DIGITAL SUPPORT for ALCOHOL MODERATION and SMOKING CESSATION in CANCER SURVIVORS

Ajla Mujčić

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DIGITAL SUPPORT
for ALCOHOL MODERATION
and SMOKING CESSATION
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Digitale ondersteuning bij minderen met alcohol en stoppen met roken
voor mensen die kanker hebben (gehad)

Thesis

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Tebi
Voor jou

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GENERAL INTRODUCTION

Alcohol use and tobacco use are leading risk factors for the development of several types of cancer. For people who have already been diagnosed with cancer these behaviours have additional adverse health effects. Treatment success, side-effects of treatment and development of recurrent cancers are impacted by alcohol and tobacco use. However, rates of alcohol and tobacco use among cancer survivors are similar to the general population and there is a lack of dedicated support options for this specific group. Support for alcohol moderation and smoking cessation could therefore greatly benefit the well-being of cancer survivors. Digital interventions have the potential to reach the growing population of cancer survivors efficiently with evidence-based alcohol moderation and smoking cessation support. This thesis centres around the evaluation of two newly developed digital interventions to support cancer survivors who intend to address alcohol or tobacco use.

Health burden of alcohol and tobacco use

Alcohol use and tobacco use have been among the top 10 leading risk factors for the global burden of disease for years [1]. In 2019, alcohol use was estimated to contribute to 2.07 million deaths in men, 0.37 million deaths in women and 3.7% (95%CI 3.3 to 4.1) of Disability Adjusted Life Years (DALYs) among all ages. Despite the hopeful decrease in exposure to tobacco use by 1% annually since 2010 [1], tobacco use remains the second most important risk factor for mortality, only being preceded by high systolic blood pressure, accounting for 6.56 million deaths in men and 2.15 million deaths in women, and contributing to 7.9% (95%CI 7.2 to 8.6) of DALYs among all ages [1].

The health burden of alcohol and tobacco use is in part due to these behaviours being among the main avoidable risk factors for the development of cancer (malignant neoplasms) [1, 2].

General population

While the impact of alcohol use is often underestimated, it contributes considerably to cancer development. Alcohol use increases the risk of cancers of the mouth, pharynx and larynx, oesophageal cancer, breast cancer, colorectal cancer, and liver cancer [3]. Tobacco use increases the risk of at least 20 types of cancer including cancers of the lip, oral cavity and pharynx, oesophageal cancer, lung cancer, stomach cancer, pancreatic cancer, colorectal cancer, liver cancer, kidney cancer, ovarian cancer, bladder cancer, urinary tract cancer, cervical cancer, and acute myeloid leukaemia [2]. These lists are conservative, as for several other cancers there is suggestive, but not conclusive evidence for a causal relationship (e.g., alcohol use and pancreatic cancer or tobacco use and prostate cancer) [2, 3].

This translates into global estimates of 5.5% of all cancer cases [4] and 4-5% of all cancer deaths being attributable to alcohol use [5]. Tobacco use is estimated to attribute to 10-30%

(depending on region and sex) of cancer cases in Europe [6] and 25% of cancer deaths globally [5]. For The Netherlands specifically, these estimates are higher: it is estimated that 6.8% of cancer deaths are attributable to alcohol use and 31.2% to tobacco use [5]. All in all, the impact of alcohol and tobacco use on cancer incidence and mortality is high.

Cancer survivors

For cancer survivors, alcohol and tobacco use are associated with higher risk of second primary cancers (alcohol: [7], tobacco: [8, 9]), higher risk of recurrent cancers (alcohol: [10, 11], tobacco: [8, 9]), worse treatment response (alcohol: [12], tobacco: [8, 9]), increased treatment-related toxicity (alcohol: [12], tobacco: [9]), exacerbation of side-effects of treatment (alcohol: [12], tobacco: [13]), lower survival (alcohol: [14, 15], tobacco: [8, 9]), and poorer quality of life (tobacco: [8]). Research on the effect of alcohol and tobacco use on the course of cancer and prognosis is limited compared to the research on their effect on cancer incidence. These studies are complicated as cancer is a collection of many different subtypes that might respond differently to alcohol and tobacco use, in addition to the broad range of types and stages of treatment which can apply to cancer survivors. Current evidence of the adverse effects of tobacco use is generally stronger than that of alcohol use, which shows some conflicting results (e.g. [16, 17]), but there are indications of adverse effects of both behaviours on cancer related health outcomes.

Concept definition of cancer survivors

Throughout this thesis, cancer survivors are defined as individuals with any history of cancer, from the time of cancer diagnosis. This definition is also adopted by the National Cancer Institute in the USA [18] and the Dutch Cancer Registry (NKR) [19]. In research and monitoring studies, this can be further specified to account for the time since diagnosis, e.g. 5-year cancer survivors or 10-year cancer survivors. In chapter 5 and 6 of this thesis the concept of cancer survivors is further operationalised as 10-year cancer survivors.

There is no direct translation of ‘cancer survivors’ in use in The Netherlands. The terms ‘(ex-) cancer patients’ (in Dutch: [ex]-kankerpatiënten) or ‘people who have (had) cancer’ (in Dutch: mensen met kanker/mensen die kanker hebben of hebben gehad) are more common. In this thesis, the terms ‘cancer survivors’ and ‘cancer patients’ will be used interchangeably.

It must be noted that not all who are included in this definition of cancer survivors, identify with this term [20]. Some have long since finished treatment or are in palliative care. This will be touched upon further in Chapter 4.

Health guidelines for alcohol and tobacco use

Because of their detrimental health effects, international and national health organizations advise against using tobacco at all and to limit alcohol use. Public health organizations and governments advise not to use alcohol at all, or to limit alcohol intake [21]. Local guidelines vary in the maximum number of (standard) glasses a day that is recommended and guidelines can vary for women and men. Furthermore, depending on the country, a standard glass is defined as 8 (United Kingdom) to 14 g (United States) of alcohol, with exceptions of 20 g (Austria) [21]. The Dutch national health council's advice on low risk-alcohol use for both men and women states: "Do not drink alcohol, or in any case no more than 1 glass a day" [22]. In The Netherlands, as in most countries, a standard glass is defined as 10 g of alcohol. These recommendations also apply to cancer survivors [3].

The difference in recommendations on alcohol (moderation or cessation) and tobacco use (only cessation) can in part be explained by the fact that the effect of the amount and pattern of alcohol use (e.g. binge drinking or daily drinking) on different types of cancer is not yet clear and needs furthers investigation, whereas for smoking there is general consensus on the fact that every smoked cigarette is detrimental to health [23]. However, there is no evidence for a safe threshold for alcohol consumption from the perspective of cancer prevention [3], as even one drink can increase the risk of breast cancer or oesophageal cancer. We also know that there is a dose-response relationship: increased alcohol intake leads to increased risk of cancer, although thresholds at which this risk increases differ for different types of cancer [3] and can differ by populations [2].

Prevalence of alcohol and tobacco use

Despite the recommendations, it is estimated that globally 2.4 billion people use alcohol [24] and 1.1 billion people use tobacco [5], but there are large geographical variations. Per capita alcohol consumption is highest in Europe [25], whereas smoking rates in Europe are at the global average [26].

To accurately describe patterns of alcohol use, there are several distinctions: drinking above guidelines, heavy drinking, excessive drinking and binge drinking. Heavy drinking is defined as drinking 6 or more glasses of alcohol on one day for men or 4 or more glasses for women, at least once a week. Excessive drinking is defined as drinking more than 21 drinks per week for men and more than 14 drinks per week for women. Binge drinking is drinking more than 5 drinks on one occasion [27]. Drinking above (Dutch) guidelines is defined as drinking more than 7 standard drinks per week [22]. In this thesis, we will adhere to these definitions. For tobacco, the most common smoking pattern is daily use [5]. Current smokers are defined as those who have smoked within the last month.

General population

In The Netherlands, 79.1% of the general adult population used alcohol in the past year, 8.5% of the population can be classified as a heavy drinker and 8.5% as an excessive drinker [27]. Tobacco was used by 21.7% of the adult Dutch population. In the last 5 years a gradual decrease can be observed in rates of adults drinking above guidelines (2014: 62.6%, 2019: 58.5%) and in rates of adult smokers (2014: 25.7%, 2019: 21.7%) in The Netherlands.

Cancer survivors

Recently, a Dutch study compared drinking and smoking rates among cancer survivors and those without a history of cancer [28]. No difference in current drinking (OR = 0.98, 95%CI 0.92 – 1.04) or current smoking (OR = 1.03, 95%CI 0.95 – 1.12) was found between the two groups after adjusting for sex and age. There were indications that male cancer survivors were less likely to be current smokers than men with no history of cancer (OR = 0.83, 95%CI 0.72 – 0.96), while female cancer survivors were slightly more likely to be current smokers than women with no history of cancer (OR = 1.14, 95%CI 1.01 – 1.17). It is possible that while the prevalence of alcohol use was not different, there might have been a difference in the extent of alcohol use between the two groups, yet this was not assessed. Previous international studies also found comparable health behaviours between cancer survivors and people without a history of cancer [29, 30].

Higher continued smoking rates have been found among survivors of smoking related cancers as compared to non-smoking related cancers [31, 32]. Survivors of smoking related cancer attempted to quit less often after cancer diagnosis (40% vs 48%), and had higher proportion of failed quit attempts (59% vs 47%) [31]. Survivors of head and neck cancer, which is specifically smoking related, showed higher smoking rates when male, young and single as compared to female, older and married head and neck cancer survivors [32, 33]. A US study found that smoking cessation rates were higher among those with advanced stage cancer as compared to those with localized cancer [32].

Alcohol use was highest among younger cancer survivors, those with a smoking history, survivors of melanoma, survivors of head and neck, cervical and testicular cancer [34].

In sum, alcohol and tobacco use is prevalent among cancer survivors. In 2020, there were 604,000 10-year cancer survivors in The Netherlands [35]. Assuming that rates of smoking and alcohol use (above guidelines) in cancer survivors are comparable to the general population, there are an estimated number of 353,000 cancer survivors who drink above guidelines and 131,000 cancer survivors who smoke.

Addressing alcohol and tobacco use among cancer survivors

Alcohol use and smoking are highly prevalent behaviours and, as we have seen, both cause considerable health burden. Considering the additional adverse health effects of alcohol and tobacco use after a cancer diagnosis and the continued prevalence of these behaviours, it is important to address alcohol and tobacco use among cancer survivors.

Furthermore, the time frame of cancer diagnosis and cancer treatment is referred to as a 'teachable moment': a window of opportunity in which motivation for positive lifestyle changes is increased [36, 37]. While distress, symptoms of anxiety and depression are generally increased in cancer survivors [38, 39], several studies show that it is around the distressing time of cancer diagnosis that many are willing to make positive lifestyle changes [40–42], supporting the notion of a 'teachable moment'. However, as time since diagnosis passes, any initial changes are less sustained [37, 43] and we have also previously seen that there is little difference in health behaviours among the general population and (long-term) cancer survivors [43]. Thus, cancer diagnosis might serve as a teachable moment for some, but not all, and maintaining health behaviour change is difficult as time passes. This difference in cancer experiences is further explored in Chapter 4.

Notwithstanding the described parallels in prevalence and adverse health effects, when addressing alcohol and tobacco use several differences become clear. Alcohol use is more prevalent than tobacco use and the drinking culture in The Netherlands has been described as one of high alcohol consumption and tolerance for intoxication [44, 45] (although country-level descriptions of drinking cultures have been critiqued [46–48]). At the same time alcohol dependence is surrounded with stigma [49], drinking patterns vary more than smoking patterns (for tobacco use, daily smoking is the most prevalent pattern) [27], and knowledge of alcohol use being a risk factor for cancer is much lower [50, 51]. On top of that, there is less alcohol moderation support available for cancer survivors (Chapter 2) and recognition of alcohol use above guidelines is more difficult (Chapter 8).

Healthcare settings and addressing tobacco use among cancer survivors

In the US, the National Comprehensive Cancer Network (NCCN) issued a guideline on how to approach smoking and smoking cessation in cancer survivors specifically. This guideline recommends an individualized treatment plan combining behavioural and pharmacotherapy after a thorough assessment of tobacco use, smoking history and nicotine dependence [52]. There are Dutch guidelines on treatment of tobacco addiction, but these are not specified for oncological care [53, 54]. The guidelines state that every healthcare provider has a role in treatment of tobacco use and should encourage smoking cessation in their patients, although not every healthcare provider needs to provide the same (amount of) support. In the guideline for head-and-neck cancer care, it is stated that alcohol and tobacco use should be actively discouraged, but without further elaboration [55].

Recently, a survey on ways in which oncologists address smoking cessation was conducted among 544 respondents from 16 European countries (6,235 were invited), including 55 oncologists from the Netherlands [56]. Almost all oncologists believed that tobacco use negatively impacts treatment outcomes (94%) and that smoking cessation support should be part of routine care (95%). The majority asks most of their patients about their tobacco use (93%), but usually without a structured method and without asking about the type of tobacco products. Although most advise their patients to quit smoking (88%), only 39% discussed options for medication.

The study also focused on differences in curative (aimed at curing the underlying disease) and palliative settings (aimed at relieving symptoms). Generally, cessation advise was given less often in palliative settings (54% reported providing advice always or most of the time), but smoking cessation support was still deemed an essential part of routine care (63%). As it is possible that selection bias occurred (oncologists having a higher interest in smoking cessation being more likely to participate in the study), the actual frequency of addressing tobacco use and smoking cessation is likely to be lower still in clinical practice.

Main barriers for facilitating smoking cessation support were similar in curative and palliative settings and they included: clinicians' perceived inability to help patients to quit, concerns about patients' resistance to treatment, a lack of time, a lack of resources for referral and a lack of training; 73% believed that oncologists needed more training in addressing tobacco use [56]. These were also noted as important barriers in other studies [57–59].

Additional barriers to address smoking cessation in cancer survivors identified by previous studies were: diffusion of responsibility (i.e. it was not seen as the health care professional's role to talk about smoking cessation beyond asking about tobacco use) [59, 60], perceiving smoking as a sensitive issue that might upset patients [59, 60], fear of implying judgement or exacerbating patient's feelings of guilt [60], a perceived lack of motivation to quit in the patient [59, 61] and perceived low prioritizing of smoking cessation by the patient [61]. The knowledge and beliefs of oncological healthcare providers are thus important factors influencing delivery of smoking cessation advice, but workplace factors like lack of time and other resources, and the lack of clear protocols to avoid role confusion play an important role as well [62]. These barriers to providing smoking cessation support are not unique to oncology healthcare providers; similar barriers have been identified in other healthcare providers [62, 63].

In addition to the recent European study [56] several other studies have also noted that provision of smoking cessation in oncological health care providers has been lacking. A review showed that although the majority of oncological health care providers reported asking about smoking status (>77% at the initial visit, usually less often at subsequent visits) and providing the advice to quit smoking (>60%), generally less than 40% actively referred patients to smoking cessation support services or prescribed medication [59]. More time spent with the cancer patient,

smoking cessation counselling training and more time passed since obtaining the most senior degree predicted higher frequency of providing smoking cessation counselling [57]. Again, this is congruent with predictors in other healthcare providers [63]. Generally positive attitudes of oncological healthcare providers towards smoking cessation support in cancer survivors has also been well documented [56, 59]. Thus, there seems to be a discrepancy between the will to address smoking cessation and current practice.

Healthcare settings and addressing alcohol use among cancer survivors

Whereas there is a substantive amount of literature on ways in which tobacco use is addressed in oncological healthcare settings, there are hardly any studies focused on addressing alcohol use. A recent French study assessed ways in which oncological healthcare providers addressed alcohol use with their patients [64] and found several differences between addressing tobacco use and alcohol use: healthcare providers assessed the frequency and amount of alcohol use in a less standardized manner than tobacco use, patients more often underreported their actual alcohol use, and questions about frequency of alcohol use were often only posed to those patients that were deemed to be in a risk category (based on subjective appraisals, for instance if shame is noticed after asking about alcohol use). On the subject of referral to support, healthcare providers reported that most patients did not accept the invitation to be referred to an addiction specialist, stating they could change their behaviour on their own. A possible explanation is that patients wish to avoid the stigma of being alcohol dependent [64]. At that point, healthcare providers generally stopped further addressing alcohol use.

From studies focused more broadly on provision of healthy lifestyle behaviour advice, we know that healthcare providers see alcohol use as a sensitive topic and that they find it difficult to assess the amount of alcohol use, leading them to only address alcohol use in case of indications of problems (eg, the patient's alcohol use being brought up by a relative) [65]. Generally, some healthcare providers see lifestyle behaviours (including alcohol use, but also diet and smoking) as a personal matter that the patient should decide for themselves or they consider it of lower priority to discuss in the limited amount of time during their consultation [65]. In the UK, only 33% of healthcare providers gave advice on alcohol use to a majority of their cancer patients, which was the lowest proportion compared to all other lifestyle behaviours (smoking, diet, weight and physical activity) [66]. Important barriers that impeded with the provision of alcohol advice were: fear of blaming the patient, lack of clear guidelines, and the belief that alcohol moderation would not affect cancer outcomes [66], although this last belief is not common [67]. Most common barriers were similar to the barriers for addressing tobacco use: lack of time, lack of skills and the belief that interest in lifestyle advice in the patient is low [66, 67]. An additional important barrier for providing advice on alcohol use is lack of knowledge on guidelines [67].

To conclude, if the time frame surrounding the cancer diagnosis is indeed a teachable moment providing an opportunity for alcohol moderation and smoking cessation, it is currently not used

to its full potential. A lack of time and training are important barriers for healthcare providers to address alcohol and tobacco use.

Cancer survivors' views on addressing alcohol and tobacco use

We have seen that healthcare provider's hesitance to address alcohol and tobacco use is partly due to the belief that patients will not appreciate these subjects being brought up. However, studies provide no evidence to support this belief. Again, studies specifically focused on alcohol use are scarce and we therefore take into account studies that assessed views on multiple lifestyle behaviours, amongst them alcohol use.

Cancer survivors are open to discussion of smoking and lifestyle behaviours with their healthcare providers, in fact, they expect their healthcare providers to advise them on healthy lifestyle behaviours [60, 68]. They do expect the topic to be addressed in a considerate and supportive way [60]. It would not offend them to be offered smoking cessation support, even if they believed they did not need it [68]. Cancer survivors have actually generally felt a lack of offered support for smoking cessation [60, 68]. Cancer patients most often sought advice about alcohol intake from their healthcare providers, only preceded by questions on sun safety [67], which indicates their interest in the topic and their being open to discussion of alcohol use with their healthcare professional. Dutch cancer survivor's views on addressing alcohol and tobacco use will be explored in Chapter 4.

Interventions for alcohol moderation and smoking cessation

Various support options are available for alcohol moderation and smoking cessation in the general population: behavioural interventions, pharmacological interventions, and system support. For alcohol moderation, brief face-to-face alcohol interventions delivered in primary care settings are effective in people who drink excessively, but are not alcohol dependent [69, 70]. These interventions are known as screening and brief interventions (SBI's) and they involve a short assessment of the patient's alcohol use and conversation with the clinician, who gives feedback on the patient's alcohol intake, informs them about the harms of risky alcohol use and benefits of moderation, advises them on how to moderate and strengthens self-efficacy to moderate drinking.

For smoking cessation, a combination of pharmacotherapy and behavioural support is advised according to clinical practice guidelines [71]. Face-to-face counselling (often combined with telephone sessions) by a healthcare provider is an effective way of providing behavioural support for smoking cessation [72, 73]. These counselling interventions usually consist of identification of high-risk situations and problem-solving strategies, a review of the motivation to quit smoking, and a review of smoking history [73].

Although several interventions have proven to increase alcohol moderation and smoking cessation rates, their implementation in the real-world is lacking. Actual use of support is low for both alcohol moderation and smoking cessation [74]. Brief interventions in healthcare have low implementation rates; main barriers include clinician's lack of time, lack of training and negative beliefs about their ability to deliver the brief intervention [75]. In the Netherlands, 7.5% (95%CI 7.0-8.0) of smokers who attempted to quit (in 2016) used medication, 4.0% (95% CI 3.6-4.4) used a smoking cessation service and 1.7% (95%CI 1.4-2.0) used a quit line (telephone-based smoking cessation support). These rates are similar in other European countries, but lower than in England [74]. People who use medication to quit smoking, rarely seem to use additional behavioural support [76].

Digital interventions have the potential to overcome some of the difficulties arising during implementation of the above mentioned more traditional (face-to-face) interventions, by being more easily accessible: they lower the threshold for seeking help, they can potentially reach larger populations, be less costly, and offer the possibility of anonymity for those reluctant to discuss alcohol or tobacco use with healthcare providers. Unguided or minimally guided digital interventions could have the additional benefit of not requiring a time-consuming and costly restructure of the healthcare system, for example by not requiring instruction of healthcare providers. We will first discuss the effectiveness of digital alcohol and tobacco interventions, after which we will proceed to discuss what is known on digital interventions specifically for cancer survivors.

Digital alcohol and tobacco interventions

Throughout this thesis, digital interventions will refer to interventions delivered via the Internet that can be accessed through computers, tablets, mobile phones or other similar devices. There is currently no consensus on the terminology for interventions delivered via the Internet; other often used terms are 'Internet-delivered' or 'Internet-based' interventions [77].

Face-to-face and digital interventions differ in that face-to-face interventions are often delivered in primary care settings, whereas digital interventions could reach more people outside of these settings. Digital interventions can also offer greater feelings of anonymity to some, thus making it easier to disclose sensitive personal information on alcohol or tobacco use, while for others digital interventions and their data storage can increase concerns for their privacy [78]. There is also a wide variety among digital alcohol and tobacco interventions. They differ in intensity, interactivity, involvement from a healthcare professional (guidance), contact with peers, degree of tailoring to the participant, theoretical basis, and modality [78, 79].

Still, several common characteristics can be identified. Most digital alcohol and tobacco interventions can be accessed by a computer or through mobile apps. Some digital interventions include gaming elements [80], incorporate augmented reality functionalities [81, 82] or offer

support tailored to the location of the participant [83]. Many digital alcohol and tobacco interventions are reportedly based on the social norms approach, theory of planned behaviour, social cognitive theory, and/or the transtheoretical model of change [79, 84]. Many digital interventions also consist of components similar to face-to-face (brief) interventions: assessment of current alcohol or tobacco use, support in setting a goal and plan of action, and strategies to overcome high-risk situations [78]. The majority of digital alcohol and tobacco interventions are unguided [79, 85, 86]. Guided interventions include support through human contact, often asynchronously [85]. This support can be provided by healthcare providers, but also peer coaches and can differ in extent. Unguided interventions can be used by the participant without any human support at all, making them fully automated.

Meta-analyses have shown that digital interventions for alcohol moderation [78, 85] and smoking cessation [79, 87] are effective among the general population. For alcohol, a further reduction of about 23 to 50 g of weekly alcohol use was found for people using digital interventions compared to control groups [78, 85]. For smoking, those using digital interventions were 1.1 times more likely to remain abstinent after 6 months than those receiving no active support [79], but this meta-analysis excluded mobile phone based interventions (e.g., mobile apps) and heterogeneity was high, with several studies having found larger effects. Looking at short-term (less than 6 months) abstinence, users were 1.3 times more likely to remain abstinent [88]. For mobile phone apps supporting smoking cessation, there were too few studies and the findings were inconsistent to confidently pool the evidence.

Several characteristics of effective interventions have subsequently been identified. Tailored and interactive tobacco interventions seem most effective [79]. Alcohol interventions with some guidance seem to be more effective than interventions without guidance [85]. Digital interventions that are based on social cognitive theory or motivational interviewing (MI) have been found to be more effective than interventions lacking a theoretical base [84]. Many digital interventions for substance use have been based on cognitive behavioural therapy [89]. Another promising theoretical basis for digital substance use interventions is acceptance and commitment therapy (ACT) [90]. These theories will be further elaborated upon in Chapter 4.

Digital alcohol and tobacco interventions and their behavioural change components

We have seen that digital interventions are complex structures that can differ greatly, even when based on the same theoretical models. In recent years, efforts have therefore been directed towards identifying and describing behavioural change components (BCTs) of digital interventions in a uniform manner, to improve intervention descriptions, and ease comparison of interventions across target behaviours and treatment modalities [91]. A BCT is an "observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behavior" [91]. Examples of BCTs are the setting of a goal to limit alcohol use to 3 glasses per week ('goal setting') or listing (dis)advantages of

smoking and smoking cessation ('pros and cons'). The BCTs are defined and grouped together in the BCT Taxonomy Version 1 [91].

Digital alcohol interventions include an average of 9 different BCTs [92]. BCTs that were associated with increased effectiveness in digital alcohol moderation interventions are: providing normative information [84], providing feedback [84], prompting commitment [84], prompting review of progress towards goals [84], behaviour substitution [92], problem solving [92], and credible source [92]. However, BCTs show different associations with reductions in alcohol use for men and women, which might explain some mixed findings [84]. Interestingly, providing information on the negative health consequences of drinking was associated with smaller reductions in alcohol use [84].

In digital smoking cessation interventions, an average of 6.6 BCTs was found [88]. BCTs that were associated with higher smoking cessation rates in the long term were: problem solving, action planning, social support, and natural consequences (e.g., providing information about health consequences of smoking or social disapproval following smoking in public spaces).

An evaluation of 251 studies evaluating health behaviour interventions (of which 92 targeted smoking cessation, 48 targeted multiple health behaviour and 8 targeted alcohol use), led to the identification of several BCT groups that were associated with increased cost-effectiveness [93]. BCT group 'goals and planning' and 'comparison of behaviour' were associated with increased cost-effectiveness, while 'reward and threat' and 'natural consequences' were associated with lower cost-effectiveness. Due to the low number of studies, for some BCTs their effect could not be assessed. In short, there are several BCTs that could potentially contribute to an effective digital alcohol or tobacco intervention.

Engagement with digital interventions

One aspect that is hypothesized to influence the effectiveness of digital interventions is engagement with the intervention. Engagement with many digital interventions for cancer survivors is low, thus possibly negatively impacting their effectiveness [94]. Several strategies have been proposed to increase engagement, but detailed analyses of engagement with alcohol and tobacco interventions are lacking. In Chapter 3, we will therefore explore how a digital alcohol moderation intervention is used.

There is no consensus yet on what the construct of engagement entails, although there seems to be a tendency in eHealth research to conceptualize it as a multidimensional construct, beyond intervention usage [95]. According to a recent study, engagement with digital interventions refers to the extent of usage of an intervention and the subjective experience of attention, interest and affect [96]. Engagement is influenced by the participant's characteristics: e.g., motivation, attention, feeling of personal relevance, expectations and mental health.

