBM	Mind and Body Medicine
MBSR	Mindfulness-Based Stress Reduction
MeSH	Medical Subject Heading
mHealth	mobile Health
ML	Machine Learning
MPT	Mobile Prescription Therapy
NLG	Natural Language Generation
NLP	Natural Language Processing
NLU	Natural Language Understanding
NS	Not Specified
OR	Odd Ratio
ORBIT	Obesity-Related Behavioral Intervention Trials
PAID-5-SF	Problem Areas in Diabetes Scale-Short Form-5
PDAs	Personal Digital Assistants
PHQ-8	Patient Health Questionnaire-8
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSS-10	Perceived Stress Scale-10
RCT	Randomized Control Trial
RoB	Risk of Bias
SDM	Standardised Mean Difference
SDM	Standard Deviation
SF-12	Short Form-12 items Health Survey
SF-36	Short Form-36 items Health Survey
SF-6D	Short-Form Six-Dimension Health Survey
SMS	Short Messaging Service
SPs	Standardised Patients
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TA	Thematic Analysis
TAU	Treatment As Usual
TTMC	Transtheoretical Model of Change
UCD	user-centred design
UE	User Engagement
UEQ	User Experience Questionnaire
UES-SF	User Engagement Scale-Short Form
UX	User Experience
VC	Virtual Coach
WHO	World Health Organization
WHO-5	World Health Organization-5 Well-Being Index
WHO-DTSQ	World Health Organization-Diabetes Treatment Satisfaction Questionnaire
WOZ	Wizard of Oz

Appendix

Table A1. Excluded Studies with reasons

N.	Author, year	Reasons for exclusion
1	Agarwal P, 2019	The study included participants with Diabetes Mellitus (DM) medical diseases.
2	Aikens JE, 2015	The study is not a Randomized Controlled Trial (RCT); the study's population did not meet the age range criterion of the current meta-analysis; participants with DM medical diseases (i.e., hypertension, cardiovascular disease, cancer, stroke, arthritis, chronic lung disease) were included.
3	Anderson DR, 2010	The study included participants with medical (i.e., hypertension and asthma) and psychological (i.e., depression) diseases.
4	Arora S, 2013	The study included participants with medical (i.e., hearth or kidney disease, history of stroke, arthritis) and psychological (i.e., depression) diseases other than T1DM or T2DM.
5	Bailey DP, 2020	The study did not assess the pre-defined primary medical outcome (i.e., HbA1c) of the current meta-analysis.
6	Baron J, 2015	This article only reported about preliminary data.
7	Baron J, 2017	The study included participants with DM with a disease (i.e., "comorbidities", not otherwise specified).
8	Bertuzzi F, 2018	The study's population did not meet the age range criterion of the current meta-analysis; the study assessed none of the pre-defined primary psychological outcomes of the current meta-analysis.
9	Boaz M, 2009	The measure to assess anxiety, depression was not specified.
10	Boels AM, 2018	This article only reported about preliminary data.
11	Bonn SE, 2018	This article only reported about preliminary data.
12	Bujnowska-Fedak MM, 2011	The study's population did not meet the age range criterion of the current meta-analysis.
13	Cho JH, 2017	The study's population did not meet the age range criterion of the current meta-analysis.
14	Clark TL, 2020	The study's population did not meet the age range criterion of the current meta-analysis.

15	Döbler A, 2018	The study's population did not meet the age range criterion of the current meta-analysis.
16	Dobson R, 2018	The study's population did not meet the age range criterion of the current meta-analysis.
17	Doupis J, 2018	This article's full text is not available online.
18	Drion I, 2015	The authors used median and IQR with non-parametric analyses; therefore, following Cochrane handbook, it was not possible to turn into mean and standard deviation, respectively.
19	Egede LE, 2017a	The study's population did not meet the age range criterion of the current meta-analysis; the study assessed none of the pre-defined primary psychological outcomes of the current meta-analysis.
20	Egede LE, 2017b	The study's population did not meet the age range criterion of the current meta-analysis; the study assessed none of the pre-defined primary psychological outcomes of the current meta-analysis.
21	Egede LE, 2018	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a psychological disease (i.e., depressive disorder).
22	Fortmann AL, 2016	This article is a conference abstract.
23	Gong E, 2020	The study included participants with DM with a medical disease (i.e., "diagnosed comorbidities" not otherwise specified).
24	Heitkemper E, 2017	This article's full text is not available online.
25	Hilmarsdóttir E, 2020a	The study's population did not meet the age range criterion of the current meta-analysis.
26	Hilmarsdóttir E, 2020b	This article is a conference abstract.
27	Holland-Carter L, 2017	The study's population did not meet the age range criterion of the current meta-analysis.
28	Holmen H, 2014	The study included participants with DM with medical diseases (i.e., "comorbidities", not otherwise specified).
29	Holmen H, 2015	This article is a conference abstract.
30	Holmen H, 2016	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a disease (i.e., "comorbidities", not otherwise specified).
31	Izquierdo RE, 2003	The study's population did not meet the age range criterion of the current meta-analysis.
32	Kardas P, 2016	The study included participants with DM with medical diseases (i.e., hypertension).
33	Kaur R, 2015	The study's design (e.g., RCT) is not clearly stated and it does not include an eHealth intervention.