Intervention characteristics that influence engagement include the extent of tailoring, extent of professionals support, control features, message tone and presence of a narrative [96]. A form of engagement is adherence, which refers to the participant's use of the intervention in the way that the intervention developers intended. Engagement and adherence are thought to considerably impact effectiveness of digital interventions, yet non-adherence of digital interventions is often high [97, 98].

Several BCTs may positively stimulate engagement: goal setting, action plans, self-monitoring and feedback [96]. The most prevalent strategies to enhance engagement in digital substance use interventions were found to be tailoring of the intervention (47%), use of reminders (40%) and incorporation of social support (40%) [99]. There is indicative evidence that specifically technology-based strategies might improve engagement with digital interventions [100]. Examples of such strategies are reminder emails, text messages or phone calls. These strategies differed in duration, sender, content, timing, frequency and extent of tailoring. No conclusions could be drawn on which (characteristics of) strategies were associated with increased engagement, due to the low number of (high quality) studies and their heterogeneity [99, 100].

Digital alcohol and tobacco interventions for cancer survivors

As the number of cancer survivors is growing, as a consequence of improvement in treatment and diagnostics, digital interventions may contribute to keeping evidence-based alcohol moderation and smoking cessation support available to all.

Before this project started, there were hardly any interventions focused on alcohol use in cancer survivors [101–103]. Most interventions address alcohol use as part of a broader lifestyle intervention. However, lifestyle interventions that target multiple health behaviours might not be the best tool to address alcohol and tobacco use. While these multiple health behaviour interventions showed beneficial effects on diet and physical activity, they hardly seem to influence alcohol use [102]. Furthermore, multiple health behaviour interventions were found less cost-effective than dedicated smoking cessation interventions [93].

There are several descriptions of dedicated smoking cessation programmes in oncological healthcare settings [104–106], but evidence still remains scarce [107, 108]. It is suggested that smoking cessation interventions for cancer survivors are less effective and that cancer survivors need a more tailored approach than the general population [107], but what would constitute an effective smoking cessation program for cancer survivors remains largely unknown. Cancer related factors such as type of cancer treatment, tumor site, and time since diagnosis were not associated with the effectiveness of a pharmacological smoking cessation treatment [109].

In Chapter 2 a systematic review with meta-analyses is presented on the effectiveness of distance-based interventions for alcohol moderation and smoking cessation in cancer survivors.

We have found that current distance-based interventions that target alcohol and tobacco use in cancer survivors are mostly telephone-based and that few are delivered over the Internet [110]. We have therefore developed two new digital interventions to support cancer survivors in alcohol moderation and smoking cessation: MyCourse – Moderate Drinking and MyCourse – Quit Smoking. Their development and evaluation are described in this thesis.

Implementation of digital alcohol and tobacco interventions

Determination of increased effectiveness of an intervention over a control condition is not sufficient to ensure public health impact. Despite the benefit of wider accessibility, implementation remains an unresolved issue for digital health interventions [89, 111]. There are many digital interventions available, many of which have not been scientifically studied or are not evidence-based: only 6 of 45 available Dutch digital smoking cessation interventions were evaluated in a trial [112]. Those that have been evaluated are often not available to the general public [113]. Implementation of effective digital interventions requires effort, planning and specific attention as barriers for implementation are multi-level and diverse, ranging from organisational issues and lack of (financial) resources to individual knowledge and beliefs about the intervention [114]. In addition, aspects of implementation cannot be evaluated well in traditional randomized controlled trials and are usually not well documented. Instead, we can gain insight into the (potential for) implementation of an intervention through implementation frameworks like the CeHRes Roadmap [115] or the RE-AIM model [116]. The CeHRes Roadmap describes five interconnected phases of e-Health development, implementation and evaluation, which structurally involves stakeholders. According to the RE-AIM framework, interventions are evaluated on four other dimensions in addition to effectiveness: reach, adoption, implementation and maintenance. In Chapter 7 we will evaluate the newly developed MyCourse interventions using the RE-AIM framework to gain knowledge on how to implement digital alcohol and tobacco interventions among cancer survivors.

Key limitations of the current evidence base

In summary, evidence on the effectiveness of digital alcohol and tobacco interventions is strongest for college and university populations [117] and the general population (e.g. [79, 85]) and there are few studies available on tailoring of digital alcohol and tobacco interventions to cancer survivors, with little evidence on their effectiveness. Implementation of digital interventions has rarely been evaluated beyond the notion that stakeholders should be involved from the beginning of the development process [111]. Few digital alcohol and tobacco interventions have been evaluated for cost-effectiveness, even among the general population [118]. There are few high quality studies on the effectiveness of mobile phone apps for alcohol and tobacco use, most studies on mobile phone-based interventions have focused on text messaging [87]. Lastly, little is known on working mechanisms and moderators of digital interventions [89]. This thesis will contribute to alleviate the paucity of literature on dedicated (digital) alcohol

and tobacco interventions for cancer survivors, and more specifically to the here mentioned research areas.

Overview of the thesis

This thesis aims to address the question how digital interventions can support cancer survivors in alcohol moderation and smoking cessation. To that end, it describes the evaluation of two newly developed digital minimally guided interventions for cancer survivors: MyCourse – Moderate Drinking and MyCourse – Quit Smoking. The following key questions are discussed in this thesis:

1. What is the effectiveness of other distance-based alcohol and tobacco interventions for cancer survivors? **(Chapter 2)**
2. How was a digital self-help alcohol moderation intervention for the general population used and can any potential intervention use moderators be identified? **(Chapter 3)**
3. How can interventions for the general population be adapted for cancer survivors **(Chapter 4)** and how can such interventions be evaluated **(Chapter 5)**?
4. What is the effectiveness and cost-effectiveness of two newly developed digital minimally guided alcohol and tobacco interventions for cancer survivors? **(Chapter 6 and 7)**
5. How can digital minimally guided alcohol and tobacco interventions be implemented among cancer survivors? **(Chapter 8)**

In **Chapter 9**, a summary of the findings is provided, and their implications and the limitations of the thesis are discussed. **Chapter 10** provides a summary of the thesis in Dutch.

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CHAPTER 2

The effectiveness of distance-based interventions for smoking cessation and alcohol moderation among cancer survivors:
a meta-analysis

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ABSTRACT

Background

The objective was to evaluate current evidence for the effectiveness of distance-based interventions to support smoking cessation (SC) or alcohol use moderation (AM) among cancer survivors. Secondary, differences in effectiveness are explored regarding multi-behaviour interventions versus single-behaviour interventions targeting SC or AM only.

Methods

A systematic search of PubMed, PsycINFO, Web of Science, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials was conducted. Intervention studies with and without control groups, and randomised controlled trials were included. Random effects meta-analyses were conducted for the main outcomes: SC and AM rates at the follow-up closest to 6 months. Using subgroup-analyses and meta-regression, effectiveness of single-behaviour versus multi-behaviour interventions was evaluated.

Results

A total of 17 studies with 3,796 participants; 9 studies on SC only, 8 studies on multi-behaviour interventions including an SC or AM module, and no studies on AM only were included. All studies had at least some concerns regarding bias. Distance-based SC interventions led to higher cessation rates than control conditions (10 studies, OR=1.56, 95%CI 1.13-2.15, p=.007). Single-behaviour SC interventions reduced smoking rates compared to baseline (RD=0.29 95%CI 0.19-0.39, p<.0001), but multi-behaviour interventions did not (RD=0.13 95%CI-0.05–0.31, p=0.15). There was insufficient evidence that distance-based multi-behaviour interventions reduced alcohol use compared to controls (3 studies, SMD=0.12, 95%CI-0.08-0.31, p=.24).

Conclusions

Distance-based SC interventions are effective in supporting SC among cancer survivors. Single-behaviour SC interventions appear more effective than multi-behaviour interventions. No evidence was found for the effectiveness of distance-based AM interventions for cancer survivors.

Trial registration: PROSPERO identifier CRD42017074567 on 31 October 2017.

INTRODUCTION

Alcohol and tobacco are classified as group I carcinogens [1, 2] and their use is one of the largest preventable risk factors for cancer occurrence [3]. Alcohol and tobacco use contribute to cancer recurrence and second cancers [4–6], cancer mortality [7, 8] and iatrogenic effects of treatment [9]. Smoking and alcohol use contribute considerably to the total number of cancer cases [10, 11]. Attributable cancer deaths in the United States are estimated at 28.8% and 4.0%, respectively [12, 13].

Smoking cessation (SC) and alcohol moderation (AM) are important for cancer survivors [14]. This is particularly true for patients with cancers known to be strongly associated with smoking or alcohol use (e.g., lung, breast, colorectal, head and neck cancer) [3]. Nonetheless, rates of smoking and excessive alcohol use among cancer survivors are high [15–17]. One study among 50,000 US cancer survivors found that 16.1% smoked and 5.1% were heavy drinkers, rates similar to those for people without cancer (18.6% and 6.0%, respectively) [18].

Several psychological interventions to reduce alcohol and tobacco use among cancer survivors are available. These interventions are generally provided face-to-face or via telephone, and their effectiveness has been described in several reviews. One meta-analysis on SC interventions for all cancer survivors was published in 2013 [19] and a second one on SC counselling interventions for head and neck cancer survivors in 2016[20]. A narrative review without meta-analysis on both AM and SC interventions for head and neck cancer survivors was published in 2018[21]. Until now, no meta-analysis has been published on AM interventions for cancer survivors.

The two meta-analyses on SC interventions included randomised controlled trials (RCTs) and non-randomised studies. Nayan and colleagues[19] reviewed 10 RCTs and 3 prospective cohort studies and found no evidence for the effectiveness of SC interventions compared to control groups after a mean follow-up time of 5 weeks (OR=1.54, 95%CI 0.91-2.64, p=.108) and 6 months (OR 1.31, 95%CI 0.931-1.84, p=.120). However, SC interventions delivered in the peri-operative period were found to be effective (OR 2.31, 95%CI 1.32-4.07); possibly because the pre-operative period functions as a 'teachable moment' associated with increased motivation to change unhealthy lifestyle behaviours. Klemp and colleagues[20] reviewed SC interventions for head and neck cancer patients, and found 3 RCTs, 3 cohort studies, and 2 case studies, concluding that counselling increased the cessation rate with 26% (RR=0.76 favouring experimental condition, 95%CI 0.59-0.97, p=.03).

One study [21] systematically reviewed RCTs on SC and AM interventions among head and neck cancer survivors and patients with oral dysplasia, finding only 3 eligible RCTs and no RCT aimed solely at AM. Results on AM interventions among cancer survivors are clearly scarce, but reviews of studies among the general population are available. A systematic review comparing AM guided and unguided low-intensity Internet interventions found that participants used on

average 22 g of ethanol less than controls [22]. A systematic review on brief AM interventions delivered in a primary care setting found similar results (mean difference of-20 g/week, 95%CI -28 to-12) [23]. Assessment of incorporated behaviour change techniques (BCTs), theoretical underpinnings and modes of delivery contributes to gaining further insight into factors possibly influencing effectiveness of SC and AM interventions [24].

Health behaviour interventions can focus on changing a single behaviour [25] or multiple health behaviours simultaneously, sometimes referred to as multiple health behaviour change interventions [26]. Theoretically, multiple-behaviour interventions can have benefits over single-behaviour interventions because of greater real-world applicability and information provision on effective treatments for co-occurring behaviours, e.g. alcohol and tobacco use [27]. However, a Cochrane review based on 12 RCTs concludes that multiple-behaviour rehabilitation interventions for cancer survivors might be less effective than single-behaviour interventions with regard to maintaining or improving physical and psychosocial well-being [28], but this has not yet been evaluated for SC and AM specifically. In addition, improvement on all targeted behaviours of a multiple-behaviour intervention is scarce [29] and cancer survivors are less likely to choose alcohol as the first behaviour to change [30]. Findings are mixed in non-cancer survivor populations receiving intensive substance use treatment for alcohol and smoking [31–33].

The increasing population of cancer survivors [34] suggests an increased need for scalable evidence-based SC and AM interventions. Furthermore, self-management strategies have shown several beneficial effects in cancer survivors, including increase of self-efficacy [35]. Distance-based interventions (i.e. telephone-, print- or web-based) offer autonomy and reassurance to cancer survivors [36] and may be effective and/or cost-effective [37, 38]. A systematic review and meta-analysis of studies testing the effectiveness of distance-based SC and AM interventions for cancer survivors which encourage smoking cessation and reduce alcohol intake is lacking.

Therefore, in this systematic review and meta-analysis we will address the following questions:

1. Do distance-based interventions increase smoking cessation rates and/or reduce alcohol use among cancer survivors?
2. Are single-behaviour interventions targeting SC or AM more effective than multi-behaviour interventions including SC and/or AM modules?

METHODS

Search strategy

A systematic literature search of PubMed, PsycINFO, Web of Science, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials was conducted from inception to December 20, 2017, updated on November 8, 2018. The search string included a combination of synonyms for

smoking, alcohol use, health behaviours, intervention and cancer survivors (Appendix 1). Due to the expected paucity of literature and to optimally cover the available evidence, we included both RCTs and intervention studies with and without a control group. This review was conducted in accordance with the PRISMA statement [39], and was registered in the international prospective register of systematic reviews (PROSPERO identifier: CRD42017074567).

Eligibility criteria

We included English peer-reviewed publications which evaluated the effectiveness of distance-based interventions aiming to reduce alcohol use, encourage SC or both, targeted cancer survivors, reported relevant outcomes, and were designed as an RCT or non-randomised study with or without control group. Interventions should be aimed at behaviour change of the individual. "Distance-based" was operationalized as an intervention delivered at least 80% remotely and/or asynchronously, meaning that no more than 20% of total session time was delivered face-to-face or, in cases where information on session time was unavailable, no more than 20% of the total number of sessions. For example, interventions were included containing one-time face-to-face contact and continuation with several sessions by telephone or other remote-delivery modes. Cancer survivors are defined as those ever diagnosed with cancer, irrespective of treatment phase or life expectancy. Any participant who identifies as a smoker or had smoked in the past seven days was considered a smoker. Anyone who had not smoked in the last seven days or identifies as a non-smoker was considered a non-smoker. Anyone who drank alcohol in the past week was considered a drinker.

Study selection and data extraction procedures

First, two researchers (AM and LL) independently screened titles and abstracts for eligibility and then read the full-texts of potentially eligible articles. Disagreements were resolved through consensus meetings; when necessary a third author (MB) was consulted. Reference lists of included papers were checked for additional eligible articles.

Extracted data from each article included: title, author, year, country, participant characteristics, cancer site, study design, relevant outcome measures, effect sizes (number of smokers, number of non-smokers, non-responders, drinks per day/week, standard deviation, and p-values), follow-up period, control group and intervention characteristics. Delivery mode, guidance level, number of sessions, main intervention target, theoretical base, control group, relevant outcome measures, and reported BCTs according to Michie's taxonomy [24] were coded by two researchers (AM and LL). Study protocols or intervention development papers mentioned in the included papers were also checked, mainly to extract intervention characteristics and to assess Risk of Bias (RoB). Authors of the included studies were contacted in case of uncertainty regarding outcome data.

Studies reporting sufficient outcome details were included in the meta-analysis. The outcome assessment (closest to) 6 months after randomisation was used in all analyses, as done in a previous similar review [20].

Risk of bias and methodological quality assessment

Risk of Bias (RoB) was assessed at the outcome level using the Cochrane RoB tool 2.0 [40] (RCTs), ROBINS-I tool [41] (non-randomised studies with a control group [NR+CG]) and a standardized form for quality assessment of before- and after studies without control group from the U.S. National Heart, Lung and Blood Institute [42] (non-randomised studies without a control group [NR-CG]). Two authors (AM and JB) independently assessed RoB and reached consensus.

Statistical methods

Random effects meta-analysis was conducted for SC and AM interventions separately. A pooled effect size was calculated between groups (intervention vs. control, primary analysis) and within groups (before vs. after intervention) where possible. For AM, mean number of drinks per week at baseline and follow-up were used to calculate Hedges' *g* (intervention vs. control: between group change) or SMC (standardized mean change, before vs. after intervention: within group change). For the AM within-group comparison, SMC was calculated with a conventionally assumed pre-/post-test correlation of r=.70 [43] and following the Morris (2008) procedure [44].

For SC studies, the numbers of smokers, non-smokers and non-responders at baseline and follow-up were extracted, for both intervention and control groups. Non-responders were excluded from the analysis as some studies included non-smokers at baseline and baseline smoking status of the non-responders was not always clear, thus the 'missing is smoking' procedure could not be applied. Because this procedure is more common in SC research, sensitivity analyses applying this procedure to appropriate studies, resulting in intention-to-treat analyses, were carried out. For the SC within-group meta-analyses, risk differences (RD) were reported; ORs were used as effect sizes when comparing intervention to control groups.
Heterogeneity was quantified in both AM and SC using the I^2 statistic, and tested for significance using the Q-test. Using subgroup analyses and random effects meta-regression analysis with study as the random component, a possible source of heterogeneity, i.e. dimensionality, was explored [45]. Publication bias was intended to be visually evaluated by means of funnel plots, Egger's regression test and the rank sum correlation test.

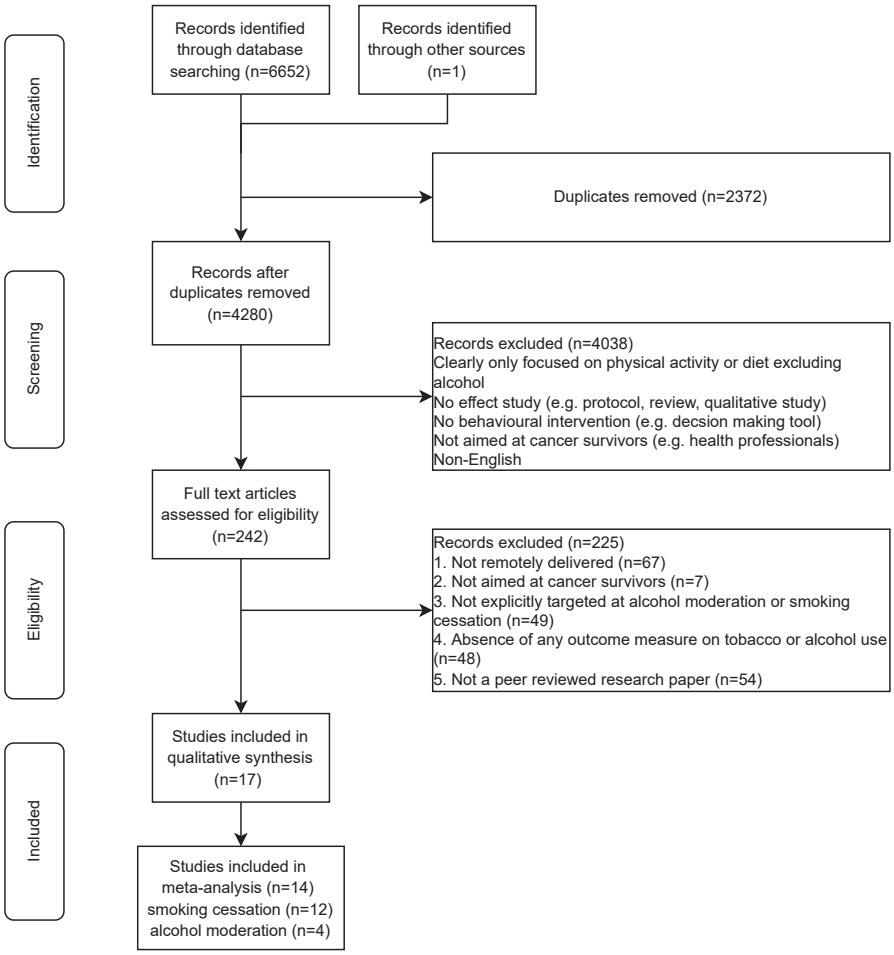
A two-sided p-value of <.05 was considered statistically significant. All statistical analyses were conducted in R software (version 3.5.1), with meta-analyses performed using the metafor package [46].

RESULTS

Study selection

The initial search strategy identified 6,652 records, which included 2,372 duplicates as identified by software programs Covidence [47] and Mendeley (version 1.19.2) [48]. After abstract screening of the remaining 4,280 records, 242 records were reviewed in full-text. One additional study was identified through reference list searching of included studies. This yielded 17 studies for inclusion in the systematic review, of which 14 could be used for meta-analysis (Figure 1); one study did not provide sufficient outcome data for meta-analysis [49] and two were secondary studies of the same trial[50], describing an additional follow-up assessment [51] and process evaluation [52].

Figure 1. Study selection process



Study characteristics

Most studies (76%, 13/17) were published between 2010 and 2018, the remainder being published between 2005 and 2009. Studies were carried out in the United States (76%, 13/17), two in Australia, one in the Netherlands and one in the United Kingdom. Most studies were RCTs (71%, 12/17); four were NR-CG (23%) and one was NR+CG (6%). Two articles described secondary studies [51, 52] of an already included trial [50]; as these reported the same sample of participants they were excluded from the quantitative analyses. The remaining 15 studies included a total of 3,796 participants, with a mean sample size of 253.1 (*SD*=236.5), a mean participant age of 52.8 (*SD*=14.3) years; 58.6% were women (see Table 1).

Table 1. Study characteristics

Author & Year	Country	Sample size (n)	Age (Mean years)	Gender (% Female)	Study design	Control group	Relevant outcome measures	Cancer site
Amato, 2015[53]	USA	250	61.9	59.8	NR-CG	-	SC:7	thoracic
Berg, 2014[49]	USA	24	23.38	70.8	NR-CG	-	AM:1, SC: 4	lymphoma, leukemia, osteosarcoma, thyroid, glioblastoma, Wilm's tumor
Duffy, 2006[54]	USA	184	57	16	RCT	Enhanced care as usual: Face-to-Face assessment and brief counseling, handout with resources, referrals	AM:9, SC:7	head and neck
Emmons, 2005[50]	USA	796	31	47	RCT	Printed information brochure	SC:7,8	leukemia, CNS, lymphoma, kidney, neruoblastoma, soft tissue sarcoma, bone
Emmons, 2009[51][a]	USA	565	31	51.0	RCT	Printed information brochure	SC:7,8,5	leukemia, CNS, lymphoma, kidney, neruoblastoma, soft tissue sarcoma, bone
Emmons, 2013[25] **+protocol**[55]	USA	374	32	49.7	RCT	Active: Printed, tailored and targeted self-help manuals, NRT/ Pharmacotherapy	SC:5,7,8	leukemia, CNS, lymphoma, bone, other
Fazzino, 2016[56] **+protocol**[57]	USA	37	57.8	100	RCT	Active: bi-weekly information brochures	AM:3	breast
Grimmett, 2015[58]	United Kingdom	29	65	62	NR-CG	-	AM:2	colorectal
Hawkes, 2009[59]	Australia	20	66.0 (median)	50	NR-CG	-	AM:1, SC:4	colorectal
Hawkes, 2013[60] **+protocol**[61]	Australia	410	66.4	46.1	RCT	Printed information brochure	AM:2,3 SC:7	colorectal

Author & Year	Country	Sample size (n)	Age (Mean years)	Gender (% Female)	Study design	Control group	Relevant outcome measures	Cancer site
Kanera, 2016[26] **+protocol**[62]	The Netherlands	462	55.9	79.9	RCT	Waitlist	SC:7	breast (71%), other
Klesges, 2015a[63]	USA	519	-	45.1	RCT	Active: participant initiated telephone counselling and 2 weeks of NRT/ pharmacotherapy (compared to caregiver initiated and 4 weeks of NRT)	SC:6,7,8	NR
Klesges, 2015b[64]	USA	427	-	67.0	RCT	Active: participant- initiated telephone counselling and 2 weeks of NRT/pharmaco-therapy (compared to caregiver- initiated and 4 weeks of NRT)	SC:6,7	NR
Ostroff, 2014[65]	USA	185	55.9	53	RCT	Active: counselling and NRT	SC:5,7	thoracic, head and neck, breast, gynaecological, urology, other
Park, 2006[52][b]	USA	398	30.9	47.5	RCT	Printed information and manual on cessation	SC:5,7,8	leukaemia, CNS, lymphoma, kidney, neuroblastoma, soft tissue sarcoma, bone
Park, 2011[66]	USA	49	57.7	59.2	NR+CG study	Care as usual: not further specified	SC:6,7	thoracic
Pollak, 2018[67]	USA	30	56.8	73	RCT (pilot)	Waitlist	SC:5,6,7	breast 33%, lung 20%, colon 10%, other

Note. 1=days of drinking; 2=number of drinks or grams of alcohol per week; 3=number of drinks or grams of alcohol per day; 4=days of smoking; 5=cigarettes per day; 6=smoking abstinence/smoking status biochemically verified; 7=smoking abstinence/smoking status self-report; 8=quit attempts; 9=AUDIT; NR=not reported; NR-CG=non-randomised without control group; NR+CG=non-randomised with control group; RCT=randomised controlled trial; SC=smoking cessation; AM=alcohol moderation, USA=United States of America.

[a] Describes additional follow-up to Emmons (2005).

[b] Secondary study on intervention participants of Emmons (2005).

Intervention characteristics

Fifteen unique interventions are described (Appendix 2). Most interventions were delivered by telephone (12/15) [50, 53, 67, 54, 56, 58–60, 63, 64, 66], often supplemented with printed materials (6/12) [50, 54, 58–60, 67] and explicit encouragement of pharmacotherapy or nicotine replacement therapy (NRT) (8/12) [50, 53, 54, 63–67]; three interventions involved face-to-face contacts in addition to remote delivery [54, 65, 66]. The remaining interventions were unguided web-based (3/15) [25, 26, 49], with one explicitly encouraging use of pharmacotherapy or NRT [25]. Half of interventions targeted smoking only (7/15) [25, 50, 53, 63–66]; one multiple-behaviour intervention targeted smoking, alcohol use and depression [54], and one multiple-behaviour intervention targeted smoking and pain management [67]. None of the interventions targeted alcohol use solely. The remaining multiple-behaviour interventions targeted general lifestyle and health-related behaviours including diet and physical activity (6/15), of which four included an SC module [26, 49, 59, 60] and six an AM module [26, 49, 56, 58–60]. Reported theoretical/therapeutic underpinnings varied and included motivational interviewing (MI) (5/15) [50, 60, 65–67], cognitive behavioural therapy (CBT) (4/15) [54, 63, 64, 67], and problem solving therapy (3/15) [26, 56, 60].

Risk of bias within studies

At least some concerns regarding risk of bias were identified for all RCTs (Appendix 3). Risk of bias in selection of the reported result was high or with some concerns in all but one study [60], as these studies did not refer to a published protocol paper with pre-specified analyses. Bias due to missing outcome data was low in 6 studies [25, 26, 50, 54, 60, 65], indicating robustness of the outcomes against the impact of missing data. As the randomisation process was often well described and (lack of) baseline imbalances well reported, no studies were at high risk of bias. Most studies elicited some concerns about bias due to deviations from intended interventions or bias in measurement of the outcomes (because blinding was not reported or absent). For detailed risk of bias and quality assessments of all studies, including NR-CG and NR+CG studies, see Appendix 3.