34	Kempf K, 2017	The study's population did not meet the age range criterion of the current meta-analysis.
35	Kumar D, 2018	The study assessed none of the pre-defined primary medical nor psychological outcomes of the current meta-analysis.
36	Kumar DS, 2020	The study did not assess the pre-defined primary medical outcome of the current meta-analysis.
37	Logan AG, 2012	The study included participants with DM with a medical disease (i.e., hypertension and cardiovascular disease) and did not assess the pre-defined primary medical outcome of the current meta-analysis.
38	Mayberry LS, 2019	The study is not a RCT and does not include an eHealth intervention.
39	Mora P, 2017	The study is not a RCT.
40	Nicolucci A, 2015	The study included participants with DM with a medical disease (i.e., hypertension, dyslipidemia and cardiovascular complications).
41	Nobis S, 2015	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a psychological disease (i.e., depression); the study did not assess the pre-defined primary medical outcome of the current meta-analysis.
42	Noviani L, 2020	This article is a conference abstract (not available online).
43	Peiris D, 2016	This article only reported about preliminary data.
44	Piette JD, 2000	The study did not assess the pre-defined primary medical outcome of the current meta-analysis; the study did not assess the pre-defined primary medical outcome of the current meta-analysis.
45	Polonsky WH, 2020	This study is not a RCT.
46	Poppe L, 2019	The study assessed none of the pre-defined primary medical nor psychological outcomes of the current meta-analysis.
47	Quinn CC, 2011	The study included participants with DM with a medical disease (i.e., hypertension and coronary artery disease).
48	Quinn CC, 2017	The study included participants with DM with a medical disease (i.e., hypertension and coronary artery disease).
49	Ramallo-Fariña Y, 2015	This article only reported about preliminary data.

50	Skrøvseth SO, 2015	The study assessed none of the pre-defined primary psychological outcomes of the current meta-analysis.
51	Tang PC, 2013	The study's population did not meet the age range criterion of the current meta-analysis.
52	Torbjørnsen A, 2014	The study included participants with DM with a disease (i.e., "comorbidities", not otherwise specified).
53	Torbjørnsen A, 2015	This article is a conference abstract.
54	Trief PM, 2006	The study's population did not meet the age range criterion of the current meta-analysis.
55	Van Bastelaar KMP, 2011	The study included participants with DM with a psychological disease (i.e., depression).
56	Van der Weegen S, 2015	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a medical disease (i.e., chronic obstructive pulmonary disease).
57	Von Storch K, 2019	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a medical disease (i.e., "multimorbidities", specified as "chronic diseases"); the study assessed none of the pre-defined psychological outcomes of the current meta-analysis.
58	Wang Y, 2019	The study assessed none of the pre-defined primary medical nor psychological outcomes of the current meta-analysis.
59	Wayne N, 2015	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with psychiatric diagnoses.
60	Weinstock RS, 2011	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with a disease other than T1 or 2 Diabetes (i.e., "comorbidities", not otherwise specified).
61	Whittemore R, 2019	This article is a conference abstract.
62	Williams ED, 2012	The study's population did not meet the age range criterion of the current meta-analysis; inclusion of participants with DM with a medical disease (i.e., hypertension, kidney disease, cardiovascular disease).

63	Yaron M, 2019	The study included participants with DM with a medical disease (i.e., hypertension, hyperlipidemia).
64	Zhang L, 2018	This article is a conference abstract.