SC and AM outcome measures

Smoking status or abstinence was assessed in most SC studies, except for Berg (2014) [49] who reported number of smoking days instead of smoking status. Hawkes (2009) [59] reported smoking status based on smoking days, cigarettes per day and age of commencing and quitting smoking. Self-reported smoking status was available in the 11 remaining SC studies, operationalized as 7-day point prevalence abstinence[26, 50, 63–65, 67] , 30-day point-prevalence abstinence [25], 24-hour abstinence [53], or unspecified duration of quit status [54, 60]. In five studies, self-reported abstinence was verified with cotinine assessments [63, 64, 66, 67]. Duration of follow-up differed from end of treatment (6 weeks) to a maximum of 18 months. For SC meta-analyses only one study could not be included as it reported number of smoking days, but not number of smokers [49].

Assessment of alcohol use varied. Two studies measured mean alcohol use in grams per day [56, 60], the others measured drinking days in the past month [49], alcohol units per week [58] or AUDIT scores, a standard screening measure for alcohol problems [54]. Hawkes (2009) [59] classified participants in high-risk, low-risk and non-drinker categories. For AM meta-analyses, two studies [54, 59] could not be included, because no SMC could be calculated from the reported AUDIT scores and drinking days. See Appendix 4 for an overview of study outcomes.

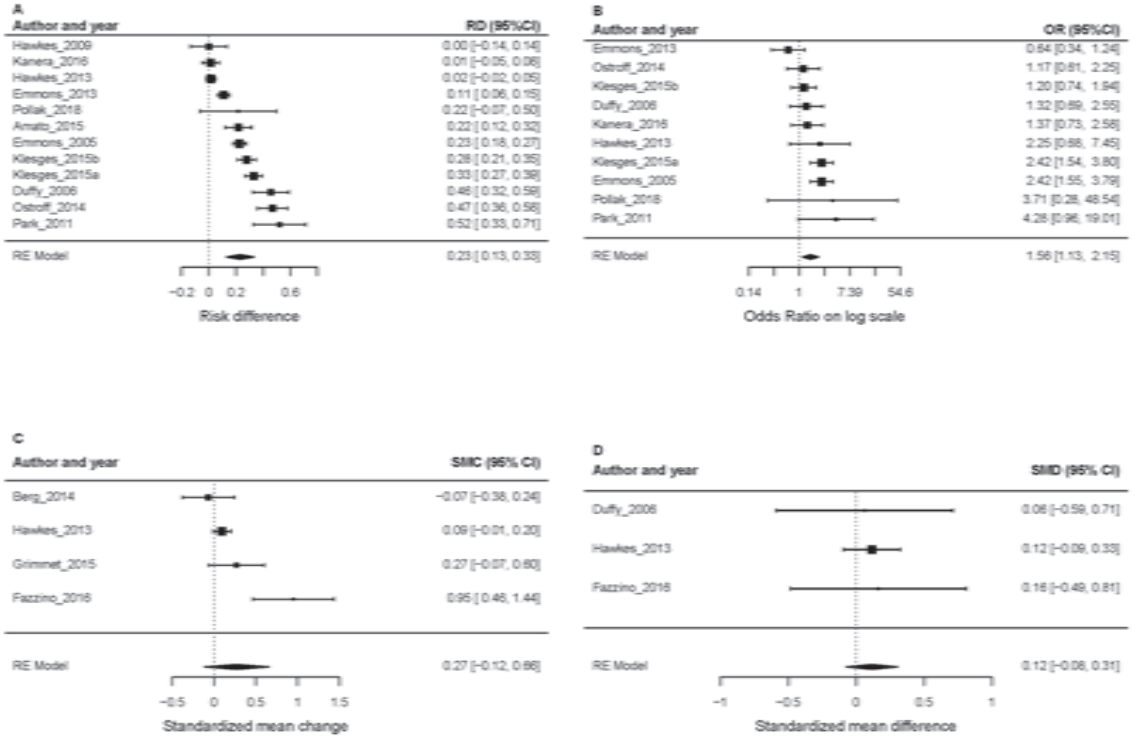
Effects on smoking

Within groups

Based on the within-group data (pre- and post-intervention) from 12 studies [25, 26, 66, 67, 50, 53, 54, 59, 60, 63–65], a pooled RD of 0.23 (95%CI 0.13–0.33, p<.0001) was found in favour of distance-based interventions (Figure 2). Mean follow-up time was 4.7 months (range 1.5-15, SD=3.9). A high level of heterogeneity was observed (I^2=96.07%, Q=207.9, p<.0001). Results were similar when including RCTs only [25, 26, 50, 54, 60, 63–65, 67] (RD=0.23, 95%CI 0.12–0.34, p<.0001, I^2=96.63%, Q=186.6, p<.0001).

Subgroup-analyses were carried out on single-behaviour focussed interventions and multiple-behaviour interventions. Single-behaviour interventions [25, 50, 53, 63–66] yielded a significant pooled RD of 0.29 (95%CI 0.19-0.39, p<.0001). After excluding one outlier[25] the pooled RD was 0.32 (95%CI 0.23-0.41, p<.0001), heterogeneity between studies was reduced (I^2 =86.42%, Q=25.9, p<.0001). Multiple-behaviour interventions [26, 54, 59, 60, 67] produced a non-significant pooled RD of 0.13, heterogeneity remained high (95%CI -0.05–0.31, p=0.15; I^2=95.39%, Q=41.9, p<.0001). After excluding one outlier [54], the pooled RD was 0.02 (95%CI -0.01-0.05, p=.26; I^2=0.11%, Q=2.0, p=.58). A meta-regression also pointed towards a larger intervention effect for single-behaviour compared to multiple-behaviour interventions, but failed to reach significance (B=0.17, 95%CI-0.02-0.36, p=.08).

Figure 2. Forest plots of intervention effects



Note. A. Intervention effect within groups: before and after intervention effect on smoking cessation rate.
B. Intervention effect between groups: intervention and control group effect on smoking cessation rate.
C. Intervention effect within groups: before and after intervention effect on alcohol moderation.
D. Intervention effect between groups: intervention and control group effect on alcohol moderation.

Between groups

Ten studies included a control group [25, 26, 50, 54, 60, 63–67], nine of which were RCTs. Overall smoking rates in intervention groups were lower than in control groups (OR=1.56, 95%CI 1.13-2.15, *p*=.007; I^2=53.59%, Q=19.2, *p*=.02), see Figure 2. Mean follow-up time was 5.3 months (SD=4.0). When excluding one non-randomised study [66]) the result did not change notably (OR=1.50, 95%CI 1.08-2.07, *p*=.01; I^2=55.18%, Q=17.5, *p*=.03).

Subgroup-analyses showed similar ORs for single-behaviour (OR=1.56, 95%CI 0.97-2.50, *p*=.06; I^2=73.30%, Q=17.9, *p*<.01) [25, 50, 63–66] and multiple-behaviour interventions (OR=1.47, 95%CI 0.97-2.24, *p*=.07; I^2=0, Q=1.1, *p*=.77) [26, 54, 60, 67]. A meta-regression showed no heterogeneity was explained by dimensionality (B=0.04 95%CI -0.72-0.80, *p*=.91). No notable differences from the main within-group and between-group analyses were found in sensitivity analyses applying the 'missing=smoking' procedure to appropriate studies [25, 60, 63–67].

Effects on alcohol use

Within groups

Pooled SMC was not significant at 0.27 (95%CI -0.12-0.66, *p*=.17; I^2=87.15%, Q=13.5, *p*<.01), based on within group (pre- and post-intervention) analysis of four included studies [49, 56, 58, 60]. All included AM interventions were multi-behaviour focused. Mean follow-up period was 7.5 months (SD=7.1).

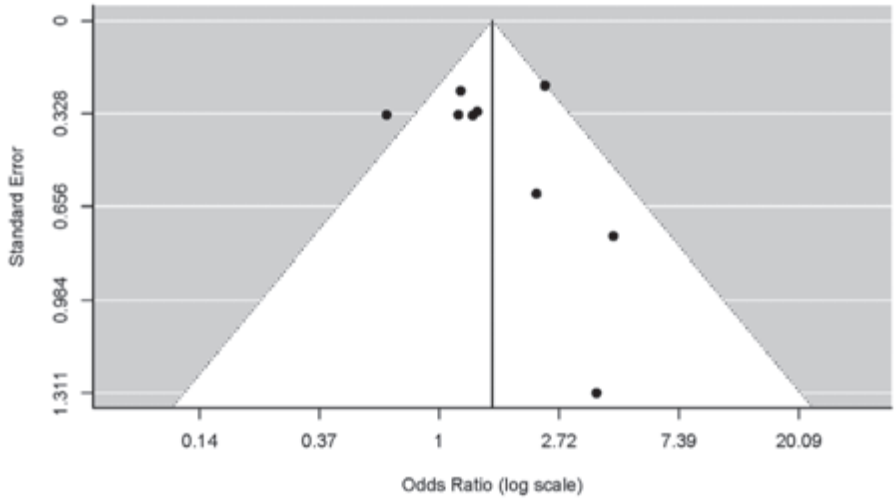
Between groups

Three studies included a control group [54, 56, 60]. The pooled effect estimate was SMD=0.12 (95%CI -0.08-0.31, *p*=.24; I^2=0%, Q=0.05, *p*=.98) (Figure 2). Mean follow-up period was 10 months (SD=6.9). All included AM interventions were multi-behaviour focused.

Risk of publication bias across studies

The number of studies involved in the between-group comparison meta-analyses was low for SC (n=10) and especially for AM (n=3). The initial funnel plot for SC does not show noteworthy deviations (see Figure 3), and the Egger's test (*p*=.90) and the Rank correlation test (*p*=1.0) indicate that there is no statistical reason to assume a publication bias. No notable differences occur when only including RCTs (n=9). Publication bias for AM studies was not assessed as there were inadequate numbers of included trials to properly assess a funnel plot.

Figure 3. Funnel plot for smoking cessation intervention vs. control comparisons (between group variation)



DISCUSSION

Based on the synthesis of the evidence collected in our review, we conclude that distance-based SC interventions are effective in reducing tobacco use among cancer survivors. For AM, we found insufficient evidence that distance-based interventions are effective for cancer survivors. We also found evidence that single-behaviour focused SC interventions appear to be more effective than multiple-behaviour interventions based on within-group pre- versus post-intervention outcomes for SC. This difference between single- and multiple-behaviour interventions was not found in the meta-regression or between-group analyses, which are at lowest risk of bias. As we found no single-behaviour AM interventions, we could not assess a possible difference in effectiveness between single-behaviour and multiple-behaviour AM interventions.

The current findings match and extend the findings of earlier meta-analyses on SC interventions for cancer survivors [19, 20]. SC interventions are more effective than control interventions, although one review only found an effect for interventions around the peri-operative period [68]; this discrepancy might be explained by the inclusion of more recent studies in the current meta-analysis. We found no effect on AM, possibly due to the low number of reported AM studies for cancer survivors. Nonetheless, this review identified more studies on interventions targeting AM in cancer survivors than a previous review by Shingler [21], which only included three RCTs. Previous reviews on AM interventions in the general population have been based on single-behaviour interventions aimed solely at AM [22, 23], while our review only included multiple-behaviour interventions. This could also explain the lack of evidence regarding the effectiveness of distance-based AM interventions.

Our within-group findings, suggesting that multiple-behaviour interventions are less effective than single-behaviour focused interventions, are based on subgroup analyses of single and multi-behaviour interventions comparing before and after SC rates. The meta-regression on before and after SC rates pointed in the same direction, although it failed to reach significance (B=0.17, 95%CI -0.02-0.36, *p*=.08). Neither the subgroup analyses nor the meta-regression on between group differences showed a difference in effectiveness for single and multi-behaviour interventions. These findings match evidence from a Cochrane review on multidimensional rehabilitation programmes for cancer survivors [28]. Pollak (2018) [67] and Duffy (2006) [54] found a larger effect (RD=0.22, 95%CI -0.07-0.50 and RD=0.46, 95%CI 0.32-0.59, respectively) than the other multi-behaviour studies, but focused on a limited number of behavioural targets (SC and pain management or SC, AM and depression reduction), whereas the other multiple-behaviour interventions targeted lifestyle in a much broader sense.

A recent systematic review of alcohol interventions in older people based on individual patient-data reported marked control group effects [69] and might partly explain the differing results in within- and between-group analyses for single and multi-behaviour SC interventions. Three studies that included a face-to-face component [54, 65, 66] show the greatest effect in the within-group analyses but not in the between-group analyses (see Figure 2), where this effect might have been moderated by the control group, diminishing the contrast.

The current review used a robust search strategy and is reported according to PRISMA-guidelines. In order to optimally cover the available evidence on distance-based and scalable SC and AM interventions for cancer survivors, this review included studies on all cancer types, non-randomised studies (NR+CG and NR-CG) and multiple-behaviour studies with an AM or SC module. Results for RCTs are described separately when there were more than 2 RCTs to be pooled.

Study limitations

The current findings should be considered in light of the study limitations. The number of studies included in the meta-analyses was low, particularly for AM, and statistical heterogeneity in both SC and AM studies was relatively high. This heterogeneity can be due to several factors; heterogeneity in modes of delivery, effect sizes, follow-up periods and study designs. Use of RD's can also account for the very high heterogeneity in the within-group SC comparison, as these are absolute outcomes [45]. If included, control groups also varied considerably; several were handed printed information materials, while others were provided with active counselling and medication. In one study, control groups were waitlisted [26] and in another the control group condition was not further specified [66]. Bias could have been introduced as no information was available on correlation between pre- and post-intervention measures and therefore a conventional pre-post-test correlation of .70 was assumed. There was considerable loss of data in several studies due to non-response (Appendix 4), but applying the 'missing=smoking' procedure for appropriate studies (not including non-smokers at baseline) did not yield different

conclusions. Furthermore, for all outcome measures there were at least some concerns about the risk of bias. Subgroup analyses covering cancer site, mode of delivery or other potential moderators were not possible because of the low number of studies. Identified BCTs in the current systematic review (Appendix 2) are limited as intervention information was only extracted from published intervention descriptions.

Clinical implications

The current review demonstrated that distance-based SC interventions are more effective in encouraging SC than controls. SC interventions differed in number of sessions, theoretical and therapeutic underpinnings, and level of guidance, suggesting that a diverse set of interventions can be effective and that tailoring the intervention according to the patient's wishes or caregiver's possibilities could be a positive feature. Considering the demonstrated possible superior effect of single-behaviour over multiple-behaviour interventions for SC, there is opportunity for further developing distance-based single-behaviour AM interventions for cancer survivors. Direct comparisons between multiple-behaviour and single-behaviour interventions in randomized trials are needed to be conclusive. Future work should also focus on conducting and reporting SC and AM trials among cancer survivors according to CONSORT statement guidelines in order to limit risk of bias and further explore possible moderators.

Conclusions

Distance-based SC interventions can be effective in addressing SC in cancer survivors, although the amount and the quality of the evidence are suboptimal. Factors upon which effectiveness depends need to be further investigated. There are indications that single-behaviour focused SC interventions are more effective than multi-behaviour interventions. We did not find sufficient evidence to draw firm conclusions on the effectiveness of distance-based AM interventions. More high quality studies are needed.

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APPENDICES

Appendix 1

Search strategy PubMed

Date: 20 December 2017

Update: 08 November 2018

("smoking"[MeSH Terms] OR "smoking"[tiab] OR "tobacco use"[MeSH terms] OR "smoking cessation"[MeSH terms] OR "tobacco use cessation"[MeSH terms] OR "tobacco"[tiab] OR "cigarettes"[tiab] OR "alcohol"[tiab] OR "alcohol drinking"[tiab] OR "drinking behaviour"[tiab] OR "drinking behavior"[tiab] OR "alcohol misuse"[tiab] OR "alcohol use"[tiab] OR "alcohol drinking"[MeSH terms] OR "drinking behavior"[MeSH terms] OR "health behaviour"[tiab] OR "health behavior"[tiab] OR "health behavior"[MeSH Terms] OR health promot*[tiab] OR "health promotion"[MeSH terms])

AND

("intervention"[tiab] OR "self-help"[tiab] OR "web-based"[tiab] OR "online"[tiab] OR "telephone"[MeSH Terms] OR "Telemedicine"[MeSH Terms] OR "program"[tiab] OR "programme"[tiab] OR "internet"[tiab] OR "internet-based"[tiab] OR "ehealth"[tiab] OR "e-health" OR "mhealth"[tiab] OR "m-health"[tiab] OR "digital"[tiab] OR "digitalized"[tiab] OR "electronic mail"[tiab] OR "email"[tiab] OR "mobile app*"[tiab] OR "computer"[tiab] OR "web portal"[tiab] OR "web app"[tiab] OR "website"[tiab] OR "telephone"[tiab] OR "smartphone"[tiab] OR "mobile phone"[tiab] OR "print"[tiab] OR "print-based"[tiab] OR text-messag*[tiab])

AND

(((("neoplasms"[MeSH Terms] OR "neoplasms"[tiab] OR "cancer"[tiab]) AND ("survivors"[MeSH Terms] OR "survivors"[tiab] OR "survivor"[tiab])) OR "cancer survivors"[tiab] OR "cancer patients"[tiab])

Appendix 2

Table S2. Intervention Characteristics

Author & Year	Theoretical base	Number of sessions max, mean, range	Intervention description	Reported BCTs	Guidance (level of counsellor involvement)	Intervention target	Mode of Delivery
Amato et al, 2015[53, 70]	None specified (5A's)	max=8, median=2, mean=2.27	RPCI TACS: automated electronic health record-based tobacco assessment and cessation referral program to address the "5 As" [2]	1.1, 1.2, 4.2, 5.1, 5.3, 11.1	Guided multiple sessions	Smoking	Telephone
Berg et al, 2014[49]	Theory of Reasoned action	max=12 modules, 6 weeks, 91.7% completed ≥ 1 modules, mean adherence rate=77.8%	Web-based intervention delivered via e-mail, targeting health promoting behaviours among young adult cancer survivors and offering deals for healthy goods and services	2.2, 2.3, 5.1, 12.5	Unguided	General lifestyle and health related behaviours, incl. smoking and alcohol	Web-based
Duffy et al, 2006[54]	CBT	max=9-11, mean=9, range=0-31	Nurse-administered telephone-counselling and workbook on alcohol use, smoking and depression for head and neck cancer patients	1.1, 1.2, 2.3, 4.1, 4.2, 5.1, 11.1	Guided multiple sessions	Smoking, alcohol use and depression	Telephone, print, face-to-face component
Emmons et al, 2005[50]	Social Ecological Model, MI	range=0-6	PFH: Peer-delivered telephone counselling on smoking cessation tailored to stages of readiness to quit and based on motivational interviewing for childhood cancer survivors	1.1, 1.2, 2.2, 3.1, 5.1, 11.1	Guided multiple sessions	Smoking	Telephone, print
Emmons et al, 2013[25]	None specified	mean web visits = 3.25, 58% logged on ≥1 times	PFH-2: Web-based program based on PFH-1 counselling, see Emmons et al, 2005	1.1, 1.2, 2.2, 3.1, 5.1, 6.2, 11.1	Unguided	Smoking	Web-based
Fazzino et al, 2016[56]	Problem Solving Therapy	52 (6 months weekly, 12 months bi-weekly)	Group phone-based weight management intervention for breast cancer survivors in rural area's consisting out of a weight loss and a weight maintenance phase	1.1,1.2,1.3, 1.4, 2.2, 2.3, 2.4, 2.7, 3.1, 4.1, 8.1, 8.3, 8.6, 8.7, 12.1, 12.5	Guided multiple sessions	General lifestyle and health related behaviours incl. alcohol	Telephone

Author & Year	Theoretical base	Number of sessions max, mean, range	Intervention description	Reported BCTs	Guidance (level of counsellor involvement)	Intervention target	Mode of Delivery
Grimmett et al, 2015[58]	Self Regulation Theory	6 (12 weeks bi-weekly)	Researcher-administered telephone-based intervention on diet, physical activity and alcohol use for colorectal cancer survivors	1.1, 1.5, 2.2, 2.3, 3.1, 4.1, 5.1, 8.7	Guided multiple sessions	General lifestyle and health related behaviours incl. alcohol	Telephone, print
Hawkes et al, 2009[59]	Social Cognitive Theory	max=6	CanChange: 6-weekly health-coach administered telephone-based lifestyle intervention for colorectal cancer survivors, grounded in Social Cognitive Theory	1.1, 1.4, 1.6, 4.1, 5.1	Guided multiple sessions	General lifestyle and health related behaviours incl. smoking and alcohol	Telephone, print
Hawkes et al, 2013[60]	ACT, MI, Problem Solving Therapy	max=11	CanChange: 6-month health coach administered telephone-based lifestyle intervention for colorectal cancer survivors, based on ACT (differs from CanChange in Hawkes et al, 2009), including a pedometer	1.1, 1.2, 1.4, 1.5, 2.2, 2.3, 4.1, 5.1, 7.1, 11.2	Guided multiple sessions	General lifestyle and health related behaviours incl. smoking and alcohol	Telephone, print and pedometer
Kanera et al, 2016[26]	Social Cognitive Theory, Problem Solving Therapy	max=8, mean=2.23 modules	Cancer Aftercare Guide: web-based intervention on lifestyle and psychosocial challenges for cancer survivors	1.1,1.2,1.4, 2.3, 3.1, 5.1, 6.3, 7.1, 9.2	Unguided	General lifestyle and health related behaviours incl. smoking and alcohol (no outcomes for alcohol reported)	Web-based
Klesges et al, 2015a[63]	CBT	max=6, mean proactive=3.2, mean reactive=0.9	Proactive telephone-based cognitive behavioural smoking cessation intervention for childhood cancer survivors, including 4-week supply of nicotine patches or gum	1.1, 1.2, 1.4, 4.1, 8.7, 11.1, 12.3	Guided multiple sessions	Smoking	Telephone
Klesges et al, 2015b[64]	CBT	max=6 Proactive: ≥1=25.8%; all 6=10.6%, Reactive: ≥1 =82.8%; all 6 =0.7%	Proactive telephone-based cognitive behavioural smoking cessation intervention for adult onset cancer survivors, including 4-week supply of nicotine patches or gum	1.1, 1.2, 1.4, 4.1, 5.1, 8.7, 11.1, 12.3	Guided multiple sessions	Smoking	Telephone

Author & Year	Theoretical base	Number of sessions max, mean, range	Intervention description	Reported BCTs	Guidance (level of counsellor involvement)	Intervention target	Mode of Delivery
Ostroff et al, 2014[65]	MI	max=5, mean=4.1	Tobacco treatment specialist-administered counselling sessions, all but one (face-to-face) session delivered through telephone, and scheduled reduced smoking through handheld computer 'Quitpal' for newly diagnosed cancer survivors	1.2, 4.1, 5.1, 8.7, 11.1	Unguided	Smoking	Telephone, face-to-face component, and handheld computer
Park et al, 2011[66]	MI	max=7, mean=6	Tobacco Treatment Counselor-administered 12-week smoking cessation program based on 5 A's, including varenicline, for thoracic cancer patients	1.1, 1.4. 5.1, 5.6, 7.1, 11.1	Guided multiple sessions	Smoking	Telephone, face-to-face component
Pollak et al, 2018[67]	CBT, MI	max=4	Breathe intervention: a combined smoking cessation and pain management intervention administered by PhD interventionists through 4 weekly telephone sessions, a workbook, self-help quitting materials, and offering NRT	1.1, 11.1, 12.6	Guided multiple sessions	Smoking and pain management	Telephone, print

Note. For coding of Behaviour Change Techniques (BCTs) only published effect papers or mentioned intervention development papers were used. ACT=acceptance and commitment therapy; CBT=cognitive behavioural therapy; MI=Motivational Interviewing. BCTs: 1.1. Goal setting (behaviour) 1.2. Problem solving 1.3. Goal setting (outcome) 1.4. Action planning 1.5. Review behaviour goal(s) 1.6. Discrepancy between current behaviour and goal 2.2. Feedback on behaviour 2.3. Self-monitoring of Behaviour 2.4. Self-monitoring of outcome(s) of behaviour 2.7. Feedback on outcome(s) of behaviour 3.1. Social support (unspecified) 4.1. Instruction on how to perform the behaviour 4.2. Information about Antecedents 5.1. Information about health Consequences 5.3. Information about social and environmental consequences 5.6. Information about emotional consequences 6.2. Social comparison 6.3. Information about others' approval 7.1. Prompts/cues 8.1. behavioural practice/rehearsal 8.3. Habit formation 8.6. Generalisation of target behaviour 8.7. Graded tasks 9.2. Pros and cons 11.1. Pharmacological support 11.2. Reduce negative emotions 12.3. Avoidance/reducing exposure to cues for the behaviour 12.5. Adding objects to the environment.

Appendix 3

Table S3.1. Cochrane Risk of Bias tool 2.0 (RoB 2.0) for RCTs (detailed)

		1. Bias arising from the randomization process				2. Bias due to deviations from intended interventions					
Author year	**Outcome assessed for bias**	1.1 Was the allocation sequence random?	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	1.3 Were there baseline imbalances that suggest a problem with the randomization process?	RoB judgement	2.1 Were participants aware of their assigned intervention	2.2 Were carers and trial personnel aware of participants' assigned intervention	2.3 If Y/PY/NI to 2.1/2.2: deviations from intended intervention beyond expected	2.4 If Y/PY to 2.3: Were these deviations unbalanced between groups AND likely affect outcome?	2.5 If Y/PY to 2.3: Were any participants analysed in a group different from the one to which they were assigned?	2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact of analysing participants in the wrong group?
Duffy 2006	P-values at FU 6m: smoking=0.048, alcohol problem=0.853	NI	NI	PN	some concerns	NI	PY	NI	x	N	x
Emmons 2005	P-value at FU 8m: <0.0003	NI	NI	PN	some concerns	NI	PY	PN	x	N	x
Emmons 2013	P-value at FU 15m: .87 OR=1.07 (0.50-2.26)	PY	PY	PY	some concerns	PN	NI	PN	x	PN	x
Fazzino 2016	P-value at FU 18m: 0.80	NI	Y	NI	low risk	PN	PY	NI	x	PN	x
Hawkes 2013	P-value at FU 6m: .259	Y	Y	N	low risk	PN	NI	NI	x	PN	x
Kanera 2016	P-value at FU 6m: ITT: χ^2=1.18, p= .278, OR=2.61	Y	PY	PN	low risk	PY	PN	NI	x	PN	x
Klesges 2015a	P-value at FU 8w: point prevalence self p= <.001;	NI	NI	PN	some concerns	Y	PY	NI	x	PN	x
Klesges 2015b	P-value at FU 8w: point prevalence self p=.54	Y	Y	PN	low risk	Y	PY	NI	x	PN	x
Ostroff 2014	FU 3m: 7day PP self: OR=0.85 (0.42 – 1.72)	Y	PY	PN	low risk	NI	PY	NI	x	PN	x
Pollak 2018	FU 2m: 14% vs 6% smokers	PY	Y	NI	low risk	PY	PY	NI	x	PN	x

Note. FU = follow-up period, m = months, w = weeks, OR = odds-ratio, RoB = risk of bias, ITT = intention-to-treat analysis. Possible ratings: N = No, PN = Probably not, Y = Yes, PY = Probably yes, NI = No information. Possible risk of bias judgement: low, some concerns, high.

	3. Bias due to missing outcome data				4. Bias in measurement of the outcome			5. Bias in selection of the reported result			Overall Bias
RoB judgement	3.1 Were outcome data available for all, or nearly all, participants randomized?	3.2 If N/PN/NI to 3.1: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	3.3 If N/PN/NI to 3.1: Is there evidence that results were robust to the presence of missing outcome data?	RoB judgement	4.1 Were outcome assessors aware of the intervention received by study participants?	4.2 If Y/PY/NI to 4.1: Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	RoB judgement	5.1. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	5.2 ... multiple analyses of the data?	RoB judgement	
some concerns	N	PY	NI	low risk	NI	NI	some concerns	NI	NI	some concerns	some concerns
low risk	N	PN	Y	low risk	NI	NI	some concerns	NI	NI	some concerns	some concerns
low risk	N	Y	NI	low risk	NI	PN	low risk	PN	PY	high risk	high risk
some concerns	NI	NI	NI	some concerns	NI	PN	low risk	PY	NI	high risk	high risk
some concerns	N	Y	NI	low risk	NI	NI	some concerns	PN	PN	low risk	some concerns
some concerns	N	PN	Y	low risk	Y	PN	low Risk	PN	NI	some concerns	some concerns
some concerns	N	PN	NI	high risk	PY	NI	some concerns	NI	NI	some concerns	high risk
some concerns	N	PN	NI	high risk	PY	NI	some concerns	NI	NI	some concerns	high risk
some concerns	N	NI	PY	low risk	NI	PN	low risk	NI	NI	some concerns	some concerns
some concerns	N	N	NI	high risk	PY	PN	low risk	NI	NI	some concerns	high risk

Table S3.2. Risk Of Bias in Non-randomized Studies- of Interventions (ROBINS-I) for NR+CG studies (non-randomised with control group), summary

Author year	Outcome assessed for bias	1. Bias due to confounding	2. Bias in selection of participants in study	3.Bias due to classification of intervention	4. Bias due to deviation from intended intervention	5. Bias due to missing data	6. Bias due to measurement of outcomes	7. Bias due to selection of reported result Is the reported effect estimate likely to be selected, on the basis of the results, from...	Overall bias
Park 2011	p-value at FU 12w: OR 2.85 primary: p=0.18, OR=3.14 (95%CI 0.59 –16.62) secondary: p =0.09, OR=4.11 (95%CI 0.79–21.48)	Serious	Moderate	Low	NI	Low risk	Low risk	NI	Serious

Note. FU = follow-up period, w = weeks, RoB = risk of bias. Possible ratings: N = No, PN = Probably not, Y = Yes, PY = Probably yes, NI = No information. Possible risk of bias judgement: low, moderate, serious, critical.

Table S3.3. Quality assessment of before-and after studies without control group from the U.S. National Heart, Lung and Blood Institute for NR-CG studies (non-randomised without control group)

Author year	Outcome assessed for bias	1. Was the study question or objective clearly stated?	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/ interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Quality Rating (Good/Fair/Poor)
Amato 2015	2nd FU: current tobacco user= 78(58,2%), quitter=56(41,8%)	N	Y	Y	N	NR	N	N	N	N	N	N	NA	Poor
Berg 2014	p values at FU12w: days of drinking=.59, days of binge drinking=.86, days of smoking=.25	Y	Y	N	N	N	Y	Y	N	N	Y	N	NA	Poor
Grimmett 2015	FU 12w: Mean(SD)= 4(9.1)	Y	Y	Y	N	N	Y	N	N	N	N	N	NA	Poor

Author year	Outcome assessed for bias	1. Was the study question or objective clearly stated?	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/ interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Quality Rating (Good/Fair/Poor)
Hawkes 2009	FU 6w: smoking: current smoker=5%, previous smoker=50%, non-smoker=45%; alcohol: non-drinker=27.8%, high risk-drinker=16.7%, low-risk drinker=55.6%	Y	Y	Y	NR	N	Y	Y	N	Y	N	N	NA	Poor

Note. FU = follow-up period, w = weeks. Possible ratings: N = No, Y = Yes, NR = Not reported, NA = Non-applicable.

Appendix 4

Table S4.1. Outcomes for smoking cessation

Study	bl exp smoker %(n)	N bl exp non-smoker %(n)	N bl ctrl smoker %(n)	bl ctrl non-smoker %(n)	fu exp smoker %(n)	fu exp non-smoker %(n)	fu ctrl smoker %(n)	fu ctrl nonsmoker %(n)	exp missing %(n)	ctrl missing %(n)	follow-up	RCT[†]	single or multi-behaviour[‡]
Amato 2015	80 (200)	20 (50)	NA	NA	31 (78)	22 (56)	NA	NA	46 (116)	NA	2	0	S
Duffy 2006	80 (74)	20 (19)	68 (62)	32 (29)	28 (26)	55 (51)	34 (31)	51 (46)	17 (16)	15 (14)	6	1	M
Emmons 2005	100 (398)	0 (0)	100 (398)	0 (0)	57 (228)	17 (67)	70 (280)	9 (34)	26 (103)	21 (84)	8	1	S
Emmons 2013	100 (230)	0 (0)	100 (144)	0 (0)	79 (181)	10 (22)	74 (106)	14 (20)	12 (27)	13 (18)	15	1	S
Hawkes 2009	5 (1)	95 (19)	NA	NA	5 (1)	95 (19)	NA	NA	0 (0)	NA	1.5	0	M
Hawkes 2013	4 (8)	96 (197)	4 (9)	96 (196)	2 (4)	81 (167)	4 (9)	82 (167)	17 (34)	14 (29)	6	1	M
Kanera 2016	12 (27)	87 (204)	14 (32)	86 (199)	8 (18)	69 (158)	12 (28)	77 (179)	24 (55)	10 (24)	6	1	M
Klesges 2015a	100 (260)	0 (0)	100 (259)	0 (0)	54 (141)	27 (70)	71 (185)	15 (38)	19 (49)	14 (36)	2	1	S
Klesges 2015b	100 (214)	0 (0)	100 (213)	0 (0)	59 (126)	23 (49)	58 (123)	19 (40)	18 (39)	23 (50)	2	1	S
Ostroff 2014	100 (96)	0 (0)	100 (89)	0 (0)	43 (41)	39 (37)	44 (39)	34 (30)	19 (18)	22 (20)	3	1	S
Park 2011	100 (32)	0 (0)	100 (17)	0 (0)	38 (12)	44 (14)	65 (11)	18 (3)	19 (6)	18 (3)	3	0	S
Pollak 2018	100 (14)	0 (0)	100 (16)	0 (0)	50 (7)	14 (2)	81 (13)	6 (1)	36 (5)	13 (2)	2	1	M

Note. [†] 0=non-randomised study, i.e. non-randomised with control group or non-randomised without control group, 1=randomised controlled trial; [‡] M=multi-behaviour focused intervention, S=single-behaviour focused intervention; bl = baseline; fu = follow-up; follow-up = follow-up period in months; exp = intervention condition; ctrl = control condition; NA=not applicable. Percentages may not total 100 due to rounding.

Table S4.2. Outcomes for smoking cessation in Berg et al (2014)

Study	Measure	bl exp mean	bl ctrl mean	fu exp mean	fu ctrl mean	bl exp sd	bl ctrl sd	fu exp sd	fu ctrl sd	bl exp n	bl ctrl n	fu exp n	fu ctrl n	follow-up
Berg 2014	days of smoking	2.55	NA	1.32	NA	8.11	NA	5.74	NA	24	NA	19	NA	3

Note. bl = baseline; fu = follow-up; follow-up = follow-up period in months; exp = intervention condition; ctrl = control condition, NA=not applicable.

Table S4.3. Outcomes for alcohol moderation

Study	Measure	bl exp mean	bl ctrl mean	fu exp mean	fu ctrl mean	bl exp sd	bl ctrl sd	fu exp sd	fu ctrl sd	bl exp n	bl ctrl n	fu exp n	fu ctrl n	follow-up
Berg 2014	days of drinking	5.00	NA	5.42	NA	5.92	NA	7.24	NA	24	NA	19	NA	3
Fazzino 2016	mean g p day	17.0	20.5	3.52	5.1	13.5	20.9	7.9	10.7	17	20	17	20	18
Grimmet 2015	units p week	7	NA	4	NA	10.8	NA	9.1	NA	22	NA	22	NA	3
Hawkes 2013	mean g p day	4.6	6.2	3.6	4.9	10.6	13.8	11.76	10.61	205	205	171	176	6

Note. bl = baseline; fu = follow-up; follow-up = follow-up period in months; exp = intervention condition; ctrl = control condition; g = gram, NA=not applicable.

Table S4.4. Outcomes for alcohol moderation in Duffy et al. (2006) and Hawkes et al. (2009)

Study	bl exp nonimpr	bl exp impr	bl ctrl nonimpr	bl ctrl impr	fu exp nonimpr	fu exp impr	fu ctrl nonimpr	fu ctrl impr	exp missing	ctrl missing	follow-up
Duffy 2006	25	0	27	0	17	8	19	8	0	0	6
Hawkes 2009[†]	2	18	NA	NA	4	16	NA	NA	0	NA	1.5

Note. [†] For Hawkes (2009) high risk drinkers were considered non-improved, and low and no-risk drinkers were considered improved; bl = baseline; fu = follow-up; follow-up = follow-up period in months; exp = intervention condition; ctrl = control condition; g = gram; impr = improvement, NA=not applicable.

CHAPTER 3

Engagement with motivational interviewing and cognitive behavioural therapy components of a digital alcohol intervention, elicitation of change and sustain talk, and its impact on drinking outcomes:

Secondary data analysis

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ABSTRACT

Background

Down Your Drink (DYD) is a widely used unguided digital alcohol moderation program for the general public based on cognitive behavioral therapy (CBT) and motivational interviewing (MI); it provides users with many opportunities to enter free-text responses. The aim of this study was to assess participants' use of key CBT and MI components, the presence of change talk and sustain talk within their responses, and whether these data are associated with drinking outcomes after 3 months.

Methods

An exploratory secondary data analysis was conducted on data collected in 2008 from the definitive randomized trial of DYD (N=503). Past week alcohol use at baseline and 3-month follow-up were measured with the TOT-AL. Covariates included baseline alcohol use, age, gender, education level, and word count of the responses. Use of MI and CBT components and presence of change talk and sustain talk were coded by two independent coders (Cohen κ range 0.91-1). Linear model regressions on the subsample of active users (n=410) are presented along with a negative binomial regression.

Results

The most commonly used component was the listing of pros and cons of drinking. The number of listed high-risk situations was associated with lower alcohol use at 3-month follow-up (B_{adj} −2.15, 95% CI −3.92 to −0.38, *P*=.02). Findings on the effects of the percentage of change talk and the number of listed strategies to deal with high-risk situations were inconsistent.

Conclusions

An unguided digital alcohol moderation program can elicit change talk and sustain talk. This secondary analysis suggests that the number of listed high-risk situations can predict alcohol use at 3-month follow-up. Other components show inconsistent findings and should be studied further.

INTRODUCTION

Interventions aimed at reducing risky alcohol use are diverse and vary in many ways, including their mode of delivery (eg, in-person, bibliotherapy, digital), theoretical approach, and length (ranging from ultrabrief to extended interventions). This variation is also reflected in digital alcohol interventions [1]. Ultrabrief digital alcohol interventions are usually limited to self-monitoring exercises and personalized feedback (eg, decisional balance feedback [2]). Brief interventions can consist of self-monitoring exercises combined with personalized feedback and additional modules such as identification of high-risk situations, which help reduce alcohol use in specific situations (eg, the digital personalized feedback program Drinktest [3]). On the other hand, extended interventions offer a digital form of intensive treatment, including multiple sessions (eg, the self-help alcohol intervention Balance [4]).

Several systematic reviews have shown that digital alcohol interventions can be effective at reducing alcohol use in adult populations, finding small and moderate effect sizes [5–7]. Moderators of effectiveness have been studied and include length of intervention [1], level of guidance, setting, and integrated therapeutic principles [5]. Multiple studies have examined ways to increase engagement with alcohol and other health behavior interventions. Although these studies have conceptualized engagement in different ways, such as the received dose, adherence, degree of involvement over a longer period of time, or process of linked behaviors [8], engagement is mostly linked to frequency and length of use or to the use of specific components. However, few studies have examined users' engagement with specific components of digital alcohol interventions in detail [1].

Furthermore, although many alcohol interventions are partly based on motivational interviewing (MI) [1], few studies have explored the presence of change talk and sustain talk, which are important components of this "collaborative, goal-oriented style of communication with particular attention to the language of change, designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion [9]." Change talk can be defined as language referring to movement toward change of a target behavior, including verbalizations of consideration, motivation, or commitment to change. Sustain talk is language referring to movement toward sustaining the target behavior and the status quo. In a meta-analysis from 2018 on MI processes, including 21 studies on alcohol use that mostly involved face-to-face treatment, it was found that a higher proportion of change talk was associated with reductions in risk behaviors [10]. One recent study looked at the presence of change talk and sustain talk in a digital intervention; however, the intervention targeted physical activity, not alcohol use [11]. To the best of our knowledge, no study has explored the presence of change talk and sustain talk in a digital alcohol intervention.

The Down Your Drink (DYD) website is a digital alcohol intervention aimed at the general population [12]. DYD has some distinct features. First, it is targeted at opportunistic electronic help (e-help)–seekers who are not enrolled in an alcohol treatment pathway and who differ from dependent help seekers [13]. Another important feature of DYD is that it is one of the first digital extended alcohol interventions based on MI techniques and cognitive behavioral therapy (CBT). Other examples are digital self-help alcohol interventions from the Netherlands [14] and Norway [4]. DYD attempted to translate components of usual face-to-face treatment to a digital, unguided setting and encourages self-monitoring of drinking behavior in the Drinking Episode Diary. Lastly, it offers many opportunities for free-text responses, which provides an opportunity to study the way digital alcohol interventions are understood and used.

The original trial reported descriptive data on engagement with DYD, namely number of logins and number of pages viewed [15]. However, user data, that is, actual responses provided by participants to MI questions designed to strengthen personal motivation for and commitment to a specific goal, were not analyzed. Understanding how DYD was used and whether it encouraged people to think about changing their drinking is imperative to optimize future digital alcohol programs. With this secondary analysis, we aim to answer the following research questions:

1. Does DYD elicit change talk and sustain talk?
2. Are the MI and CBT components of DYD used actively (ie, users responded to questions related to the component at least once)?
3. Do user responses indicating change talk and sustain talk and ii) users making use of the separate MI and CBT components have an impact on change in alcohol consumption (intervention effectiveness)?

METHODS

Design

This paper reports on an exploratory secondary data analysis conducted on data from the definitive randomized trial of DYD (see the next section for further details). Ethical approval for the secondary analyses conducted in this study was granted by the University College London (UCL**)** Research Ethics Committee ("Engagement with internet-based alcohol moderation intervention 'Down Your Drink'" project ID: 3770/002).

DYD Trial

Data used for this study were collected during the definitive DYD trial from October 2007 to May 2009. This two-arm randomized controlled trial aimed to assess the effectiveness of DYD in reducing alcohol consumption and alcohol-related harm at 3- and 12-month follow-up. People aged 18 years or older who had internet access, scored 5 or more on the Alcohol

Use Disorders Identification Test-Consumption (AUDIT-C), understood written English, and were willing to complete follow-up questionnaires could participate. A total of 2652 adults with scores of 5 or higher on the AUDIT-C were included [16]. During the pilot and main trial extension phases, another 5238 participants were included. The primary outcome measure of alcohol consumption in the past week was collected using the TOT-AL [17]. The entire study was conducted on the internet. A more extensive description of the main trial procedures can be found in Murray et al [18] and Wallace et al [15].

Participants

For this study, we included the DYD trial participants who were randomized to the intervention group in 2008 (the only full calendar year of inclusion during the main trial) and who reported their alcohol use at 3-month follow-up. This ensured that participants who enrolled at various time periods during the year were all included. The sample provided a sufficient yet manageable number of participants for the analysis. In 2008, a total of 2543 participants were randomized; of those, 1271 were randomized to the intervention group. After removing participants who withdrew consent during the course of the study (n=41) and those who had not reported their alcohol use at 3-month follow-up (n=727), the final sample consisted of 503 participants. In addition to this full sample, we independently analyzed the active use sample, a subsample of 410 participants who actively engaged with the program at least once, defined as those who responded to at least one of the questions within the DYD program.

Intervention

DYD is a digital alcohol intervention that is primarily based on two evidence-based approaches that are widely used in the psychological treatment of alcohol misuse, namely MI and CBT; the latter is a goal-oriented therapeutic approach that systematically addresses dysfunctional emotions, behaviors, and thought processes. For example, CBT includes components urging participants to set a goal, recognize high-risk situations, and articulate their attitudes concerning (moderating) their drinking behavior. Self-monitoring of drinking behavior (eg, amount, type, setting, cost) is facilitated in the Drinking Episode Diary. The Alcohol Units Counter is another self-monitoring exercise; however, it does not keep track of changes in drinking over time. DYD delivers the MI approach by presenting a series of questions prompting free-text responses. The effectiveness of MI depends on how people respond to the questions, that is, whether their responses suggest that they wish to reduce their drinking (ie, change talk) or not (ie, sustain talk). For a more extensive description of the intervention, see [12].

Measures

Measures from the DYD trial included in the current analyses are past week self-reported alcohol consumption in UK units (ie, 1 unit=8 grams of ethanol) at baseline and 3-month follow-up measured using the TOT-AL (total past week alcohol consumption)[17], age (continuous

variable), gender (male/female), and education level (university degree or equivalent/A Levels or equivalent)/GCSE or equivalent/other qualifications/no qualifications). Ethnicity and relationship status were used to describe the sample but were not included as covariates in the model. This study included measures on the use of DYD components, which will be described further in the Qualitative Analysis section. To assess the effects of change talk and sustain talk, the percentage of change talk (change talk frequency over the sum of change talk frequency plus the sustain talk frequency) was included as recommended [19]. Lastly, the total number of words entered into the program was computed for each participant.

Qualitative Analysis

The coding scheme (see Appendix 1) included the main MI components and CBT components, and it was informed by the Client Language EAsy Rating (CLEAR) coding system [19] and items from the Revised Cognitive Therapy Scale (CTS-R) [20]. CLEAR is a coding system that can be used to assess change talk and counter change talk (ie, sustain talk) in a participant's responses. It was originally developed for in-therapy client language. MI components that were coded for included the presence of change talk, the presence of sustain talk, listing of the pros and cons of drinking alcohol, and noting of values (what is most important and meaningful to oneself). For each of these components, participants were assigned either a 1 (present) or a 0 (not present) depending on their responses. Furthermore, we coded the number of times the following were uttered: change talk, sustain talk, and pros and cons of drinking. Note that the frequency of change talk included the uttered cons of drinking and all other change talk present in response to the other questions as evaluated using CLEAR. The frequency of sustain talk included the number of mentioned pros of drinking and all other sustain talk present in response to other questions within the program.

The CTS-R is a scale for measuring therapist competence in cognitive therapy; it lists several key components of cognitive therapy, which helped us identify the main CBT components. We coded the following CBT components: setting a start date for alcohol moderation, setting a goal for alcohol moderation, completing another part of the moderation plan (eg, noting someone who might help), noting alcohol use prior to DYD, noting high-risk situations for alcohol use (eg, places, people, emotions), noting strategies to deal with high-risk situations, exploring feelings of craving, exploring relapse prevention (eg, thinking back to circumstances around a previous relapse), making a relapse plan (eg, stating who to call in case of a lapse), exploring thoughts (about drinking), monitoring alcohol use (ie, type, frequency, and amount of drinking). For all these codes, participants were assigned either a 1 (present) or a 0 (not present) depending on their responses. Furthermore, we coded the number of times the following were mentioned: high-risk situations and strategies to handle high-risk situations.

The coding was completed by two coders (AM and AP); SL was consulted on any discrepancies. Each coder coded 50% of the sample independently, and 51 (10.1%) of the sample were coded by both. Interrater reliability was high for both the dichotomous variables, as addressed with

Cohen's kappa (range 0.91-1, mean 0.97), and the continuous variables, as addressed with intra-class correlation (range 0.90 – 0.99, mean 0.97). Continuous variables included the number of times the following were present: change talk, sustain talk, pros, cons, high-risk situations, and ways to handle high-risk situations.

Quantitative Analysis

Descriptive statistics for each DYD use variable were computed to assess the presence of change talk and sustain talk within the responses and the use of CBT and MI components. All analyses described in this study are exploratory, as they were not preregistered. Multiple hierarchical regression models and analyses were used to assess the predictive value of the different components as well as of the change talk and sustain talk on alcohol use reduction at 3-month follow-up. In accordance with CLEAR guidelines, change talk and sustain talk were entered into the model as percentage change talk [19]. In the first step, a linear model was generated containing the baseline drinking level and the following covariates: number of words entered in all responses by the participant, age, gender, and education level. This model was then compared to a linear model containing all the variables of interest to assess the added explained variance of the full model. The distribution of the alcohol consumption outcome was highly skewed; therefore, two sensitivity analyses were conducted. The first sensitivity analysis used a linear model in which the alcohol consumption variables were log-transformed (after adding 1 unit per week). In the second sensitivity analysis, a negative binomial regression was performed, as the log transformation of drinking outcomes did not result in perfectly normally distributed data. A negative binomial regression as recommended by Atkins et al [21] was used to model the alcohol count data. Model estimates are presented for data from the subset of users who engaged with the program at least once (ie, the active use sample). All analyses were conducted in R version 3.5.1 (R Project) [22].

RESULTS

Sample Characteristics

The majority of the sample was female (308/503, 61.2%) and aged 18 to 73 years (median 41, mean 40, SD 11.24) with a predominant ethnicity of White British (419/503, 83.3%). Within the total sample, 93 participants had registered accounts but did not engage with any of the interactive elements of the digital program, creating a subgroup (410/503, 81.5%) who responded to at least one question. Baseline alcohol consumption in the past 7 days was 54 units on average (median 45.4, range 0-322.1, SD 37.6) in the total sample, and 55.5 units (median 47.8, range 0-322.1, SD 36.0) in the active use sample. Past week alcohol consumption at 3-month follow-up was 37.2 units on average (median 30.6, range 0-284.6, SD 31.2) in the total sample and 37.4 units (median 30.2, range 0-284.6, SD 31.4) in the subsample. The characteristics of both the total sample and the active use sample are displayed in Table 1; there were no notable differences.

Table 1. Demographic characteristics of the participant sample

Baseline characteristic	Full sample (N=503), n(%)[a]	Active use sample[b] (n=410), n(%)[a]
Age (years)		
18-34	165 (32.9)	125 (30.6)
35-44	150 (29.9)	121 (29.6)
45-54	138 (27.5)	123 (30.1)
55-73	49 (9.8)	40 (9.8)
Not specified	1 (0.2)	1 (0.2)
Gender		
Female	308 (61.2)	258 (62.8)
Education level		
University degree or equivalent	289 (57.4)	245 (59.6)
A Levels or equivalent	88 (17.5)	68 (16.5)
GCSE or equivalent[c]	73 (14.5)	56 (13.6)
Other qualifications	39 (7.8)	32 (7.8)
No qualifications	14 (2.8)	10 (2.4)
Relationship status		
Married/long term relationship	316 (62.8)	258 (62.8)
Unmarried/divorced	187 (37.2)	152 (37.1)
Ethnicity		
White British	419 (83.3)	344 (83.9)
White other	46 (9.1)	36 (8.8)
White Irish	25 (5.0)	17 (4.1)
Mixed	4 (0.8)	4 (1.0)
Asian/Asian British	3 (0.6)	3 (0.7)
Black African/Black Caribbean/Black British	2 (0.4)	2 (0.5)
Other	4 (0.8)	4 (1.0)

Note. [a] Due to rounding, percentages may not total 100.
[b] Subsample of participants who responded to at least one question in the Down Your Drink digital alcohol intervention.
[c] GCSE: General Certificate of Secondary Education.

Table 2. Use of motivational interviewing and cognitive behavioral therapy components by participants in the Down Your Drink digital alcohol intervention

Component	Active use sample (n=410)				Users who engaged in component at least once[a]	
	n (%)	Mean (SD)	Median	Range	Mean (SD)	Median
MI[b] components (n=352, 85.9%)						
Change talk[c]	341 (83.2)	10.3 (10.02)	8	0-90	12.3 (9.79)	9
Sustain talk[c]	329 (80.2)	3.3 (2.43)	3	0-13	4.1 (2.00)	4
Percentage change talk[d]	N/A[e]	61.5% (N/A)	70%	0%-100%	72.5% (N/A)	73.7%
Any listed pros or cons	337 (82.2)	N/A	N/A	N/A	N/A	N/A
Pros[c]	334 (81.5)	2.9 (1.98)	3	0-12	3.6 (1.49)	4
Cons[c]	327 (79.8)	6.8 (4.87)	7	0-24	8.4 (3.99)	7
What is important	311 (75.9)	N/A	N/A	N/A	N/A	N/A
CBT[f] components (n=288, 70.2%)						
Setting start date	132 (32.2)	N/A	N/A	N/A	N/A	N/A
Setting a drinking goal	129 (31.5)	N/A	N/A	N/A	N/A	N/A
Completing another part of moderation plan	136 (33.2)	N/A	N/A	N/A	N/A	N/A
Noting alcohol use before DYD	251 (61.1)	N/A	N/A	N/A	N/A	N/A
Noting high-risk situations[c]	113 (27.6)	1.1 (3.04)	0	0-21	4.1 (4.60)	2
Noting strategies[c]	103 (25.1)	2.7 (7.11)	0	0-48	10.9 (10.67)	7
Exploring cravings	16 (3.9)	N/A	N/A	N/A	N/A	N/A
Exploring relapse prevention	24 (5.9)	N/A	N/A	N/A	N/A	N/A
Making a relapse plan	9 (2.2)	N/A	N/A	N/A	N/A	N/A
Exploring thoughts about drinking	49 (12.0)	N/A	N/A	N/A	N/A	N/A
Monitoring drinking[c]	141 (34.4)	12.0 (47.30)	0	0-654	34.8 (75.73)	9

Note. [a] Responses by subset of participants who entered at least one response to a question corresponding with the component (eg, for high-risk situations, a subset of 113 participants entered at least one high-risk situation).
[b] MI: motivational interviewing.
[c] Mean and median refer to the number of statements corresponding to the component.
[d] Mean, median, and range are presented for percentage change talk.
[e] N/A: not applicable.
[f] CBT: cognitive behavioral therapy.