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Table A2. Examples of Standardized Patient Case Scenario for every age (i.e., young, adult, elderly)

Young
Alessandra is a sunny and creative woman of 25 years, who has just finished the *"Accademia delle Belle Arti"* in Venice. Her passion is sculpture, and she says she will be thrilled to show her work at an exhibition one day. Alessandra is short in stature and overweight. Since she was a child, she says she has always been a bit shapely and in particular she has always loved sugars, especially chocolate. Alessandra recounts an episode in which, having one a sculpture competition, she celebrated with her best friend by sharing a whole jar of chocolate spread and a packet of biscuits, claiming "you always celebrate on a full stomach". Here, the problem is that her food portions are too large in relation to her limited physical activity; Alessandra reports that she occasionally goes jogging on the embankment near her home but has never been consistent in her sport. Alessandra reports that last year, for almost four months, she would wake up very thirsty and during the night she had difficulty sleeping because of the continuous waking up to go to the toilet. Alessandra decided to go to her general practitioner who prescribed a serious of blood tests, which revealed that she is suffering from Type 2 Diabetes Mellitus. Therefore, Alessandra had to change her diet, and this has caused her some difficulty; indeed, she says: "giving up sugars is not easy, especially for a sweet tooth like me! I have to find a solution, like sport, but I have never been very consistent".

Adult

Simona is a woman of 40 years. She is of average height and stature. Her posture is rigid, and her facial features are slightly angular. She has been working as a secretary in a dental practice for 20 years and she claims that she would never change her job: the boss is kind and polite, the environment is sunny, and she knows almost all the patients with whom she has established good relationships.

She considers herself a reasonable person, who knows how to keep her behaviour under control. She reports that she does physical activity once a week, particularly aerobics, in the gym next to her house; indeed, she says "I enjoy it a lot and I also care about my health, as the Latins say *mens sana in corpore sano!*".

Six months ago, one of her monthly medical check-ups—since she is very health conscious—she discovered she had Type 2 Diabetes Mellitus. She reports that she has a family history of diabetes: her grandmother suffered from Type 2 Diabetes Mellitus, which later led to her blindness.

Simona reports that she did not need to make many lifestyle changes, but still feels that she has to be even more careful about her health and follow her doctor's recommendations.

Therefore, Simona decides to take care of herself by continuing to eat healthily and to exercise regularly, but she feels that something has changed. This feeling brings her a certain discomfort, which she defines as fear, she says "I am afraid of the complications that diabetes can cause and the same thing that happened to my grandmother can happen to me; this thought is quite present, it really stresses me out! How do I stop it?".

Elderly

"Mirta is an elegant and good-looking woman of 70 years. Mirta is of average height but slightly overweight, which is also due to her age that makes it difficult for her to regularly exercise.

Mirta lives alone, however she has two daughters who visit her every weekend in order to take her for a stroll, although they often have to convince her to go out. In the last four months Mirta reported that she feels a bit lazy and prefers to spend her afternoons reading a good novel while sitting in an armchair. Her daughters have noticed a certain lack of interest in taking care of herself: this behavior would have seemed unlikely a short time ago.

Mirta discovered that she suffers from Type 2 Diabetes Mellitus at the age of 52. However, her lifestyle has not substantially changed since then, except for her concern about frequently checking her blood glucose levels. After being diagnosed, Mirta's concerns for her health have negatively affected her psychophysical well-being.

Mirta reports that she wakes up at dawn worrying whether her family feels well. These concerns lead her to make several phone calls to make sure that everybody is alright. Initially, these episodes were sporadic, but now they have become almost an obsession. Indeed, every morning, Mirta picks up the phone and starts calling her loved ones.

Mirta feels that doing these calls gives her more control over her worry; however, she realises that this worry has become a little invalidating, since she knows that without the morning phone call her anxiety would not disappear."

Table A3. Means and Standard Deviations of the positive items every fortnight (2nd, 4th, 6th week) (N = 18)

	Means (SD)					
	Pleasant	Profound	Cordial	Comprehensible Language	Empathetic	Attentive
Week 2	4.06 (.639)	3.28 (.669)	4.72 (.575)	4.61 (.698)	3.78 (.943)	3.94 (.725)
Week 4	3.89 (1.079)	3.00 (.907)	4.78 (.548)	4.67 (.485)	3.56 (.705)	4.00 (.767)
Week 6	4.11 (.900)	3.28 (.752)	4.78 (.428)	4.78 (.428)	3.67 (.907)	3.72 (.575)
	Motivating	Encouraging	Supportive	Trustworthy	Flexible	Interesting
Week 2	4.11 (.583)	4.28 (.669)	4.22 (.732)	4.11 (.676)	3.56 (.784)	4.11 (.676)
Week 4	4.06 (.873)	4.11 (.676)	4.06 (.802)	4.00 (.686)	3.44 (.984)	3.94 (.725)
Week 6	4.17 (.786)	4.28 (.669)	4.28 (.752)	4.00 (.686)	3.50 (.618)	4.00 (.767)