Change talk and sustain talk

On average, participants entered almost three times the number of segments classified as change talk (mean 12.3, SD 9.79) than as sustain talk (mean 4.1, SD 2.00) (see Table 2). The percentage of change talk was 61.5% on average (median 70%, range 0% to 100%). The majority of participants had entered at least one segment that was classified as change talk (341/410, 83.2%). Change talk encompassed the mention of benefits of quitting/moderating drinking, mention of disadvantages of current drinking behavior, recognition of problematic drinking behavior or needing help, and explicating the intent to change drinking behavior. Noting other people's desire for the participant to quit drinking was not classified as change talk. Examples:

I want to be in control of everything I do instead of putting things off because I want to drink alcohol.

I need help to stop drinking.

I know I am drinking too much and this number of units does not surprise me.

Sustain talk encompassed naming benefits of current drinking behavior, mentioning perceived disadvantages or fears about quitting/moderating drinking, and expressing a lack of self-confidence in changing current drinking behavior. Examples:

I feel positive about life and make plans when I have been drinking.

I look forward to drinking.

[…] But fear [losing] the good side of alcohol and how it makes me feel.

Don't feel confident to change.

I have no will power.

Use of MI and CBT components

Descriptive information on the use of the MI and CBT components is shown in Table 2. Listing the pros or cons of drinking was the component actively engaged with by the most participants (337/410, 82.2%). The components engaged with by the fewest participants were exploring cravings (16/410, 3.9%), exploring relapse prevention (24/410, 5.9%), and making a relapse plan (9/410, 2.2%).

MI components

Participants responded to questions about the pros and cons of drinking by listing their own perceived pros and cons of drinking. Pros often referred to the experience of alcohol drinking as enjoyable; they also stated that it aided their relaxation and confidence in social situations.

Examples:

It makes me more confident and talkative.

It takes the edge off things.

I enjoy the taste.

Cons of drinking most often centered on worries about alcohol drinking affecting the participants' health condition, lowered mood after alcohol drinking, and worries about drinking removing inhibitions, which sometimes led to regrettable behavior. Other cons focused on more practical issues, such as the cost of drinking. Examples:

It's bloody expensive!

Feeling low and depressed the next day and having no motivation

Concerns about health effects

Out of control

Say/do things I regret

A specific part of the DYD program encouraged participants to think about what is most important to them. The responses differed; most participants gave to-the-point answers, whereas others elaborated extensively on the role alcohol played in their lives. Examples:

Good health, friends, my family.

The most important things in my life are my children.

My job and how drinking affect that

My children! […] I want to be a good role model for them and never make them feel worried about me when they are older. I want to be able to have just one drink and not feel as though I can't stop. I'd like to enjoy alcohol socially without feeling ashamed of myself the next day. I want to lose weight, feel good about myself every day and be as healthy as possible for my children and future grandchildren. […]

CBT components

Some CBT components were rarely engaged with (eg, making a relapse plan and exploring cravings); however, those that were used showed a large variation in responses, with some participants adding large amounts of detail to their responses and others noting only keywords. Most responses were related to alcohol drinking, but not all; for example, in the "goal setting" component, some participants related a broader life goal instead of a specific drinking goal. Examples of goal setting nonspecific to drinking are:

To repay my debts and be good at my job

To keep friends with people, to make new friends and to be respected

Lose weight, be better Mum, get pregnant

Drinking goals also varied in their specificity. Some participants set a clear maximum number of drinks, and others stated a general goal of drinking less. Examples:

To reduce my drinking and the habits that surround it.

To put a stop to the binge drinking sessions

Limit myself to 2 large glasses in the evening and have x2 alcohol free nights

Stated high-risk situations varied from negative feelings to times of day, social situations, and events. Peer pressure was also frequently mentioned. Responses showed an overall good comprehension of the questions, although some answers were unspecific. Examples:

Anger, loneliness, despair

Boredom in the evenings

Going on holiday at New Year will also be a time of temptation

Seeing friends. Alcohol just makes the conversation flow easier. This is probably the hardest situation.

Getting another [because] everyone else is

Social situation

Strategies to cope with high-risk situations could either be selected from a list or noted in free-text responses. Free-text responses were generally unspecific, aimed at distraction or avoidance, and did not account for any difficulties that might arise from the coping strategies. However, some responses seemed to have incorporated strategies that were suggested in the DYD program. Examples:

Don't buy it

Read or watch a film

Doing activities

Drinking slowly and make glass last longer

Use of DYD and Drinking Outcomes

Model estimates are presented for data from the subset of users who engaged with the program at least once, namely the active use sample (n=410). Lower alcohol use at 3 months, when controlled for age, gender, education level, alcohol use at baseline, and number of words, was associated with a greater percentage of change talk (B_{adj} −0.17, 95% CI −0.32 to −0.02, *P*=.03) and a higher number of listed high-risk situations (B_{adj} −2.15, 95% CI −3.92 to −0.38, *P*=.02). In the unadjusted models, listing any high-risk situations (B_{unadj} −8.31, 95% CI −14.88 to −1.74, *P* =.01) and the number of listed strategies to deal with high-risk situations (B_{unadj} −8.31, 95% CI −14.88 to −1.74, *P*=.01) also showed significant associations with alcohol use at 3-month follow-up but not when adjusted for all other components (adjusted R^2 0.38). The complete results are shown in Table 3.

Table 3. Linear model estimates for the subsample of active users (n=410)

Model and variable	Unadjusted[a]			Adjusted[b]		
	B	95% CI	*P* value	B	95% CI	*P* value
Null model[c]						
Covariates						
Baseline alcohol use	N/A[d]	N/A	N/A	0.54	0.47 to 0.62	<.001[e]
Gender (male)	N/A	N/A	N/A	−6.01	−11.45 to −0.56	.03[e]
Education (A level)	N/A	N/A	N/A	4.25	−2.75 to 11.24	.23
Education (O level)	N/A	N/A	N/A	4.52	−2.94 to 11.99	.23
Education (other)	N/A	N/A	N/A	2.22	−7.34 to 11.79	.65
Education (no qualification)	N/A	N/A	N/A	−4.70	−20.70 to 11.30	.56
Age	N/A	N/A	N/A	0.27	0.03 to 0.51	.03[e]
Number of words	N/A	N/A	N/A	0.00	−0.01 to 0.02	.53
Full model[f]						
MI[g] components						
Percentage change talk	−0.11	−0.20 to −0.01	.02[e]	−0.17	−0.32 to −0.02	.03[e]
Any pros or cons listed	−1.17	−8.02 to 5.68	.74	0.34	−13.07 to 13.76	.96
Number of pros	1.31	−0.05 to 2.67	.06	1.60	−0.46 to 3.67	.13
Number of cons	−0.17	−0.83 to 0.50	.62	−0.14	−1.16 to 0.88	.78
What is important	−0.36	−6.64 to 5.91	.91	5.52	−4.23 to 15.27	.27
CBT[h] components						
Setting a start date	−1.41	−7.59 to 4.78	.65	17.50	−4.81 to 39.82	.12
Setting a drinking goal	−2.15	−8.39 to 4.09	.50	2.88	−16.05 to 21.81	.77
Completing another part of the moderation plan	−3.22	−9.38 to 2.94	.30	−13.32	−36.97 to 10.34	.27
Noting alcohol use before DYD[i]	−4.40	−9.83 to 1.03	.11	−5.00	−11.53 to 1.53	.13
High-risk situations	−8.31	−14.88 to −1.74	.01[e]	−11.86	−24.22 to 0.49	.06
Number of high-risk situations	−1.82	−3.12 to −0.52	.01[e]	−2.15	−3.92 to −0.38	.02[e]
Any strategies	−1.21	−8.22 to 5.80	.73	5.51	−5.08 to 16.58	.30
Number of strategies	0.01	−0.47 to 0.49	.01[e]	0.64	−0.09 to 1.37	.09
Exploring cravings	2.90	−11.19 to 16.98	.69	3.71	−11.74 to 19.17	.64

Model and variable	Unadjusted[a]			Adjusted[b]		
	B	95% CI	*P* value	B	95% CI	*P* value
Exploring relapse prevention	−1.65	−14.71 to 11.41	.80	−0.24	−15.42 to 14.95	.98
Making a relapse plan	3.52	−14.92 to 21.97	.71	5.05	−15.03 to 25.13	.62
Exploring thoughts about drinking	−0.41	−9.16 to 8.34	.93	−4.00	−15.09 to 7.09	.48
Any monitoring of drinking	2.66	−3.00 to 8.32	.36	1.77	−4.38 to 7.93	.57
Number of times drinking was monitored	0.00	−0.05 to 0.06	.87	−0.01	−0.07 to 0.04	.62

Note. [a] Unadjusted coefficients are based on a series of models in which alcohol use at 3-month follow-up is regressed based on baseline alcohol use, covariates, and each single intervention component.
[b] Adjusted coefficients are based on a model in which alcohol use at 3-month follow-up is regressed based on baseline alcohol use, covariates, and all intervention components.
[c] For the null model only containing the covariates, the adjusted R^2 value is 0.36.
[d] N/A: not applicable.
[e] P value <.05.
[f] For the full model, the adjusted R^2 value is 0.38.
[g] MI: motivational interviewing.
[h] CBT: cognitive behavioral therapy.
[i] DYD: Down Your Drink.

Sensitivity Analyses

When comparing the estimates from the linear model without log transformation (Table 3) with the model estimates including log transformations of alcohol use variables (adjusted R^2 0.20, see Appendix 2), and the model estimates resulting from a negative binomial regression (McFadden R^2 0.31, see Appendix 3), a higher number of listed high-risk situations predicted lower alcohol use at 3-month follow-up in both the model with log-transformation (B_{adj} −0.10, 95% CI −0.16 to −0.04, *P*=.001) and the negative binomial model (B_{adj} −0.07, 95% CI −0.12 to −0.03, *P*=.001). However, a higher number of listed strategies also predicted higher alcohol use at 3-month follow-up in both the log-transformed model (B_{adj} 0.04, 95% CI 0.01 to 0.06, *P*=.002) and the negative binomial model (B_{adj} 0.03, 95% CI 0.01 to 0.05, *P*=.01). No evidence was found in either of the sensitivity analyses for the effect of the percentage of change talk (log-transformed: B_{adj} 0.00, 95% CI −0.01 to 0.00, *P*=.07; negative binomial: B_{adj} 0.00, 95% CI −0.01 to 0.00, *P*=.22). The findings for these latter two components are therefore inconsistent. For all other components, none of the models showed an effect.

DISCUSSION

Principal Findings

Participants were found to actively use both the MI and CBT components of the DYD website, with MI components used by more participants. The CBT components pertaining to relapse prevention and exploration of cravings were rarely used by participants. Change talk and sustain talk were elicited by the most participants (341/410, 83.2%, and 329/410, 80.2%, respectively); generally, more instances of change talk (median 8) than sustain talk (median 3) were reported, although the between-person variance was large (SD 10.02 and 2.43, respectively). One explanation for the more frequent use of MI components than of CBT components is that the former are presented at the beginning of the program. Participants were free to choose how to move through the program; however, the ordering may still have contributed to the more frequent use of the MI components. A significant finding was that a higher number of listed high-risk situations robustly predicted a greater reduction in alcohol use at 3-month follow-up (P=.02).

Analyses were repeated with log-transformed measures of alcohol use at baseline and 3-month follow-up and by applying negative binomial regression. All the models showed an effect of the number of listed high-risk situations; however, there were also some inconsistent findings. There were differences between the models in the effects of the percentage of change talk and the number of listed strategies to deal with high-risk situations. The number of strategies to deal with high-risk situations predicted higher alcohol use in the log-transformed and negative binomial models but not in the linear model without log transformation. The percentage of change talk was only found to have an effect on reduction of alcohol use in the linear model without log transformation. All other components showed null findings.

The lack of effects of the percentage of change talk found in the sensitivity models may be due to a lack of evidence rather than the absence of a true effect. A meta-analysis by Magill [10] summarized 58 MI process studies, including 21 on face-to-face alcohol interventions. A higher proportion of change talk was found to be related to the reduction of all risky behaviors, including reduction of alcohol use. It is noteworthy that the latest guidance on MI practice suggests removing the pros and cons decisional balance exercise [9], as it can have the undesired effect of encouraging sustain talk [23].

A higher number of noted strategies was associated with a slight increase in alcohol use at 3-month follow-up according to the sensitivity analyses. A possible reason for this seemingly paradoxical finding is that participants who are having more severe alcohol problems may work more extensively on the program. For this group, a digital alcohol intervention may offer insufficient support to actually reduce their alcohol use, thereby possibly leading to increased alcohol use. As only some of the participants were asked to fill in the complete AUDIT questionnaire in the original trial, this hypothesis could not be tested in this study.

However, a recent individual patient data meta-analysis (19 trials) revealed no difference in the effectiveness of internet interventions between binge drinkers and non–binge drinkers, nor any difference in effectiveness related to the amount of alcohol consumption at baseline (heavy drinkers vs nonheavy drinkers) [5].

Another component that is often considered an "active ingredient" of brief alcohol interventions is self-monitoring of alcohol use [24]. Self-monitoring (ie, entry of drinks into the Drinking Episodes Diary), was actively used at least once by only 141/410 (34.4%) of the active participants. Also, for participants who did use it, the amount of times they reported their drinking was very skewed: half of them reported their drinking a maximum of 9 times (mean 34.8, SD 75.73). Among DYD users, there was also a lack of active engagement with relapse prevention exercises and exercises on craving. Craving was previously found to be an important predictor of relapse [25].

Future research should focus on testing the roles of components of interest in encouraging alcohol reduction using a preregistered analysis plan while considering the influence of the ordering of components on their use and subsequent effects.

Strengths and Limitations

This study made use of a large sample of active users of a digital alcohol intervention program. These users were e-help–seekers who were not currently enrolled in a treatment pathway. Uniquely, in this study, we were able to analyze a large number of free-text responses, thus obtaining insight into how well the participants understood the questions and whether key MI and CBT components were actively used. The free-text responses also enabled the assessment of key MI mechanisms of change talk and sustain talk, which may influence drinking outcomes [26]. Whether the program encouraged change talk or softened sustain talk (counter change talk) over time could not be assessed in this study. The presence of these key MI mechanisms and the use of the separate components were assessed independently by two coders with high interrater reliability. Change talk and sustain talk were coded using the CLEAR coding system [19], which was developed for coding of in-therapy client language. To account for the amount of total activity within the program as a possible confounder, the total number of words was included as a covariate within the model. These analyses were exploratory and were not preregistered; several sensitivity analyses are therefore presented. It is possible that significance of the effects of some components may be detected when using a larger sample, as we included many parameters without any effects in the full model. The generalizability of the study is limited because the sample only consisted of participants whose alcohol use at 3-month follow-up was known; this complete case analysis limits the generalizability of the results to nonresponders. Furthermore, the DYD intervention was closely modeled on the face-to-face MI/CBT approach used in therapeutic settings, and it required engagement and reflection across many different exercises. DYD was only accessible on a computer (ie, not compatible

with smartphones, which were less prolific in 2007 when DYD was first launched). The current results are therefore only generalizable to similar extensive digital MI/CBT interventions. More recent digital interventions are responsive websites or apps, which tend to include a small number of "active" behavior change components that can be used easily and quickly, and are not intended to elicit change talk or sustain talk.

Conclusions

A digital alcohol intervention was able to elicit both change talk and sustain talk. A higher number of listed high-risk situations can predict lower alcohol use at 3-month follow-up. Other components show inconsistent findings and should be studied further using a preregistered analysis plan. This study points to components of the DYD website that may constitute effective internet alcohol moderation programs and thus complies with the high research priority of studying specific components of digital interventions.

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APPENDICES

Appendix 1

Coding scheme for responses within the Down Your Drink (DYD) programme

Code	Label	Coding criteria
CBT components		
CBT1	Has set a start date	Set a start date for working on drinking goal = 1 No response = 0
CBT2	Has set a goal	Answered a question about goal setting with a drinking goal, either specific or unspecific = 1 Answered to questions about goal setting with a goal, but not related to alcohol use or no response = 0
CBT3	Has completed another part of the moderation plan	Answered a question in the Making a Plan section other than goal setting or start date e.g. reviewing day, method, difficulties = 1 No response = 0
CBT4	Has noted alcohol use prior to starting DYD	Filled in how many units they drank before starting DYD programme = 1 No response = 0
CBT5	Has noted risky situations	Answered a question about potential risky situations that lead to drinking (more than intended) across multiple sections = 1 No response or not related to drinking = 0
CBT5.number		Number of listed risky situations for drinking (more than intended)
CBT6	Has noted strategies to deal with risky situations	Answered a question about dealing with risky situations across multiple sections = 1 Not responded to questions about dealing with risky situations with meaningful strategies = 0
CBT6.number		Frequency of listed strategies to deal with risky situations
CBT7	Has explored feelings of craving	Answered a question about cravings across multiple sections = 1 No response = 0
CBT8	Has explored relapse prevention	Answered a question about relapse prevention across multiple sections = 1 No response = 0

Code	Label	Coding criteria
CBT9	Has made a relapse plan	Answered a question about a relapse plan e.g. who to call = 1 No response = 0
CBT10	Has examined his/her thoughts about dirnking	Answered a question about his/her thoughts about drinking in 'The Scottish Social Attitudes Survey (2004)' or related sections = 1 No response = 0
CBT11	Has monitored units of drinking	Monitored alcohol use at least once in Drinking Episodes Diary = 1 No response in the Drinking Episodes Diary = 0
CBT11.number		Frequency of monitoring of drinking
MI components		
MI1	Presence of change talk	Presence of change talk in free text responses across all parts of the programme= 1 No presence of change talk = 0
MI1.number		Frequency of change talk statements
MI2	Presence of sustain talk	Presence of sustain talk in in free text responses across all parts of the programme = 1 No presence of sustain talk = 0
MI2.number		Frequency of sustain talk statements
MI3	Has noted pros and cons of drinking	Answered a question about pros and cons of drinking across multiple sections = 1 No response or not related to drinking= 0
MI3. pronumber		Number of listed pros of drinking
MI3. connumber		Number of listed cons of drinking
MI4	Has noted what is most important and meaningful to oneself	Answered a question about what really matters to them in their life = 1 No response = 0
General components		
G1	Has responded to any of the questions	Responded to at least one of the questions = 1 No response entered into the programme = 0

Engagement with the DYD programme corresponded to certain cognitive behavioural therapy (CBT) and motivational interviewing (MI) components which were coded in three ways. Firstly, they were coded in a binary fashion with presence (1) or no presence of response (0). Some components allowed for free text response in which each utterance/statement counted to provide frequencies. Lastly, change and sustain talk was recorded throughout responses using the CLEAR guidelines.

Coders ensured a clear connection to drinking was present in order to count it as change or sustain talk. Otherwise it was classified as neutral talk. We coded utterances, not number of unique risky situations or unique strategies to handle them etc. So repeatedly stating the same thing was also counted.

Example:
Utterance: “to drink less and be less dependent on it”

Coded:

- CBT2 (Set a goal) = 1
- MI1 (Presence of change talk) = 1
- MI1.number: counted as instance of change talk

Appendix 2

Table S2. Linear model estimates with log-transformed alcohol use variables at baseline (independent variable) and 3-month follow-up (dependent variable) for the active use sample (n=410)

Variables	Unadjusted[a]			Adjusted[b]		
	B	95%CI	*P* value	B	95%CI	*P* value
Covariates						
Baseline alcohol use	-	-	-	0.63	0.49 to 0.78	<.001
Gender (male)	-	-	-	−0.05	−0.23 to 0.13	.59
Education (A level)	-	-	-	0.14	−0.09 to 0.38	.24
Education (O level)	-	-	-	0.13	−0.13 to 0.38	.32
Education (other)	-	-	-	−0.07	−0.40 to 0.25	.65
Education (no qualification)	-	-	-	−0.28	−0.83 to 0.26	.30
Age	-	-	-	0.01	0.00 to 0.02	.04
Number of words	-	-	-	0.00	0.00 to 0.00	.63
MI components						
Percentage change talk	0.00	−0.01 to 0.00	.02[d]	0.00	−0.01 to 0.00	.07
Any pros or cons listed	−0.08	−0.31 to 0.15	.51	−0.08	−0.54 to 0.37	.72
Number of pros	0.04	0.00 to 0.09	.07	.06	−0.01 to 0.13	.09
Number of cons	−0.01	−0.03 to 0.02	.52	−0.01	−0.04 to 0.03	.69
What is important	−0.04	−0.25 to 0.18	.74	0.15	−0.18 to 0.48	.36
CBT components						
Setting start date	−0.07	−0.27 to 0.14	.54	0.35	−0.40 to 1.11	.36
Setting a drinking goal	−0.08	−0.30 to 0.13	.44	−0.03	−0.67 to 0.61	.93
Completing another part of moderation plan	−0.10	−0.30 to 0.11	.37	−0.14	−0.95 to 0.66	.73
Noting alcohol use before DYD	−0.11	−0.29 to 0.08	.26	−0.12	−0.34 to 0.10	.29
Any risky situations	−0.21	−0.44 to 0.01	.06	−0.12	−0.54 to 0.30	.59
Number of high-risk situations	−0.06	−0.11 to −0.02	.01[d]	−0.10	−0.16 −0.04	.001[d]
Any strategies	−0.13	−0.37 to 0.11	.29	−0.14	−0.51 to 0.22	0.44
Number of strategies	0.00	−0.01 to 0.02	.56	0.04	0.01 to 0.06	0.002[d]
Exploring cravings	−0.03	−0.50 to 0.45	.91	−0.07	−0.60 to 0.45	.79

Variables	Unadjusted[a]			Adjusted[b]		
	B	95%CI	*P* value	B	95%CI	*P* value
Exploring relapse prevention	0.07	−0.38 to 0.51	.76	0.31	−0.21 to 0.82	.24
Making a relapse plan	0.04	−0.59 to 0.67	.90	0.09	−0.59 to 0.77	.80
Exploring thoughts about drinking	−0.05	−0.34 to 0.25	.75	−0.25	−0.63 to 0.12	.19
Any monitoring of drinking	0.12	−0.07 to 0.31	.22	0.11	−0.09 to 0.32	.28
Number of times drinking was monitored	0.00	0.00 to 0.00	.99	0.00	0.00 to 0.00	.38

Note. Null model only containing covariates adjusted $R^2 = 0.17$, full model adjusted $R^2 = 0.20$.
[a] Unadjusted coefficients are based upon a series of models in which log-ransformed alcohol use at three months follow-up is regressed upon baseline log-ransformed alcohol use, covariates and each single intervention component.
[b] Adjusted coefficients are based upon a model in which log-transformed alcohol use at three months follow-up is regressed upon baseline log-transformed alcohol use, covariates and all intervention components.
[c] For interpretation of coefficients: exponentiated coefficients correspond with percentage increase of alcohol use after one unit increase of the independent variable. For interpretation of baseline alcohol use coefficient: every 10% increase in baseline alcohol use results in $(1.10)^B$ increase in alcohol use at three month follow-up.
[d] *P* value < .05.

Appendix 3

Table S3. Negative binomial model estimates for the active use sample (n=410)

Variables	Unadjusted[a]			Adjusted[b]		
	B	95%CI	*P* value	B	95%CI	*P* value
Covariates						
Baseline alcohol use	-	-	-	0.01	0.01 to 0.01	<.001[c]
Gender (male)	-	-	-	−0.08	−0.22 to 0.07	.29
Education (A level)	-	-	-	0.08	−0.11 to 0.27	.41
Education (O level)	-	-	-	0.12	−0.07 to 0.33	.22
Education (other)	-	-	-	−0.07	−0.32 to 0.19	.58
Education (no qualification)	-	-	-	−0.27	−0.68 to 0.18	.22
Age	-	-	-	0.00	0.00 to 0.01	.04[c]
Number of words	-	-	-	0.00	0.00 to 0.00	.41
MI components						
Percentage change talk	0.00	0.00 to 0.00	.16	0.00	−0.01 to 0.00	.22
Any pros or cons listed	−0.01	−0.20 to 0.17	.89	−0.10	−0.46 to 0.25	.58
Number of pros	0.03	0.00 to 0.07	.06	0.05	−0.01 to 0.11	.08
Number of cons	0.00	−0.02 to 0.02	.99	0.00	−0.03 to 0.03	.85
What is important	0.01	−0.16 to 0.18	.89	0.10	−0.17 to 0.36	.45
CBT components						
Setting start date	−0.08	−0.24 to 0.09	.36	0.37	−0.25 to 0.94	.22
Setting a drinking goal	−0.10	−0.27 to 0.07	.23	−0.07	−0.60 to 0.41	.77
Completing another part of moderation plan	−0.11	−0.27 to 0.06	.20	−0.23	−0.82 to 0.40	.47
Noting alcohol use before DYD	−0.06	−0.21 to 0.08	.41	−0.07	−0.24 to 0.10	.44
Any risky situations	−0.21	−0.38 to −0.03	.02[c]	−0.17	−0.51 to 0.15	.30
Number of high-risk situations	−0.05	−0.09 to −0.02	.002[c]	−0.08	−0.12 to −0.03	.001[c]
Any strategies	−0.08	−0.27 to 0.11	.40	0.03	−0.26 to 0.32	.83
Number of strategies	0.00	−0.01 to 0.01	.77	.03	0.01 to 0.05	<.001[c]
Exploring cravings	−0.16	−0.53 to 0.23	.40	−0.15	−0.55 to 0.27	.47
Exploring relapse prevention	−0.13	−0.48 to 0.24	.48	0.14	−0.28 to 0.57	.51

Variables	Unadjusted[a]			Adjusted[b]		
	B	95%CI	*P* value	B	95%CI	*P* value
Making a relapse plan	−0.02	−0.48 to 0.49	.94	0.08	−0.44 to 0.63	.78
Exploring thoughts about drinking	−0.08	−0.31 to 0.16	.51	−0.23	−0.53 to 0.08	.13
Any monitoring of drinking	0.07	−0.08 to 0.23	.34	0.10	−0.06 to 0.26	.23
Number of times drinking was monitored	0.00	0.00 to 0.00	.72	0.00	0.00 to 0.00	.24

Note. Null model only containing covariates McFaddens' R^2 = 0.26, full model McFaddens' R^2 = 0.31.
[a] Unadjusted coefficients are based upon a series of models in which alcohol use at three months follow-up is regressed upon baseline alcohol use, covariates and each single intervention component.
[b] Adjusted coefficients are based upon a model in which alcohol use at three months follow-p is regressed upon baseline alcohol use, covariates and all intervention components.
[c] *P*-value < .05.

CHAPTER 4

Cancer survivors' views on digital support for smoking cessation and alcohol moderation:
a survey and qualitative study

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ABSTRACT

Background

Digital interventions may provide low-threshold support for smoking cessation (SC) and alcohol moderation (AM) to the growing population of cancer survivors. The objective was to explore preconditions of successful AM and SC digital interventions for cancer survivors.

Methods

Using a multi-method approach we conducted a survey (n=240), a qualitative study consisting of four focus groups (n=15) and semi-structured interviews with Dutch cancer survivors (n=8). To help interpretation of our results we interviewed experts in the field of eHealth and cancer survivors (n=6) and we organized an expert meeting (n=7). Qualitative data were analysed using the Framework approach and were double-coded by two coders.

Results

Survey results show the majority of drinkers had not previously considered AM (n=158, 84.9%), often because they deemed their alcohol use to be non-problematic. All current smokers in the survey had considered SC before. In focus groups and interviews it became clear that SC efforts did not always stem from their own willingness to quit smoking, but originated from a wish to please their social environment. Main themes to be addressed in digital SC and AM that emerged from the interviews and focus groups, centred on the different ways of identification as cancer survivors, need for autonomy, differential beliefs about SC and AM, and the importance of a positive, non-patronizing tone-of-voice. Several specific preferences for digital interventions were formulated, although some cancer survivors prefer no support or face-to-face contact.

Conclusions

Cancer survivors are a diverse group with diverse preferences for AM and SC support. Digital AM and SC interventions for cancer survivors are perceived to be of value by some, especially when they incorporate a positive, non-judgemental and non-patronizing tone-of-voice, address concerns specifically relevant to cancer survivors, offer possibilities for personalization, and emphasize autonomy throughout. To encourage AM specifically, problem recognition and awareness of the health benefits of AM should be improved.

INTRODUCTION

Alcohol and tobacco use are among the main behavioural risk factors for cancer [1], but also important risk factors for second cancers and iatrogenic effects of cancer treatment [2, 3]. Yet, rates of smoking and alcohol use among cancer survivors are high. Cancer survivors are defined as people diagnosed with cancer at some point in their lives, irrespective of treatment phase. Currently, there seem to be few effective interventions for alcohol moderation (AM) and smoking cessation (SC) in cancer survivors [4, 5].

A recent meta-analysis of 21 SC interventions for cancer survivors found that SC interventions are not more effective than control groups (d = 0.030, 95%CI –0.042 to 0.101) [5]. A meta-analysis on distance-based SC and AM interventions (i.e., telephone, print or web-based) found distance-based SC interventions to be more effective than control group interventions (10 studies, OR = 1.56; 95% CI, 1.13-2.15, *P* = .007) [4], but found no evidence for the effectiveness of distance-based AM interventions in three studies, (SMD = 0.12; 95% CI, –0.08 to 0.31, *P* = .24).

Digital interventions might provide a low threshold for seeking help and reach a large population. They have shown their effectiveness in the general population [6, 7]. To inform the development of two digital interventions for SC and AM we sought to explore the factors contributing to the use of digital support by cancer survivors.

Several previous qualitative studies have described views of cancer survivors and healthcare professionals on smoking [8], SC [9], lifestyle behaviour change [10, 11] and online self-management (eg, [12]). Recurring themes are (the importance of) enjoying life, being open to discussion of SC with a healthcare professional, and scepticism of benefits of SC (after cancer). Only one study described bladder cancer survivors' experiences with alcohol cessation, in a peri-operative setting [13], and reported that cancer treatment can function as a teachable moment, an opportunity for positive lifestyle behaviour change, in that way possibly encouraging SC and AM. However, the return to daily life and accompanying shift of focus to day-to-day life increased the risk of relapse. One French study has described health professionals' views on AM and SC in head and neck cancer survivors [14]. To the best of our knowledge, no study yet has looked specifically into views on digital interventions for SC and AM for cancer survivors.

In this study, we aimed to explore the preconditions for successful digital alcohol and tobacco interventions for cancer survivors. These findings were collected and used to inform the development of digital interventions MyCourse – Quit Smoking and MyCourse – Moderate Drinking, both specifically designed for cancer survivors [15]. This study explored the following research questions:

1. What are cancer survivors' views on SC and AM?
2. What are cancer survivors' preferences regarding digital support for SC and AM?
3. What are experts' recommendations for successful digital AM and SC support for cancer survivors?

METHODS

Design

To answer our research questions, we employed a multi-method approach. We conducted a survey, focus groups and semi-structured interviews with Dutch cancer survivors. We started with a survey to assess preferences for (digital) support in SC and AM, the survey results subsequently informed the topics that were discussed further during the focus groups. The interviews provided more insight into (altered) interests and concerns after the cancer diagnosis and views on (digital) support. In addition, to better understand preconditions for successful digital SC and AM interventions for cancer survivors, we consulted experts in the field of lifestyle behaviour change, cancer survivorship, design and implementation of digital interventions, SC and AM. Experts were consulted in semi-structured interviews and during an expert meeting to discuss the main findings. The study was performed in accordance with the Consolidated criteria for reporting qualitative research (COREQ) guidelines.

Recruitment

Cancer survivors for the survey were recruited on the largest Dutch online cancer survivor platform; Kanker.nl. Adult members who- based on their account information- were diagnosed with cancer at some point in their lives, excluding those in palliative phase, and who had agreed to be contacted for participation in scientific studies, received an invitation to the online survey (n=635). Interviewed cancer survivors were a convenience sample recruited using social media and snowball sampling. They were either smokers, former smokers or currently using alcohol. Former smokers were invited because they could share their insights into what helped them quit smoking. Focus group participants were respondents of the survey, who had given consent to be contacted for future studies. They were invited via email and filled out a short questionnaire to indicate their availability. All respondents were contacted and the most suitable dates were selected. Interviewed experts were purposively sampled researchers with experience in development and implementation of digital support for cancer survivors (n=4) and healthcare professionals experienced in supporting SC and AM (n=2). For the expert meeting, we invited researchers with expertise in lifestyle behaviour change, AM and SC, eHealth development, and implementation (n=7).

Data collection

Survey

The survey was conducted during a period of two weeks in January 2016. Members of the cancer platform received an online invitation and a one-time online reminder. The online survey focused on alcohol and tobacco use, help-seeking for lifestyle behaviour change and preferences for digital support in cancer survivors. See Appendix 1 for survey questions. It contained both closed and open-ended questions. Alcohol use was assessed using the questions

"Do you (sometimes) drink alcohol or do you not drink alcohol at all?", "How often do you drink alcohol?" and "How much do you usually drink on a drinking day?", measured in standard units corresponding to 10 g of ethanol per unit. Tobacco use was assessed by the questions "Do you (sometimes) smoke or do you not smoke at all?" and "How many cigarettes do you smoke per day?". Online informed consent was provided before the start of the questionnaire. The survey lasted approximately 5 minutes. Survey respondents received no reimbursement for their participation.

Interviews

Semi-structured face-to-face interviews were conducted with 8 cancer survivors in April and May of 2016 during the development of the MyCourse interventions. The interviews focused on themes that arose from survey results and the first two focus groups. Specifically, they centred on (altered) interests and concerns after the cancer diagnosis, views on AM and SC and the use of technology in quitting smoking or moderating alcohol use. Written informed consent was obtained from the cancer survivors. Interviews lasted between 30 and 60 minutes and were conducted at the participants' home or other location of their choosing. Interviews were conducted in Dutch by a Masters student trained in qualitative research methods. Interviewees received no reimbursement for their participation. For a topic list see Appendix 2. All identifiable information was removed from the transcripts. No information on age or education level was collected from interviewees.

Focus groups

Two sets of two focus groups (one on alcohol, one on smoking) were held in March 2016 and again in June 2016; before and after a concept version of the digital MyCourse interventions was developed. The first two focus groups mainly discussed experiences with quitting smoking or moderating alcohol use and preferences for how to receive support while quitting/moderating use. The last two focus groups mainly discussed themes that should be addressed in the interventions, ways to target cancer survivors without stigmatizing them, preferred tone-of-voice of the texts of the interventions and they could provide feedback on concept versions of the interventions. Focus groups lasted approximately 2 hours including a short break. All focus groups were conducted at the Trimbos Institute, which is centrally located in The Netherlands and participants received a €30 gift card for their participation and reimbursement for their travel costs. At the start of each focus group a paper and pencil Timeline Follow Back (TLFB) questionnaire was filled out by the participants to assess participants' tobacco and alcohol use. TLFB is an assessment tool that obtains estimates of substance use in the past seven days [16]. Focus groups were conducted by a masters student and AMu. Written informed consent was obtained at the start of the focus group. For a topic list see Appendix 3.

Experts

We interviewed 6 experts in April and May 2016 and held a face-to-face expert meeting in May 2016 at the Trimbos Institute. Experts received no reimbursement. During the meeting, results from the survey and findings from the first round of focus groups and interviews were discussed. For a topic list see Appendix 4. All identifiable personal information was removed from the transcripts before the analysis.

Data Analyses

Quantitative analysis

Descriptive statistics are provided for the survey sample. Chi-square tests were used to assess any differences between male and female participants and different education levels, applying a conventional statistical significance level ($a \leq 0.05$). All survey responses were analysed with R version 3.5.1 [17].

Qualitative analysis

Interviews, focus groups and the expert meeting were all recorded and transcribed verbatim. The analysis of the transcripts was carried out according to the Framework method [18]. Authors AMu and DY both individually double coded all transcripts. In addition to these transcripts, responses to one open-ended question from the survey were thematically analysed: "How does a lifestyle intervention for cancer survivors differ from a lifestyle intervention for the general public?" After immersion with the transcripts, an inductive process of open coding was started. Each analysed transcript was discussed in periodic meetings between AMu and DY, and any discrepancies were resolved. Next, these codes were analysed and categorized into broader sub-themes, again using an inductive approach. Afterwards, transcripts were compared to the coding schemes and sub-themes, to ensure robustness of the analysis process and to confirm that all data were reflected in the coding. The main findings were summarised and clustered into larger themes. Authors BB and MB each read and compared two manuscripts to the themes and sub-themes and checked for any missing sub-themes or connections. Software program MaxQDA 18.2.3 was used for management of the transcripts and coding schemes [19]. All quotes provided in this article were translated from Dutch into English. To ensure anonymity any personal information was removed from quotes.

RESULTS

Quantitative analysis

Sample characteristics

The final survey sample consisted of 240 participants. Majority of the participants were female (n=151, 62.9%), had a high (n=117, 48.8%) or middle level education (n=79, 32.9%), and had been treated for cancer in the past, but were not currently receiving treatment (n=124, 51.7%). Mean age of the sample was 54.9 years (SD = 10.56, range = 20-77 years). Participants were diagnosed with a broad range of types of cancer, most often breast cancer (27.5%) and lymph node cancer or leukaemia (15.8%). See Table 1 for detailed sample characteristics. All but three participants reported having ever used the Internet to find information on health or health care (n=237, 98.8%).

Alcohol and tobacco use in survey sample

Most participants were former smokers (n=132, 55.0%). Current smokers (n=29, 12.1%) mostly smoked 1-10 cigarettes a day (n=13, 44.8%) and the majority of all smokers considered quitting smoking (n=23, 79.3%). A large majority of the participants drank alcohol at the time of the survey (n=186, 77.5%). They most often drank at least 2 times a week (n=99, 53.2%) with at least 3 standard drinks per drinking day (n=176, 94.6%) and most did not consider moderating or quitting their alcohol use (n=158, 84.9%). Most participants never drank more than 6 glasses a day (n=118, 63.4%), followed by those that did so less than once a month (n=49, 20.4%). A minority drank more than 6 glasses a day monthly (n=10, 5.3%), weekly (n=6, 2.5%) or (almost) daily (n=3, 1.3%). See Table 2 for alcohol and tobacco use outcomes. Tobacco use differed between age groups ($\chi^2 = 21.39$, $P < .01$); participants over 55 years old were more often former smokers, while those aged between 20 and 45 years old were more often never smokers. Drinking status differed between women and men ($\chi^2 = 9.38$, $P < .01$); women being more often never-drinkers than men, and men more often being current drinkers.

Table 1. Demographic characteristics of survey participant sample

Characteristics	Full sample (N=240), n (%[a])
Age (years)[c] (mean, SD)	54.91 (10.56)
Gender	
Female	151 (62.9%)
Education level	
High level education	117 (48.8%)
Middle level education	79 (32.9%)
Lower level education	38 (15.8%)
No qualifications	1 (0.4%)
Self-reported cancer status[b]	
I have cancer	83 (34.6%)
I am currently undergoing treatment for cancer	83 (34.6%)
I have been treated for cancer in the past, but not anymore	124 (51.7%)
Cancer type[c]	
Breast	66 (27.5%)
Lymphatic or leukaemia	38 (15.8%)
Bowel or colon	30 (12.5%)
Bladder or urinary tract	19 (7.9%)
Prostate	16 (6.7%)
Head and neck	16 (6.7%)
Rather not say	1 (0.4%)
Other[d]	68 (28.3%)

Note. High level education: bachelor's or master's degree. Middle education: four to six years of high school education or secondary vocational education. Lower education: three years of high school or less.
[a] Due to rounding and some missings, percentages may not add up to 100%.
[b] Some participants identified with multiple statuses.
[c] Some participants were diagnosed with multiple types of cancers.
[d] Other types include: stomach, multiple myeloma, skin, lung, pancreas, oesophagus, endometrial, ovary and more.

Table 2. Alcohol and tobacco use in survey participant sample

Variable	n (%[a]), N=240
Smoking status	
Current smoker	29 (12.1)
Former smoker	132 (55.0)
Never smoker	78 (32.5)
Number of cigarettes per day	
1-10	13 (44.8[b])
11-20	8 (27.6[b])
21 or more	4 (13.8[b])
0, I smoke incidentally	4 (13.8[b])
First cigarette, in minutes after waking up	
Within 5 minutes	3 (10.3[b])
6-30 minutes	13 (44.8[b])
31-60 minutes	7 (24.1[b])
More than 60 minutes	6 (20.7 [b])
Considering to quit smoking	
Yes	23 (79.3[b])
No	6 (20.7[b])
Drinking status	
Current drinker	186 (77.5)
Former drinker	29 (12.1)
Never drinker	24 (10.0)
Frequency of drinking	
Never	1 (0.5[c])
Once a month or less	31 (16.7[c])
2 to 4 times a month	55 (29.6[c])
2 to 3 times a week	51 (27.4[c])
4 or more times a week	48 (25.8[c])
Standard units on a drinking day[d]	
1 or 2	141 (75.8[c])
3 or 4	35 (18.8[c])
5 or 6	7 (3.8[c])
7 or more	3 (1.6[c])
Considering to quit or moderate drinking	
Yes	27 (14.5[c])
No	158 (84.9[c])

Note. [a] Due to rounding and missings, percentages may not add up to 100.
[b] Proportion of current smokers, total n = 29.
[c] Proportion of current drinkers, total n = 186.
[d] 1 standard unit = 10 g ethanol.

AM and SC in survey sample

Alcohol use was discussed during treatment with only 21.3% (n=51) of all participants and 19.4% (n=36) of current drinkers, tobacco use was discussed with 40.4% (n=97) of the total sample and 69.0% of current smokers (n=20). Discussion of alcohol use was not associated with drinking status ($\chi^2 = 5.11$, P = .08). Discussion of tobacco use was associated with smoking status ($\chi^2 = 22.5$, P < .01).

Of those participants drinking at the time of diagnosis (n=200, 83.3%), almost half had not tried to moderate their alcohol use before, during or after cancer treatment (n=85, 42.5%), those who did, mostly did so during treatment (n=70, 35%). A fourth of participants reported smoking at the time of their cancer diagnosis (n=59, 24.6%). Participants most often attempted to quit or moderate smoking before treatment started (n=26, 44.1%), followed by during treatment (n=17, 28.8%), and a minority attempted to quit after the treatment phase (n=11, 18.6%).

Reasons for quitting or moderating alcohol use were mostly related to health (n=57, 44.2%) and cancer treatment (eg, not being able to tolerate alcohol during treatment) (n=6, 4.7%). No one reported advice from a doctor as a reason for AM. Most often reported reasons for not quitting alcohol use were: one's alcohol use reportedly being limited and not deemed problematic (n=72, 38.7%), alcohol being enjoyed and enjoyment valued as important (n=31, 16.7%), and not seeing the benefits of quitting at this point (n=27, 14.5%). Remarkably, 6 participants reported that alcohol use benefited their health or that a doctor had encouraged them to keep drinking (moderately). Most frequently reported reason for trying to quit smoking was also related to health benefits (n=36, 66.7%). Current smokers most often reported having tried, but not being able to quit as a reason for not quitting (n=9, 31.0%). Two participants reported that they were told by a doctor that SC was unnecessary if they kept it at a few cigarettes a week or that SC would cause so much stress that it would be more detrimental to treatment.

Preferences for support

Current and former smokers and drinkers preferred different types of support (see Appendix 5). Nearly half of (former) drinkers and about a third of (former) smokers did not want any support (n=100, 46.5% and n=58, 36.0%, respectively). Most preferred options among those who wanted support were: online information, a printed information flyer, and face-to-face support. A free online self-management course was preferred most by current smokers (n=5, 17.2%) and least by former drinkers (n=1, 3.4%). Face-to-face support was preferred more for SC (14.3%) than for AM (n=14, 6.5%).

When asked about whom they would like to be supported by, many did not want support from anyone for AM (n=101, 47.0%) or SC (n=67, 41.6%). For both AM and SC, support from family (AM: n=25, 11.6%; SC: n=35, 21.7%) and a coach (AM: n=29, 13.5%; SC: n=33, 20.5%) was most preferred.

Qualitative analysis

Sample characteristics

Eight cancer survivors and six experts were interviewed. Cancer survivors were a convenience sample recruited using social media and snowball sampling. They were either smokers, former smokers or currently using alcohol. Interviewed experts were researchers with experience in development and implementation of digital support (eg for emotional well-being) for cancer survivors (n=4) and healthcare professionals experienced in supporting SC and AM (n=2).

Focus groups consisted of 6, 5, 3 and 6 participants respectively. Five participants attended two focus groups, before and after the development of a concept intervention, resulting in a sample of 15 unique focus group participants. The expert meeting (n=7) was attended by researchers from the Trimbos Institute with experience in developing digital lifestyle or depression prevention interventions.

All cancer survivor interviewees (n=8) and focus group participants (n=15) were adults diagnosed with cancer at some point in their lives. Majority of the interviewees and focus group participants were highly educated. Interviewees were diagnosed with a broad range of types of cancer, see Table 3 for more characteristics. Below, we present the main themes that were extracted from the interviews and focus groups.

Table 3. Demographic characteristics of cancer survivors in focus groups and interviews

Characteristics		Focus groups (N=15), n	Interviews (N=8), n
Gender			
	Female	5	5
Education level			
	High level education	11	-
	Middle education	3	-
	Lower education	1	-
Smoking status			
	current smoker	3	6
	non-smoker[a]	3	0
	former smoker	9	2
	missing	0	0

Characteristics		Focus groups (N=15), n	Interviews (N=8), n
Drinking status			
	current drinker	13	4
	currently non drinker	2	2
	missing	0	2
Type of cancer			
	breast	3	1
	melanoma	1	3
	prostate	3	0
	non-Hodgkin	3	0
	other[b]	5	4

Note. High level education: bachelor's or master's degree. Middle education: four to six years of high school education or secondary vocational education. Lower education: three years of high school or less.
[a] Unknown whether they are a former or never smoker.
[b] Other reported cancers were: cancer of the bladder, colon, oesophageal, stomach, lung, Hodgkin's lymphoma, and head and neck cancer.

Cancer survivors' perspectives on AM and SC

Identification as cancer survivors The time from cancer diagnosis to treatment and afterwards was described by almost everyone as impactful, although for each different aspects stood out; ranging from the shock of the diagnosis, severity of the treatment phase and physical limitations, to worries about job security and the multitude of instructions on what (not) to do, for example what to eat. Often repeated is the newly developed lack of trust in the body, causing them to be vigilant at aches or pains.

> *"Having cancer has a great impact and affects many aspects of your life. Recognizing and understanding this is key in a lifestyle intervention." [survey participant P81, colon cancer survivor, female, current drinker]*

> *"You see, before that I could trust my body, sometimes I felt something, but I was convinced it would pass. But now whenever I feel something, I go: 'Oh no, you don't think it's…' It's a different type of life, really."[focus group participant FS2A, non-Hodgkin cancer survivor, male, current smoker]*

Notwithstanding this impact, many would not identify as 'cancer survivors', rather feeling better addressed by the terms: 'people who have had cancer' or 'people with cancer'. They would most like to move on from that part of their lives, only identifying as a cancer survivor when a doctor's appointment comes up:

"There are many periods that cancer is not on my mind at all. But then an appointment date for a control or scan comes up and slowly I start to become aware of it"[focus group participant FS1B, prostate cancer survivor, male, former smoker]

Furthermore, when asked about the differences between a lifestyle program for the general population and for cancer survivors, many responded surprised and stated there 'should be no difference'. Survey responses showed that this partly reflects a fear of stigmatization and that being labelled a cancer survivors is seen as something undesirable.

"You receive a stamp, the 'cancer-stamp', well you definitely don't want that." [interviewee C9, melanoma cancer survivor, female, former smoker, current drinker]

The reluctance to identify as cancer survivors combined with the view that SC and AM are important to all people, not just cancer survivors, translates into not actively seeking out programs specific to cancer survivors, but turning first towards general (health) programs. Websites specific to cancer survivors were feared to be too confronting and that they could also be at odds with the desire for a positive tone of voice, because of negative associations with cancer. However, cancer survivors were triggered when reading something about their specific type of cancer (eg, breast cancer or colon cancer). Possible benefits of an intervention aimed at cancer survivors were also mentioned: information on how AM and SC influence cancer, a safe space to discuss issues with peers (eg, smoking after lung cancer) or extra emotional support. The need for a cancer specific website seemed to depend on the time since diagnosis, a more recent diagnosis indicating a greater need:

"If I would use a program, I would use the one for the general population, because for me much time has passed since [the diagnosis]. […] the moment you get out of treatment or when you're in the middle of it, there is still so much going on. You're psychologically less stable, you experience many emotions, you have more physical complaints, apart from the withdrawal symptoms. […] So I do think in that case it should be combined." [focus group participant FA2B, Hodgkin cancer survivor, female, former smoker]

Differential beliefs about health consequences Beliefs about health consequences differ for alcohol and smoking. Participants are generally convinced of their knowledge of the harmful effects of smoking, including the increased cancer risk. Not only because of the available and known evidence, but because they have experienced the detrimental effects of smoking themselves in their coughing or deterioration of their physical condition. Some (former) smoking cancer survivors were convinced of the detrimental effects of smoking, but emphasized their disbelief that their specific type of cancer was caused by smoking.

Participants were far less aware of the harmful effects of alcohol use and its association with cancer. For example, each focus group on AM started with questions from the participants on the harmful effects of alcohol use, while no such questions were asked about smoking.

Specifically, it was unclear what amount of alcohol is detrimental, what influence alcohol has on cancer treatment and recurrence, and there was confusion about the benefits of alcohol on the cardio-vascular system, as communicated in previous years.

Differential beliefs about enjoyment and relaxation The importance of enjoying life and of relaxing was emphasized throughout all responses, interviews and focus groups, shaping views on alcohol use and smoking. Smoking was seen as a means to calm down, destress and relax. For some cancer survivors it was the only way they knew how to cope with negative emotions or feelings of stress and anxiety. Although alcohol was used to handle negative feelings as well, more often it was associated with enjoyment, having a good time and relaxation. It was seen as an important part of a lifestyle. A smoking cancer survivors explained the value smoking had for them:

> *"[when asked about smoking] This is my buddy and it's always there for me. To comfort me, or to keep me company, but it's always there for me." [interviewee C3, colon cancer survivor, female, current smoker]*

Willingness to quit These differential beliefs about smoking and alcohol use are reflected in the willingness to quit or moderate. Most former and current smokers in focus groups and in the survey, believed that all smokers would like to quit, but might be unable to or afraid. For example, one participant reported thinking about SC regularly, and she wanted to understand why, after her cancer diagnosis, she kept on smoking. However, interviewed smoking cancer survivors mostly reported not wanting to quit at all or showed ambivalence towards quitting, reporting that their wish was based on wanting to please others. They generally acknowledged and recognized their addiction. One interviewee stated after many quit attempts in the past:

> *"It doesn't bother me anymore and I don't feel the need to quit anymore. There are not that many fun things in my life anymore. […] It's a very useless motion, it's nothing, but to me it means a lot." [interviewee C3, colon cancer survivor, female, current smoker]*

Concerning alcohol use, only one participant reported trying to quit alcohol use and not succeeding, whereas for SC many failed attempts were reported. Generally, cancer survivors stated they would be able to quit their alcohol use easily if they were convinced of its detrimental effects. A doctor's advice was valued highly in this regard; a doctor's recommendation to quit drinking would make them consider moderation. Importantly, alcohol use was rarely addressed by healthcare professionals, in contrast to smoking, when cancer survivors would have expected and valued it. As only few participants were convinced of alcohol's detrimental effects, or saw it as less harmful than other detrimental behaviours, alcohol use was mostly viewed as an important aspect of their lifestyle that they did not consider changing:

> *"I'm still in the middle of this whole cancer story, so how amazing is it that in the evening I get to sit back, grab a piece of cheese and a glass of port [alcoholic beverage]. Why would I want to moderate that. On the other hand, I do think that you should do anything you can*

to keep your body and condition in shape. […] So I drink my glass of beer, but I also go to the gym. That's how I keep life a little fun. […]. [focus group participant FA2A, prostate cancer survivor, former smoker]

Autonomy is key A prominent theme was the need for autonomy; making one's own informed decisions and being as independent as possible. This need became evident in different ways. Healthcare professionals' lifestyle advice was valued highly, but should leave room for the patient's own decision on how to apply it to their personal circumstances: being able to set their own goals and pace, e.g. smoking less, even if they were not completely in line with current guidelines. Regarding peer support, cancer survivors would like to stay as independent as possible, not relying too heavily on others and not burdening them. The central role of autonomy became most clear when discussing motivations for behaviour change.

In many different wordings, the importance of something we have named 'intrinsic motivation' for AM and SC was stressed: "taking responsibility", "willpower", "coming from the inside out", "my own wish", "supporting your own decision". Participants made a distinction between undertaking AM and SC efforts to please others (eg, partner, family or doctor), or out of their own will to quit smoking or moderate their drinking. The first was related to failed quit attempts, whereas the second was seen as a prerequisite for AM and SC.