Note. SD = Standard Deviation

Table A4. Means and Standard Deviations of the negative items every fortnight (2nd, 4th, 6th week) (N = 18)

	Means (SD)						
	Annoying	Not Reliable	Unappealing	Unclear	Complicated	Not Efficient	Too Much Information
Week 2	1.72 (.752)	1.78 (1.003)	1.94 (.802)	1.39 (.608)	1.44 (.616)	1.61 (.850)	1.89 (.676)
Week 4	1.89(1.079)	1.39 (.608)	2.11 (1.183)	1.28 (.461)	1.33 (.594)	1.83 (.985)	2.11 (.963)
Week 6	1.56 (.784)	1.28 (.575)	1.72 (.826)	1.17 (.383)	1.5 (.786)	1.33 (.485)	1.72 (.575)
	Dissuading	Not Stimulating	Not Engaging	Unpredictable	Not Reflective	Conventional	Rigid
Week 2	2.5 (1.043)	1.94 (.802)	2.00 (.907)	2.33 (1.138)	1.83 (.924)	2.72 (.752)	2.5 (.985)
Week 4	2.28 (.958)	2.22 (1.003)	2.00 (.907)	1.72 (.669)	2.39 (1.145)	2.22 (.878)	2.89 (.832)
Week 6	2.39 (.698)	1.83 (.857)	2.11 (.832)	1.61 (.608)	1.78 (.548)	2.72 (.895)	2.83 (.924)

Note. SD = Standard Deviation

Table A5. Means and Standard Deviations regarding the positive items of UEQ (N = 13)

	Mean (SD)						
	Pleasant	Effective	Profound	Cordial	Comprehensible Language	Empathetic	Attentive
Session 4	4.17 (0.83)	3.67 (0.65)	3.58 (0.79)	4.83 (0.39)	4.67 (0.49)	3.58 (1.08)	3.83 (0.94)
Session 8	4.33 (0.65)	3.83 (0.83)	3.58 (0.79)	4.75 (0.45)	4.67 (0.49)	3.5 (0.80)	3.58 (0.90)
Session 12	4.31 (0.75)	3.85 (1.07)	3.7 (0.95)	4.85 (0.38)	4.77 (0.44)	3.62 (1.12)	3.46 (0.87)
	Motivating	Encouraging	Supportive	Trustworthy	Flexible	Interesting	
Session 4	4.08 (0.67)	4.33 (0.65)	3.75 (0.75)	4 (0.74)	3.58 (1.38)	4.25 (0.75)	
Session 8	3.92 (0.67)	4.08 (0.79)	4.17 (0.83)	3.83 (0.72)	3.75 (1.14)	4.17 (0.83)	
Session 12	4.23 (0.83)	4.38 (0.87)	3.77 (1.01)	4.15 (0.90)	3.69 (1.03)	4.53 (0.88)	

Note. SD = Standard Deviation

Table A6. Means and Standard Deviations regarding the negative items of UEQ (N = 13)

	Mean (SD)							
	Not Effective	Annoying	Not Reliable	Unappealing	Unclear	Complicated	Not Efficient	Too Much Information
Session 4	2.25 (1.42)	1.08 (0.29)	1.5 (1.24)	2.17 (1.34)	1.92 (1.08)	1.33 (0.65)	1.83 (1.19)	1.25 (0.62)
Session 8	1.75 (1.06)	1.5 (0.90)	1.83 (1.40)	1.67 (0.78)	1.58 (1.16)	1.42 (0.51)	1.67 (0.89)	1.75 (1.22)
Session 12	1.92 (1.32)	1.15 (0.38)	1.54 (0.88)	1.54 (0.88)	1.31 (0.48)	1.15 (0.38)	1.77 (1.09)	1.38 (0.65)
	Dissuading	Not Engaging	Not Stimulating	Unpredictable	Not Reflective	Conventional	Rigid	
Session 4	2.5 (1.31)	2.33 (1.50)	2.25 (1.22)	2.08 (1.16)	1.83 (0.83)	2.92 (0.90)	2.67 (1.07)	
Session 8	2.25 (0.97)	1.67 (0.89)	2.17 (1.19)	2.08 (0.90)	1.92 (1.08)	2.42 (1.24)	2.42 (1.44)	
Session 12	2.31 (1.18)	1.69 (1.18)	1.62 (0.87)	2.15 (0.90)	1.77 (1.17)	2.69 (1.25)	2 (1.00)	

Note. SD = Standard Deviation

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