"It needs to come from within yourself, if you don't have the willpower, then it's never going to work."[focus group participant FA2C, eye melanoma cancer survivor, male, former smoker]

"I would grant it myself, but that moment might come and then it would need to come from within me. Or it might not." [interviewee C4, lung cancer survivor, current smoker]

It remained unclear how to achieve intrinsic motivation, but cancer survivors provided several insights. Experiencing short term benefits and seeing results of AM or SC increased intrinsic motivation. A crucial insight was that being convinced of the health benefits of AM and SC, although important, was not enough for intrinsic motivation, because bigger concerns might be at play (eg, ways to destress) or other things might be valued more (eg, enjoyment). Lastly, some kind of 'momentum' should be used; capitalizing on moments when someone is receptive of lifestyle behaviour change. Cancer survivors differed in opinion on whether intrinsic motivation is needed before engaging in digital programs and other types of support, or whether these support programs might help to increase intrinsic motivation in an ambivalent phase.

Extrinsic motivation is not without importance, as illustrated by the fact that for many participants advice by a healthcare professional influenced SC or AM efforts. Furthermore, seeing others' achievements could be motivating for some. But extrinsic motivation needed to be translated into an intrinsic will in order to have a real and lasting impact on behaviour change.

Too great of an emphasis on intrinsic motivation could hinder quit attempts. Relating in particular to SC, some participants strongly stated that "with the right mentality anyone can quit cold turkey", thus confirming the detrimental, but persistent belief that SC is only a matter of firmly deciding not to smoke which leads many to not seek SC support in their quit attempts.

Cancer survivors' preferences regarding digital AM and SC support

Tone of voice An important theme that arose is the clear and explicit need for a positive, non-condemning and non-patronizing tone of voice. Positivity in the sense that there should be emphasis on complimenting accomplishments, rather than on criticizing what went wrong, emphasis on what is to be gained from AM or SC, rather than listing diseases with increased risk, and emphasis on what cancer survivors can do (better), rather than what they are limited in.

> *"For me, it's the approach. 'Oh you managed to only have one [cigarette].' Very much focused on your success, on your strength and not on judgement. Judgement is catastrophic for me, I will only smoke more." [interviewee C4, lung cancer survivor, female, current smoker]*

Some cancer survivors who use tobacco or alcohol had to deal with judgemental reactions from their social networks, as if they "had brought it on themselves". This could result in feelings of guilt: *"I start a small fight with myself and think: 'well there you go again, you're smoking again.' You're judging yourself, but then I also think: 'well it's really very nice.' " (interviewee, breast cancer survivor, female, current smoker and drinker).* Therefore a non-condemning tone-of-voice is important. A difference was perceived in societal reactions to alcohol use and smoking. Alcohol use after cancer was seen as more acceptable, whereas smoking cancer survivors often felt directly judged when smoking. On the other hand, dependency on alcohol was seen as more severe than an addiction to cigarettes, which was considered more 'normal'.

Concerning AM, participants did not want to be labelled as alcoholics or alcohol misusers, as they did not identify with those labels, but simply as people who wanted to moderate their alcohol use. Content should emphasize that cancer survivors can make their own decisions. A conversational tone of voice (e.g., asking about the nature of one's alcohol use) was preferred over only presenting alcohol's adverse effects, which was considered patronizing. The tone-of-voice was perceived as an important barrier for receiving information about or engaging in AM or SC interventions, as illustrated by a participant looking for information online:

> *"There was this website, saying that it's my fault that I got cancer. […] I read about oesophageal cancer and the combination of alcohol and smoking, and I don't know what else they dragged into it. Then I looked up some other cancer types that are not related to it, and well, then that means the whole world is living wrongly. I messaged them: 'I am a cancer patient and you are saying that it's my fault that I have cancer, and I object to that.'" [focus group participant FA1A, oesophageal cancer survivor, male, non-smoker]*

Specific intervention components Preferences for specific intervention components were discussed of which we highlight the most notable ones in Table 4, showing that cancer survivors are a diverse group resulting in differing preferences.

Table 4. Preferences concerning specific intervention components and considerations for implementation

Component	Preferences	Implementation considerations
Monitoring of alcohol or tobacco use	It is experienced as offering insight into drinking and smoking patterns. However, for some it could be too confronting, especially when goals of moderation or cessation are not met, leading people to not report drinking or smoking truthfully.	This emphasizes the need for an accepting, non-judgemental tone-of-voice throughout the program.
Peer support	Some take great support from it and emphasize benefits such as a better understanding of the cancer experience and the possibility to talk in a light-hearted way about the cancer experience. Whereas others had experienced that forums often contain negative experiences or unverified information, invoking negative emotions and worries.	Cancer survivors suggest to incorporate peer support in a non-prominent way, offering cancer survivors the choice to either engage with it or not and include monitoring of the platform to prevent the spread of false information.
Involvement of own social network (family and friends)	A clear preference for a supportive role instead of a correcting role: preference for compliments for SC or AM efforts and implicit support such as not offering cigarettes or alcohol, but not repeatedly asking whether someone had smoked or how many drinks they had had.	The social network does not always know how to best support cancer survivors or SC and AM efforts. At the same time, cancer survivors can be hesitant to let people help, recognizing the impact of the cancer experience on their family and friends.
Moment of addressing AM or SC	Some would like AM and SC addressed at the start of treatment because then they see its potential benefits, but others would only be receptive to it after finishing the treatment phase, as they have too many things on their mind during treatment.	Flexibility in moment of addressing SC or AM.
Digital delivery mode	Essential to a digital program would be the protection of personal data, not fearing that anyone but the patients themselves could get hold of their data. It should be easy to use, on both smartphones and tablets, and it should be inviting during the most difficult moments of AM and SC.	Guidance, regular updates and interactive content could help motivate use of the intervention.

Note. SC = smoking cessation, AM = alcohol moderation.

Focus group participants were all comfortable using the Internet, but some interviewees reported rarely using the Internet, or not using it for information on cancer and health because it distresses them. This last group preferred face-to-face contact over completely digital support. Cancer survivors who were comfortable using the Internet were concerned about the self-discipline and willpower that they believed digital programs require. Guidance from a healthcare professional, researcher or peers could motivate continued program use. Those who were interested in a digital program, reasoned that they "would grant themselves a try" or see it as "a stepping stone". Other perceived benefits were the flexibility to use a digital program at any place and time, and that digital programs do not require extra hospital visits.

Experts' recommendations for successful AM and SC interventions for cancer survivors

A major concern from experts was drop-out and shorter than intended use of a digital intervention. Experts recommended to clearly communicate what benefit is to be realistically expected from a digital intervention, possibly in person at the start of the intervention. Patients who have severe alcohol or tobacco dependence should be alerted to the fact that a digital intervention might offer insufficient support and they should be referred to additional support.

Experts also emphasize the importance of autonomy and intrinsic motivation. A personal and tailored approach could help achieve this motivation. To engage with digital interventions, greater levels of motivation and self-discipline were believed to be necessary:

> *"We see a lot of working people, I feel like they appreciate getting to choose when they want to engage with treatment. On the other hand, the downside is that people really need self-discipline to use the program regularly." [interviewee E2, eHealth developer and healthcare professional]*

Interventions aimed at cancer survivors should take into account pronounced fatigue and mood problems, emphasize the benefits of AM and SC for treatment and recovery, and address different coping mechanisms to deal with increased anxiety. For AM specifically, problem recognition is an issue. Most people do not identify with the general image of problematic alcohol use, even if their alcohol use is well above recommended guidelines. Healthcare professionals are in a unique position to relate health outcomes or symptoms to smoking or alcohol use, thereby increasing awareness of their health consequences and create intrinsic motivation to change drinking behaviour:

> *"And then I say: 'Your palpitations and stress might be related to the way you are handling it [by drinking].' And that's when he said: 'Yes, I should handle it differently and play more tennis with someone." [interviewee E4, healthcare professional]*

Concerning AM in particular, it should be taken into account that realizing the extent of their alcohol problems can be uncomfortable for a patient due to the stigma surrounding alcohol misuse and alcohol dependency.

Experts also mentioned referral to the digital interventions by healthcare professionals as an important implementation route, because their advice is valued by cancer survivors. For healthcare professionals, it is a benefit to be able to offer tangible digital interventions as an extra tool while addressing AM or SC. However, one healthcare professional reported that the vast amount of available SC and AM apps and uncertainty about which would work (best) for the patient was a barrier for referral.

DISCUSSION

We aimed to explore cancer survivors' views on AM and SC, their preferences regarding digital support for AM and SC, and experts' recommendations for successful AM and SC interventions for cancer survivors. This information was used to inform the development of SC and AM digital interventions [15], considering that digital interventions may provide a low threshold for seeking help and reach a large population and that they have shown their effectiveness in the general population [6, 7]. Our findings are also largely in line with findings from previous qualitative studies on health behaviour change and SC. Only limited findings were available on AM in cancer survivors. In the section below several behavioural models and theories provide a framework to understand and integrate our key findings.

What are cancer survivors' views on SC and AM?

Views on AM differed from views on SC in several ways: awareness of the health consequences was higher for smoking than for alcohol drinking, smokers more often considered quitting smoking, and for AM more low-intensity support was preferred. Enjoyment and relaxation were associated with both smoking and drinking and provided a barrier for AM and SC. Intrinsic motivation was deemed essential for successful quit attempts.

Majority of current smoking cancer survivors in the survey considered quitting, while most current drinkers did not consider moderation. This lack of interest in AM might be driven by low recognition of problematic alcohol use, alcohol use being more socially acceptable and the lack of awareness of the health benefits of AM or the association between alcohol and cancer. The way these different normative beliefs can influence the attitude towards AM or SC is predicted by the Theory of Planned Behaviour, which describes six constructs that influence intentions for behaviour change: behavioural beliefs, attitude toward the behaviour, normative beliefs, subjective norm, control beliefs and perceived behavioural control [20]. Furthermore, SC was perceived as difficult (perceived behavioural control) and seemed to lead to decreased SC efforts, despite statements of their awareness of health benefits of SC. For AM, most participants believed they could easily moderate alcohol use if they wanted to. The preference for low-intensity AM support as found in this study, could reflect both confidence in being able to moderate (perceived behavioural control) and the low problem recognition of problematic alcohol use (attitude). Cognitive Behavioural Therapy could help participants understand the

associations between cognitions (beliefs, attitudes) and smoking or drinking behaviour, and it could influence perceived behavioural control by teaching skills to cope with feelings and situations that make SC or AM difficult [21].

Heightened awareness of their health can make cancer survivors more receptive to health messages of AM and SC [22] [11]. But in some, the increased valuation of enjoying life following their cancer diagnosis can make them reluctant to moderate alcohol use or quit smoking. Smoking was also previously found to be a source of enjoyment and way of psychological coping that is highly valued [8, 10]. Still others did not see the benefit of quitting or moderating after cancer. This lack of motivation for SC or positive health behaviour change was noted earlier as well [8, 10]. Increased feelings of stress or anxiety can also contribute to the reluctance to quit smoking, because smoking has been a way of coping with negative feelings. Motivational Interviewing could help participants identify and solve ambivalence towards SC or AM [23].

What are cancer survivors' preferences regarding digital support for SC and AM?

There was great variety in cancer survivors and their experiences, and this was reflected in different practical preferences for digital AM and SC support (see Table 4) as well as different views on interventions specifically for cancer survivors. However, all participants shared the need for a positive, non-judgemental tone-of-voice that emphasized autonomy, possibilities for personalization and emphasis on short-term benefits. Face-to-face support should be available to those not interested in digital programs, for example because they are not comfortable using the Internet for health-related topics.

Not all cancer survivors would feel addressed by an intervention aimed solely at cancer survivors and might prefer an intervention for the general population, for fear of stigmatization or because of the desire to move on from the cancer diagnosis. Tailoring to this population therefore has to be done subtly, for instance by not presenting AM or SC programs as a program only for cancer survivors, but using targeted implementation strategies to reach cancer survivors. MyCourse was developed for cancer survivors specifically, to make it easier for the target population to find the intervention and as the need for a cancer-specific website may be greater around the time of diagnosis. Cancer survivors preferred information on short-term benefits of AM and SC (in contrast to long term prevention of disease), as these directly influence their daily life and are thus perceived more relevant. This is predicted by the elaboration likelihood model which postulates that presentation of highly relevant information will encourage behaviour change (Petty & Cacioppo, 1986).

Our study showed that pivotal throughout all communication about AM and SC is recognizing and emphasizing the autonomy of the cancer survivor; one way to do so is by adopting a non-patronizing, non-condemning, positive tone-of-voice. Healthy lifestyle recommendations

should be presented as advice and there should be explicit room for people to choose in what way to adhere to these guidelines (eg, leaving it to the client to decide on drinking pattern goals, and not only offer the choice to either quit or reduce to national drinking guidelines). The importance of autonomy is in line with previous findings, where it is referred to as 'personal control' [9].

The importance of intrinsic motivation for SC and AM was repeatedly noted, and failed quit attempts for SC were related to wanting to please others instead of being intrinsically motivated. Breast cancer survivors meeting physical activity guidelines actually reported higher intrinsic motivation and greater perceived autonomy support [24]. Self-determination Theory (SDT) helps understand the recurring emphasis on autonomy; it postulates that autonomy is one of the basic psychological needs, next to competence and relatedness, whose satisfaction encourages development of intrinsic motivation [25]. The more intrinsic motivation for behaviour change is, the higher the likelihood to change and persist in the behaviour, according to the theory.

Cancer survivors in the current study did not know of ways to encourage intrinsic motivation, but several of their recommendations and preferences in reference to other topics were in line with what SDT refers to as an autonomously supportive context (or encouraging a sense of autonomy, relatedness and competence), which fosters development of human's natural tendency to intrinsic motivation: positive performance feedback, absence of controlling remarks from their social network, freedom to determine one's own goals (for AM or SC) and acknowledgement of their feelings (either in peer support groups or their social network). Acceptance and commitment therapy (ACT) could help encourage intrinsic motivation, as it focuses on participant's values that guide them to the desired behaviour of AM or SC [26].

What are experts' recommendations for successful digital AM and SC support for cancer survivors?

Experts emphasized raising awareness on alcohol-related harm and alcohol problem recognition, taking into account pronounced fatigue and mood problems, and the need for engagement of healthcare professionals. They expressed concern about drop-out. The lack of discussion of SC with healthcare professionals and simultaneously the willingness to address corroborates previous findings [8, 9]. It should be noted that this study showed that addressing SC and AM by healthcare professionals is lacking, especially for AM, but that it would be valued by cancer survivors.

Strengths and limitations

This study used a variety of inductive methods to assess perspectives on support for SC and AM in cancer survivors: a survey, focus groups and interviews among cancer survivors, a meeting and interviews with experts in the field of eHealth, AM, SC and cancer survivors. These methods all complemented each other. By including eHealth experts and not only healthcare

professionals, a perspective on the specific requirements for digital AM and SC interventions was provided. There was great variation in cancer types and treatment phases in participants. Limitations include that the recruitment of most participants took place through an online cancer patient platform. This selection might have influenced results on preferences for support, as participants probably enjoy spending time online and actively seek online information. Interviewed participants were, however, not all members of the online platform and at times provided a different point of view (e.g., more often reported lack of willingness for AM or SC than focus group participants). The difficulties in recruiting participants for the qualitative part of the study might point to the intricacies of addressing AM and SC in cancer survivors and possibly the lack of awareness around the importance of these topics. The survey results cannot be generalized to all Dutch cancer survivors, as the survey was not a representative sample (e.g., it included mostly higher educated participants and women). It is possible that in a survey sample consisting of more excessive drinkers, more respondents would consider alcohol moderation, than was found in the current sample.

Clinical implications

The differences between perspectives on AM and perspectives on SC found in this study have implications for public health messages and approaches to AM and SC by healthcare professionals. Care should be taken to explain the relationship between alcohol, health and cancer. For SC, it could be promising to address the fear of quitting and replacement of the cigarette as a means for relaxation and keeping busy. Emphasizing that there does not have to be a relation between smoking or alcohol and the cause of someone's cancer, and that AM and SC have other (short-term) benefits, could help avoid feelings of guilt. It is important to encourage healthcare professionals to address AM and SC with cancer survivors, and digital self-help interventions can be a useful tool to refer patients to.

Future research

Future research should study how healthcare professionals could be encouraged to routinely address AM and SC in cancer survivors. Because of the fear of stigma and great variety in cancer types, different ways should be explored to efficiently tailor interventions to appeal to cancer survivors without stigmatizing them. More research should be conducted into ways to (intrinsically) motivate cancer survivors who are currently unwilling or ambivalent towards AM or SC.

Conclusions

Our study findings shed light on how cancer patients view AM and SC support, and informs the development of digital interventions for AM and SC in cancer survivors. To encourage AM specifically, problem recognition and the awareness of the benefits of AM should be addressed, partly by involving healthcare professionals. Although some cancer survivors prefer no support

or face-to-face contact, digital AM and SC interventions for cancer survivors are seen as a valuable solution. These interventions should incorporate a positive, non-judgemental and non-patronizing tone-of-voice, address concerns especially relevant to cancer survivors, offer possibilities for personalization and emphasize autonomy throughout. Care should be taken as to avoid stigmatization when tailoring interventions to cancer survivors.

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APPENDICES

Appendix 1

Survey questions translated from Dutch

What is your gender?

- Male
- Female

What is your age?
<numeric>

What is your highest achieved eductional level?

- No qualifications (No education/lower school)
- Lower level education (three to four years of high school)
- Middle level education (Dutch school level MBO level 2-4, HAVO, VWO)
- High level education (university or college)

In what way do you regularly use the Internet?

- I never use the Internet
- Personal computer (PC) or laptop
- Mobile phone/smartphone
- Tablet
- Other

Have you ever used the Internet to look up information on illness, health or healthcare?

- Yes
- No

What type(s) of cancer have you been diagnosed with?

- Breast cancer
- Prostate cancer
- Bowel/colon cancer
- Skin cancer
- Lung cancer
- Leukeamia or lymphatic cancer

- Bladder or urinary tract cancer
- Endometrial cancer
- Heand and neck cancer
- Ovary cancer
- Stomach cancer
- Pancreas cancer
- Kidney cancer
- I woud rather not say
- Other <free text response>

Do you smoke (sometimes) or do you not smoke at all?

- I smoke sometimes
- I do not smoke anymore but I used to smoke
- I have never smoked
- I do not know

How many cigarettes a day do you smoke?

- 1-10 cigarettes
- 11-20 cigarettes
- 21-30 cigarettes
- 31 or more cigarettes
- 0 cigarettes (I smoke incidentally / sometimes)

How quickly after waking up do you smoke the first cigarette?

- Within 5 minutes
- 6-30 minutes
- 31-60 minutes
- More than 60 minutes

Do you consider quitting smoking?

- Yes
- No

Do you (sometimes) drink alcohol or do you not drink alcohol at all?

- I sometimes drink alcohol
- I do not drink alcohol anymore but I used to drink alcohol
- I have never drunk alcohol
- I do not know

How often do you drink alcohol?

- Never
- Once a month or less
- 2 to 4 times a month
- 2 to 3 times a week
- 4 times or more per week

On a day on which you drink alcohol, how many glasses do you usually drink?

- 1 or 2
- 3 or 4
- 5 or 6
- 7 to 9
- 10 or more

How often are there occasions on which you drink more than 6 glasses of alcohol?

- Never
- Less than once a month
- Monthly
- Weekly
- Daily or almost daily

Do you consider quitting or moderating your alcohol use?

- Yes
- No

Was the importance of drinking little to no alcohol discussed with you during treatment?

- Yes
- No

Have you tried moderating your alcohol use before, during or after your treatment?

- Yes, before the treatment
- Yes, during the treatment
- Yes, after the treatment
- No, I have not tried to change my alcohol use
- No, I did not drink alcohol when I was diagnosed

What is a reason that you did not quit alcohol use?

- I have tried, but I cannot do it/I think I cannot do it
- I have bigger problems than my alcohol use
- I do not think it has any benefits to quit now
- I do not really know how to quit alcohol use
- I become anxious or stressed when I do not drink
- I lose weight when I do not drink
- Everyone in my social environment drinks alcohol
- I can focus better when I am drinking alcohol
- I have moderated my alcohol use and so I do not have any wish to quit
- Other <free text response>

When do you plan to moderate or quit alcohol use?

- Within a month
- Within half a year
- I do not know
- I am not planning to

What was the most important reason for attempting to moderate or quit alcohol use?

- My health
- Because my doctor recommended it
- Because my partner/family wanted it
- For my children's health
- To save money
- Other <free text response>

- What form of information or low-threshold support for alcohol moderation would you appreciate/have appreciated before, during or after treatment?
- I would not have appreciated any information or support
- Information online
- Printed information brochure
- Free online self-management course
- Self-help book
- Contact with peers
- Contact with a healthcare professional through skype or email
- Face-to-face contact with a healthcare professional (for example, at the hospital)
- Other <free text response>

What form of alcohol moderation support of others would you have appreciated?

- I would not appreciate support from others
- Support from my family
- Support from my fiends
- Support from social media contacts
- Support from peers who are also attempting to quit or moderate
- Support from peers who also have (had) cancer
- Support from a healthcare professional or coach
- Other <free text response>

What form of information or low-threshold support for alcohol moderation have you actually used before, during or after treatment?

- I have not used any information or support
- Information online
- Printed information brochure
- Free online self-management course
- Self-help book
- Contact with peers
- Contact with a healthcare professional through skype or email
- Face-to-face contact with a healthcare professional (for example, at the hospital)
- Other

Have you tried to quit smoking before, during or after your treatment?

- Yes, before the treatment
- Yes, during the treatment
- Yes, after the treatment
- No, I have not tried to quit smoking
- No, I did not smoke when I was diagnosed

What is a reason that you did not quit smoking?

- I have tried, but I cannot do it/I think I cannot do it
- I have bigger problems than smoking
- I do not think it has any benefits to quit now
- I do not really know how to quit smoking
- I become anxious or stressed when I do not smoke
- I gain weight when I do not smoke
- Everyone in my social environment smokes
- I can focus better when I smoke

- I have greatly reduced my smoking and so I do not have any wish to quit
- Other <free text response>

When do you plan to quit smoking?

- Within a month
- Within half a year
- I do not know
- I am not planning to

What was the most important reason for attempting to quit smoking?

- My health
- Because my doctor recommended it
- Because my partner/family wanted it
- For my children's health
- To save money
- Other <free text response>

What form of information or low-threshold support for smoking cessation would you appreciate/ have appreciated before, during or after treatment?

- I would not have appreciated any information or support
- Information online
- Printed information brochure
- Free online self-management course
- Self-help book
- Contact with peers
- Contact with a healthcare professional through skype or email
- Face-to-face contact with a healthcare professional (for example, at the hospital)
- Other <free text response>

What form of smoking support of others would you have appreciated?

- I would not appreciate support from others
- Support from my family
- Support from my fiends
- Support from social media contacts
- Support from peers who are also attempting to quit or moderate
- Support from peers who also have (had) cancer
- Support from a healthcare professional or coach
- Other <free text response>

What form of information or low-threshold support for smoking cessation have you actually used before, during or after treatment?

- I have not used any information or support
- Information online
- Printed information brochure
- Free online self-management course
- Self-help book
- Contact with peers
- Contact with a healthcare professional through skype or email
- Face-to-face contact with a healthcare professional (for example, at the hospital)
- Other <free text response>

How does a lifestyle intervention for cancer survivors differ from a lifestyle intervention for the general public?
<free text response>

Appendix 2

Interview topic guide for cancer survivors

- Context – participant's experience of cancer and its influence on their daily lives
- Smoking behaviour – smoking history, feelings and beliefs about smoking, willingness to quit, quit attempts
- Drinking behaviour – drinking history, feelings and beliefs about smoking, willingness to quit, quit or moderation attempts
- Interests and concerns after diagnosis – what concerned you most (about your health) after diagnosis
- Support in smoking cessation or alcohol moderation – discussion by healthcare professionals, received support, wishes for support
- Internet use – ways of using the internet for health related interests, which websites do your visit frequently and why
- Views on digital interventions for cancer survivors – what would make you use it, what would turn you off, views on cancer specific interventions, other recommendations

Appendix 3

Topic guide for the first two focus groups

- Experiences with digital support
- Need for digital support programs in cancer survivors
- Tailoring to cancer survivors
- Preferences for social support in alcohol moderation or smoking cessation efforts
- Monitoring of alcohol use or smoking behaviour
- When to address alcohol moderation or smoking cessation
- How to address cancer survivors specifically
- Visual preferences for digital support programs

Topic guide for the last two focus groups

- Discussion of themes that emerged in previous two focus groups and interviews
- Specific topics that a (digital) support program should cover
- Tone-of-voice in exercises and informative texts
- Discussion of draft versions of digital alcohol moderation and smoking cessation programs
- Last tips for developers and researchers

Appendix 4

Interview topic guide for healthcare professionals

- Approach – description of patients, how do you discuss AM or SC, how do you tailor your approach to the participant, what tools do you usually advice
- Preconditions for success – preconditions for successful treatment, any characteristic of successful quitters/moderators, how do you keep patients motivated
- Digital support – what works well in your experience, what are your views on online programs
- Cancer survivors – experiences with cancer survivors, any differences with the general population

Interview topic guide for experts in development and implementation of online support (for cancer survivors)

- Background – work experience, experience with cancer or cancer survivors
- Development – development process of intervention, recruitment, key factors according to participants, recommendations
- Patient participation – ways to involve patient group, barriers and facilitators, recommendations for improvements
- Specific intervention components – how to best incorporate peer support, tailoring and steer away from a patronizing tone of voice
- Implementation – implementation plan for your intervention, target group reach, involved stakeholders
- Need – views on need for (support in) behavioural changes in cancer survivors, how to accommodate those needs
- Cancer survivors – any differences with the general population

Appendix 5

Table S5. Preferences for support in current users vs former users of alcohol and tobacco

Support preferences	Current smoker (N=29), n (%)	Former smoker (N=132), n (%)	All (N=161), n (%)	Current drinker (N=186), n (%)	Former drinker (N=29) n (%)	All (N=215), n (%)
No support	11 (37.9)	47 (35.6)	58 (36.0)	88 (47.3)	12 (41.4)	100 (46.5)
Online information	4 (13.8)	13 (9.8)	17 (10.6)	20 (10.8)	5 (17.2)	25 (11.6)
Printed information flyer	1 (3.4)	11 (8.3)	12 (7.5)	19 (10.2)	3 (10.3)	22 (10.2)
Free online self-management course	5 (17.2)	6 (4.5)	11 (6.8)	7 (3.8)	1 (3.4)	9 (4.2)
Self-help book	3 (10.3)	6 (4.5)	9 (5.6)	7 (3.8)	0 (0)	7 (3.3)
Peer support	6 (20.7)	8 (6.1)	14 (8.7)	6 (3.2)	1 (3.4)	7 (3.3)
Online support from professional (email or video-call)	3 (10.3)	1 (0.8)	4 (2.5)	7 (3.8)	0 (0)	7 (3.3)
Face-to-face support from professional	9 (31.0)	14 (10.6)	23 (14.3)	10 (5.4)	4 (13.8)	14 (6.5)
Other	1 (3.4)	0 (0)	1 (0.6)	11 (5.9)	0 (0)	11 (5.1)
Not applicable to my situation	0 (0)	28 (21.2)	28 (17.4)	14 (7.5)	4 (13.8)	18 (8.4)
missing (none selected)	2 (6.9)	17 (12.9)	19 (11.8)	25 (13.4)	3 (10.3)	28 (13.0)

Note. Some participants are both (former) drinkers and (former) smokers, hence the sample sizes of the different substance users cannot be added.

CHAPTER 5

Digital self-help smoking cessation and alcohol moderation interventions for cancer survivors:
a study protocol of two RCTs

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ABSTRACT

Background

Brief interventions for smoking cessation and alcohol moderation may contribute considerably to the prevention of cancer among populations at risk, such as cancer survivors, in addition to improving their general wellbeing. There is accumulating evidence for the effectiveness of digital brief health behavior interventions. The objective is to assess the effectiveness, patient-level cost-effectiveness and cost-utility of two new digital theory-based self-help interventions among adult 10-year cancer survivors in the Netherlands. One of the interventions focuses on alcohol moderation, the other on smoking cessation. Both interventions are tailored to cancer survivors.

Methods

Effectiveness will be assessed in two separate, nearly identical 2-armed RCTs: alcohol moderation (AM RCT) and smoking cessation (SC RCT). Participants are randomly allocated to either the Intervention groups or the control groups. In the intervention groups, participants have access to one of the newly developed interventions. In the control groups, participants receive an online static information brochure on alcohol (AM RCT) or smoking (SC RCT). Main study parameters are the number of drinks post-randomisation (AM RCT) and tobacco abstinence (SC RCT). In addition, cost-data and possible effect moderators and mediators will be assessed. Both treatments are digital unguided self-help interventions: MyCourse – Moderate Drinking (in Dutch: MijnKoers – Minderen met Drinken) and MyCourse – Quit Smoking (MijnKoers – Stoppen met Roken). They are based on cognitive behaviour therapy (CBT), motivational interviewing (MI) and acceptance and commitment therapy (ACT). Both interventions are optimized in collaboration with the target population of cancer survivors in focus groups and interviews, and in collaboration with several experts on eHealth, smoking cessation, alcohol misuse and cancer survivors.

Discussion

The present study will add to scientific knowledge on the (cost-)effectiveness of digital self-help interventions to aid in smoking cessation or alcohol moderation, working mechanisms and impact on quality of life of cancer survivors. If found effective, these interventions can contribute to providing evidence-based psychosocial oncology care to a growing population of cancer survivors.

Trial registration: Trials are prospectively registered in The Netherlands National Trial Register (NTR): NTR6011 (SC RCT), NTR6010 (AM RCT) on 1 September 2016.

INTRODUCTION

In the last decades, milestones have been reached in fighting cancer. For many types of cancer, survival rates after diagnosis have improved. This has led to a lower mortality rate and a larger population of cancer survivors for many types of cancers, especially in developed countries with aging populations, such as the Netherlands [1, 2]. In 2016, 559 170 men and women in the Netherlands had been diagnosed with cancer in the previous 10 years [3] – which is our working definition of a cancer survivor. Projections indicate that this number will rise to 660 000 cancer survivors in the Netherlands in 2020 (with about equal proportions of men and women) [1]. These people are at an increased risk of facing a recurrence of cancer or second cancers [4].

One of the reasons that nowadays second cancers occur more frequently are adverse effects of cancer therapies. However, it is estimated that less than 10% of second cancers occurring among adults can be attributed to radiotherapy [5, 6], while the magnitude of the risk attributable to chemotherapy is very much dependent on the actual class of anti-cancer agent used, and the dose [5]. This suggests that other overall cancer risk factors (i.e. genetic susceptibility, age, environmental factors, lifestyle factors, and combinations of these factors) are important contributors to second cancer risk [5–7].

Smoking, excessive alcohol drinking and excessive bodyweight are among the main preventable risk factors for developing (second) cancers [7, 8], with alcohol and tobacco related cancer sites accounting for 35% of all second cancers [9]. Especially the impact of alcohol as a carcinogen is often underestimated, but like tobacco it contributes considerably to the disease burden from cancers(i.e. [8, 10, 11]). Targeting smoking and excessive alcohol use would not only potentially contribute to preventing second cancers, but also to improving cancer survivors' quality of life [12, 13]. Cancer survivors are recommended a healthy lifestyle, including a sufficient amount of daily physical activity and healthy diet, without smoking and limited or no alcohol use [14].

Smoking cancer survivors constitute a substantial subgroup of 9.3% of all cancer survivors [15]. Most of these current smokers (83%) smoked daily, averaging 14.7 cigarettes per day, and 15% for lung cancer survivors [15–17]. Alcohol use among cancer survivors does not differ from alcohol use among the general population [18], 6% of the Dutch general population [19] drinks more than the maximum amount of alcohol containing drinks to prevent cancer occurrence (1 glass/day for women, 2 glasses/day for men), as at the time recommended by the World Cancer Research Fund (WCRF) [14]. Several studies report similar results [20–22]. Male, younger aged head and neck cancer survivors seem to be more likely to engage in risky alcohol use [23]. Based on a total of 660 000 cancer survivors by year 2020, these figures (9.3% smoking and 6% excessively drinking) translate to approximately 61 000 smoking and 39 000 excessively drinking Dutch cancer survivors. For Europe it is estimated that in the year 2020, over 4 million new cancers will be identified, the previous figures imply 383 000 smoking and 247 000 excessively drinking cancer survivors [24]. These cancer survivors could potentially benefit from tailored, evidence-based support to help them quit smoking or limit their alcohol intake.

Based on recent systematic reviews of RCTs among people who smoke or drink excessively, there is accumulating evidence that guided and unguided digital interventions for alcohol moderation (AM) [25] and smoking cessation (SC) [26] can be effective but also leave room for improvement as effect sizes tend to be small. For digital alcohol interventions in particular, a recently published meta-analysis, including a total of 16 randomised controlled trials (with 23 comparisons and 5 612 participants), showed a small but significant overall effect size in favour of internet interventions, compared to waitlisted participants, information brochures, or assessment only, but this effect is not sustained after 12 months [25]. A paper integrating all recent reviews on this topic came to similar conclusions [27]. In a Cochrane review on digital SC interventions, 28 randomised or quasi-randomised trials were included, yielding data from over 45 000 participants. Results were mixed. All in all, digital interventions for SC show some positive results for the general population, but leave room for improvement beyond the standard CBT-based internet interventions [26]. A rather new promising therapeutic approach is Acceptance and Commitment Therapy (ACT), part of third-wave CBT. Both therapeutic approaches have shaped the interventions described in this paper, which will be elaborated further in the intervention descriptions.

Although the potential of digital interventions to improve lifestyle factors among cancer survivors is recognized [28], most of currently reported interventions target diet and physical exercise [29]. In a recent study, Bantum et al. [30] tested the effectiveness of a six-week Web-based multiple health behaviour change program for adult survivors compared to a waitlist condition in an RCT (n=352). Cancer survivors were eligible if they had completed their primary cancer treatment from 4 weeks to 5 years before enrolment. The web-based intervention positively impacted reduction of insomnia and frequency of exercise [30]. Further, a web-based, tailored SC program for young adult and childhood cancer survivors yielded positive SC outcomes at 15 months post-randomization in an RCT comparing web and print-based materials. Both versions yielded quit rates (n=374, web-based: 16.5%, print-based: 15.5%) that are similar to the intensive telephone counselling treatment they were based upon (15% at 12 months post-randomization) [31].

Thus far, specific AM and SC digital intervention RCTs have not specifically focused on cancer survivors, with few exceptions [31, 32]. There is a lack of knowledge on what results in terms of effectiveness and cost-effectiveness could be obtained when existing internet interventions for smoking and alcohol would be tailored to cancer survivors. Based on (Cochrane) reviews on other lifestyle interventions positive outcomes can be expected [28, 30, 33–35]. Furthermore, time of diagnosis is referred to as a 'teachable moment' [36, 37]; cancer diagnosis might trigger cancer survivors and possibly their family members[37], to adapt a more healthy lifestyle and may thus be a good moment to introduce health promotion programs.

The objective of the two RCTs presented in the current study protocol is to test the effectiveness of two newly developed digital interventions on reducing alcohol use or tobacco smoking in samples of excessive drinking or smoking cancer survivors.

METHODS

Aims and hypotheses

The overall aim of the study is to examine the effectiveness and cost-effectiveness of two digital interventions for cancer survivors. One intervention focuses on alcohol moderation (AM), the other intervention on smoking cessation (SC). Both interventions will be compared to information-only control groups (CTRL) in a randomized controlled trial (RCT).

It is hypothesized that:

1a. The experimental digital AM intervention will reduce alcohol use more than CTRL, 6 months post-randomisation.

1b. The experimental digital AM intervention will show favourable cost-effectiveness (cost per quality-adjusted life year <20 000 euro) compared to CTRL.

2a. The experimental digital SC intervention will lead to a higher quit rate than CTRL 6 months post-randomisation.

2b. The experimental digital SC intervention will show favourable cost-effectiveness (cost per quality-adjusted life year <20 000 euro) compared to CTRL.

Study design

Two separate two-arm randomised controlled trials RCTs will be carried out (alcohol moderation (AM RCT) and smoking cessation (SC RCT)), each with a follow-up duration of 12 months in an online context. Study design, procedures and measurement instruments of the two RCTs are the same – the main difference is the aim of the intervention (either alcohol moderation or smoking cessation). The RCTs have been designed in line with the CONSORT statement [38]. Both studies are registered in the Dutch Trial Register; identifiers: NTR6010 (AM RCT) and NTR6011 (SC RCT). Ethical approval to carry out the studies was obtained from an accredited medical research and ethics committee in the Netherlands (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. NL55921.101.16).

Study procedure

Applicants meeting inclusion criteria will be informed on the conditions of participation. If they would like to participate, participants are asked for necessary personal data. An invitation email

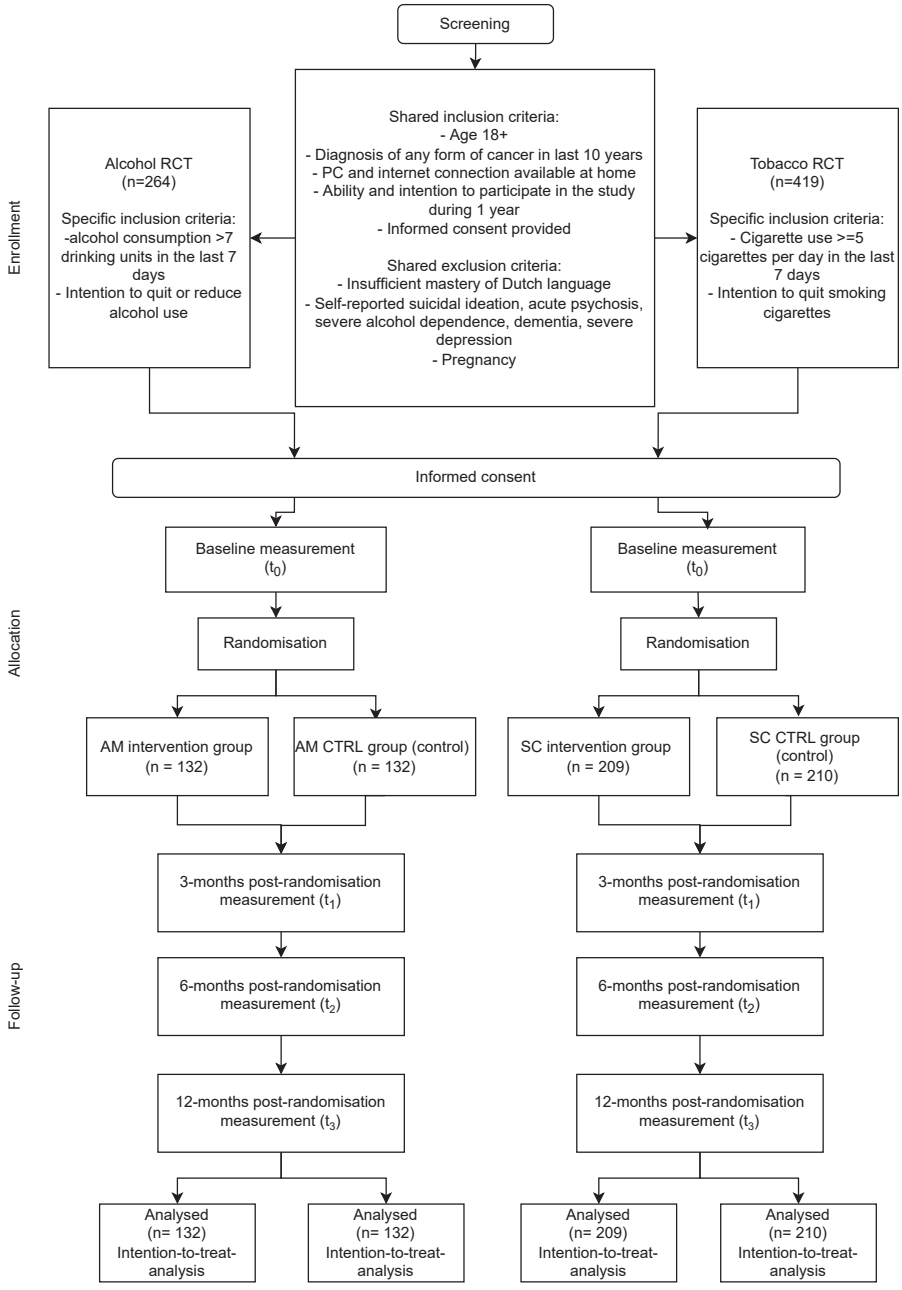
will be sent to them containing the informed consent form, all relevant patient information and a link to register. From this moment on, they have up to 30 days to decide if they want to participate or not. During these 30 days, they can contact a member of the research team responsible for the inclusion process by phone or email or face-to-face for questions regarding the study and interventions. They can also contact an independent physician during these 30 days. After their signed informed consent has been received digitally they are invited to the baseline questionnaire. After they have completed the baseline measurement, randomisation takes place. Depending on the outcome, participants are allocated to one of the two trial arms (active self-help digital intervention or passive online information brochure). Participants receive a confirmation email containing a username and instructions for logging in.

Follow-up measurement waves will take place at 3, 6 (primary endpoint), and 12 months post-randomisation (Figure 1). As other intervention studies have focused on this endpoint, this will enable better interpretation of results and comparison across studies. At each measurement point, participants receive an email including a link to the online questionnaires. Non-respondents receive three reminder emails and are subsequently contacted by telephone in case of continued non-response. As responses are collected online, all data is automatically validated (range checks etc.) on the client side, and after validation stored in a secured server-based database. All data transferred between client and server are encrypted using the Transport Layer Security cryptographic protocol.

Randomisation

After completing the baseline measurement, participants will be allocated to the two trial arms in a 1:1 ratio. As the number of participants we aim to include in each trial arm is not very large, random variation in baseline characteristics could reduce trial arm equivalence. Therefore, allocation through adaptive randomisation (Minimisation[39, 40]) will be used to balance trial arms with regard to age, sex, and education level. Adaptive randomisation implies that the randomisation sequence is not a priori known but is based on the variance in variables that need to be balanced over the trial arms. If imbalance between the trial arms in age, sex or education occurs, the probability of allocation to the trial arm that minimizes this imbalance is increased to 0.67 (instead of 0.5). The randomisation procedure is automatized and performed by triggering a server-sided PHP script using a Mersenne twister random number generator, immediately after the participant has completed the baseline measurement. After randomisation, the participant is informed about the outcome of the randomisation via an automated email, and assigned to one of the two conditions via an automated server-sided computer script. After this assignment, the researchers are informed about the outcome and assignment of the participant via an automated registration in the trial management database. As this is an open label RCT, the participants nor the researchers are blinded regarding the allocation conditions.

Figure 1. Flowchart of participant movement in the AM RCT and SC RCT



Participants

Recruitment

The population base from which the subjects will be drawn are Dutch adult cancer survivors, meeting in/exclusion criteria. A website is created, containing information on the study and the possibility to enrol as a participant. Collaboration with Dutch patient organizations is sought and all (social) media channels available will be utilized to ensure recruitment of the planned number of participants. Other recruitment strategies will include: reaching out to smoking cessation clinics, oncology nurses and meeting centers for cancer survivors, online advertisements on (health-related) websites, targeted Facebook and search engine campaigns, and advertisements in newspapers and magazines relevant to the target group.

In- and exclusion criteria

All potential participants fill out an online screening questionnaire to determine whether they fulfil all inclusion criteria and none of the exclusion criteria. There are four possible outcomes: 1) inclusion criteria are not met and applicants cannot participate in the study; 2) inclusion criteria for the alcohol RCT are met and they are invited to participate in the alcohol RCT, 3) inclusion criteria for the tobacco RCT are met and they are invited to participate in the tobacco RCT, 4) inclusion criteria for both RCTs are met and participants can choose in which one of the two RCTs they want to participate (they cannot participate in both RCTs). Participants who do not fulfil criteria for inclusion will be provided with links to websites with further alcohol/smoking information and help.

Shared inclusion criteria (for both RCTs):

- Age 18+
- Diagnosis of any form of cancer in the last 10 years
- PC and internet connection available at home
- Ability and intention to participate in the study and the intervention during the period of one year
- Informed consent provided

Additional inclusion criteria for the AM RCT only:

- Alcohol consumption of >7 standard drinking units (10 g of ethanol) in the last 7 days
- Intention to reduce or quit alcohol use as assessed by one item from the screening questionnaire

Additional inclusion criteria for the SC RCT only:

- Cigarette use of >=5 cigarettes per day in the last 7 days
- Intention to quit smoking cigarettes as assessed by one item from the screening questionnaire

Shared exclusion criteria (for both RCTs):

- Insufficient mastery of Dutch language
- Self-reported suicidal ideation, acute psychosis, severe alcohol dependence, dementia, severe depression
- Self-reported pregnancy

Sample size

For both the AM RCT and SC RCT, conventional power (1-beta=.80) and levels of statistical significance (alpha=.05) are chosen. For both trials, the primary outcome data is collected at 6 months post-randomisation.

For the AM RCT, the primary outcome variable is based on the 7-day TLFB alcohol measurement, 6 months post-randomisation. Based on the average of 2 previous RCTs on very similar self-help interventions in the Netherlands versus a control condition (see Riper 2008 and Blankers 2011 in [25]), a Cohen's d effect size of d=0.40 is expected. Using the power calculation package "pwr" [91] for R 3.0.1 [41], d=.40 translates into a minimum net sample size of 2 x 99 participants in case of 2-sided testing, or 2 X 78 participants in case of 1-sided testing. Assuming a maximum of 25% non-response at 6 months follow-up, we intend to include 99 x 2 x (100/(100-25)) = 264 (or 208 for 1-sided testing) participants in the alcohol RCT. In case the drop-out rate is lower than 25%, power will be somewhat higher than we anticipate in this calculation, i.e. in that case we are more likely to find a true effect.

For the SC RCT, the primary outcome variable is based on the 7-day TLFB smoking measurement: self-reported abstinence in the last 7 days prior to the primary measurement point, 6 months post-randomisation. Based on a study by Duffy et al. amongst cancer survivors [12], a quit-rate of 30% in the active smoking cessation intervention group, vs 15% in the smoking cessation control group can be expected. This translates into a relative risk (RR) of 2.14, which is comparable to the RR estimate in a recent Cochrane review (RR=2.05) [26]. Based on a pilot trial of an ACT smoking cessation internet intervention [42], a 23% quit rate in the experimental arm vs a 10% quit rate in the control arm can be expected (RR=2.20), at the three months follow-up. Based on the average of these RRs, a RR = 2.1 is expected. This translates into a 21% quit rate in the experimental condition, assuming a 10% quit rate in the control condition at 6 months post-randomisation. Using "pwr" [43] for R 3.0.1 [41], a 21% quit-rate vs 10% quit-rate translates

into a net sample size of 2 x 157 participants, based on 2-sided tests (2 X 124 for 1-sided tests). Assuming 25% non-response at six months follow-up, we need 157 x 2 x (100/(100-25)) = 419 participants in the SC RCT for 2-sided tests, and 331 for 1-sided tests).

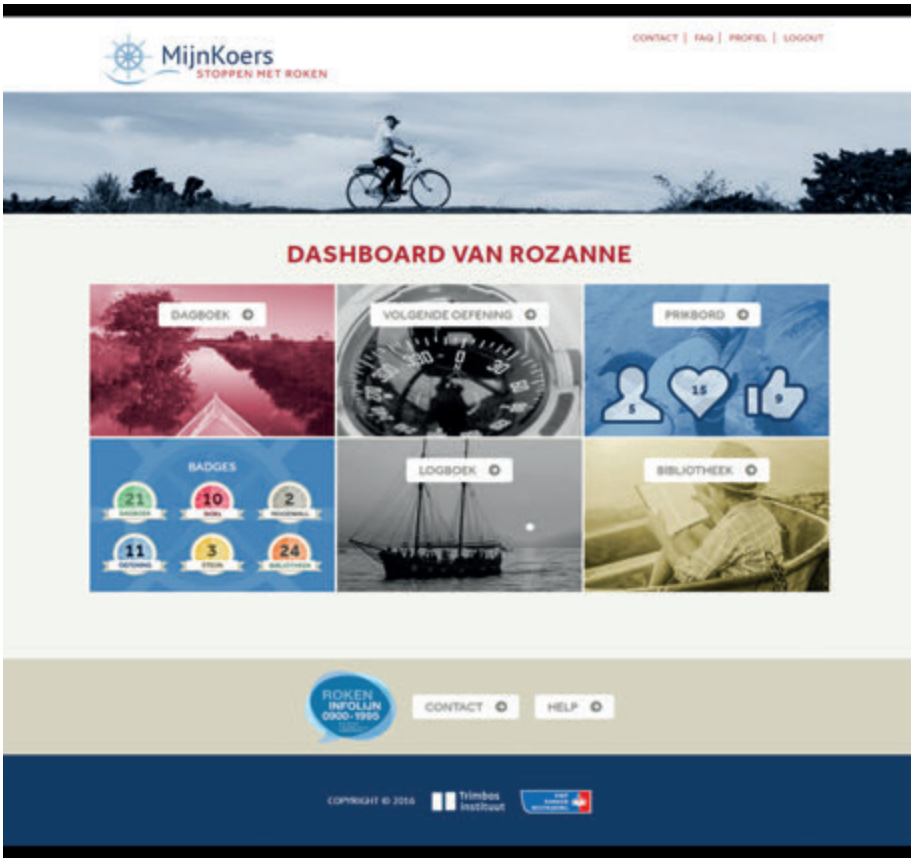
The described power analyses are conservative. We may perform half-way post-hoc power analyses for both RCTs, based on those we will evaluate our assumptions underlying these power calculations and may adjust the sample sizes if necessary. We might for example not fully compensate the expected 25% drop-out, as drop-out rates might be lower and we will perform intention-to-treat analyses including multiple imputation, which partially recovers power. One-sided testing is mentioned because it is very plausible that the interventions will have a positive effect on SC and AM [25, 26, 42]. Furthermore, within the above mentioned calculation, clustering of measurements (baseline, 3-, 6- and 12-months) within participants and related covariance has not been taken into consideration. Accounting for this could also change required sample sizes.

Conditions

MyCourse – Quit Smoking and MyCourse – Moderate Drinking

Both programs are digital lifestyle interventions optimized for cancer survivors: MyCourse – Moderate Drinking (in Dutch: MijnKoers – Minderen met Drinken) and MyCourse – Quit Smoking (MijnKoers – Stoppen met Roken) (see Figure 2). The interventions are developed and tailored in collaboration with the target population of cancer survivors in focus groups and interviews, and in collaboration with several experts on eHealth, smoking cessation, alcohol misuse and cancer survivors.

Figure 2. Main page of new digital intervention MyCourse – Quit Smoking (in Dutch)



Therapeutic approaches: CBT, ACT and MI

Both interventions are based on cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT) and motivational interviewing (MI) techniques.

CBT has been well-established as an effective therapeutic approach for treating excessive alcohol use and aiding in smoking cessation in web-based programs [25, 26, 44]. It aids participants in understanding connections between cognitions, context and behaviour and hands them skills to cope with cognitions and situations that elicit unwanted behaviour. MI techniques help participants identify their ambivalences towards quitting smoking or moderating alcohol use, and help solve them [45]. MI has demonstrated a modestly significant effect in efficacy studies on smoking cessation, (RR 1.27; 95% CI 1.14 to 1.42) [45] and excessive alcohol drinking (d 0.40; 95% CI 0.17 to 0.70) [46]. National CBT- and MI-based treatment protocols were used to shape this part of the interventions [47, 48].

ACT is an emerging theory-based treatment paradigm that has demonstrated feasibility and efficacy in SC treatment in several studies and in a variety of modalities (face-to-face, telephone-based or web-based) [42, 49–51]. Regarding AM, a pilot trial found ACT-based group therapy for alcohol disorder and comorbid affective disorder effective [52]. Including the treatment of other substance use disorders (i.e. opioids, amphetamines, polydrug use) ACT shows favourable efficacy compared to other active treatment conditions (e.g. CBT and 12-step programs) and sustains the effects for a longer follow-up period [52, 53]. Acceptance in ACT stands for allowing intense physical sensations, cognitions, and emotions which may trigger drinking (AM RCT) and smoking (SC RCT) to come and go, without trying to control them; commitment stands for keeping in mind what is important to individuals (values) in order to guide action plans (stopping smoking) [42]. Specifically, ACT focuses on identifying thoughts, feelings, and physical sensations that trigger the target behaviour [42]. Unlike traditional CBT, ACT does not teach methods to avoid or control these triggers, but it focuses on changing one's relationship with them by allowing them to be present without acting on them [42, 49, 54].

Optimization for cancer survivors

Patients participated throughout the development process. This resulted in all exercises being written in such a way as to better suit the needs of the population of cancer survivors. Information on short-term benefits is placed more prominently within the informative texts. Positive reinforcement is emphasized and effectuated in multiple ways, including badges and verbal reinforcements within the exercises. Support from the participant's own social network was deemed highly important in the focus groups, so several exercises include a feature that enables quick, easy and personalized updates by sending a direct email to a friend, partner or relative. In addition, information regarding alcohol/tobacco and cancer interactions is included in the intervention. Because cancer survivors constitute a generally older age group, design has been simplified as much as possible. Clear instructions are given on every page, always including a help button, sharp contrasts ease reading.

Intervention flow

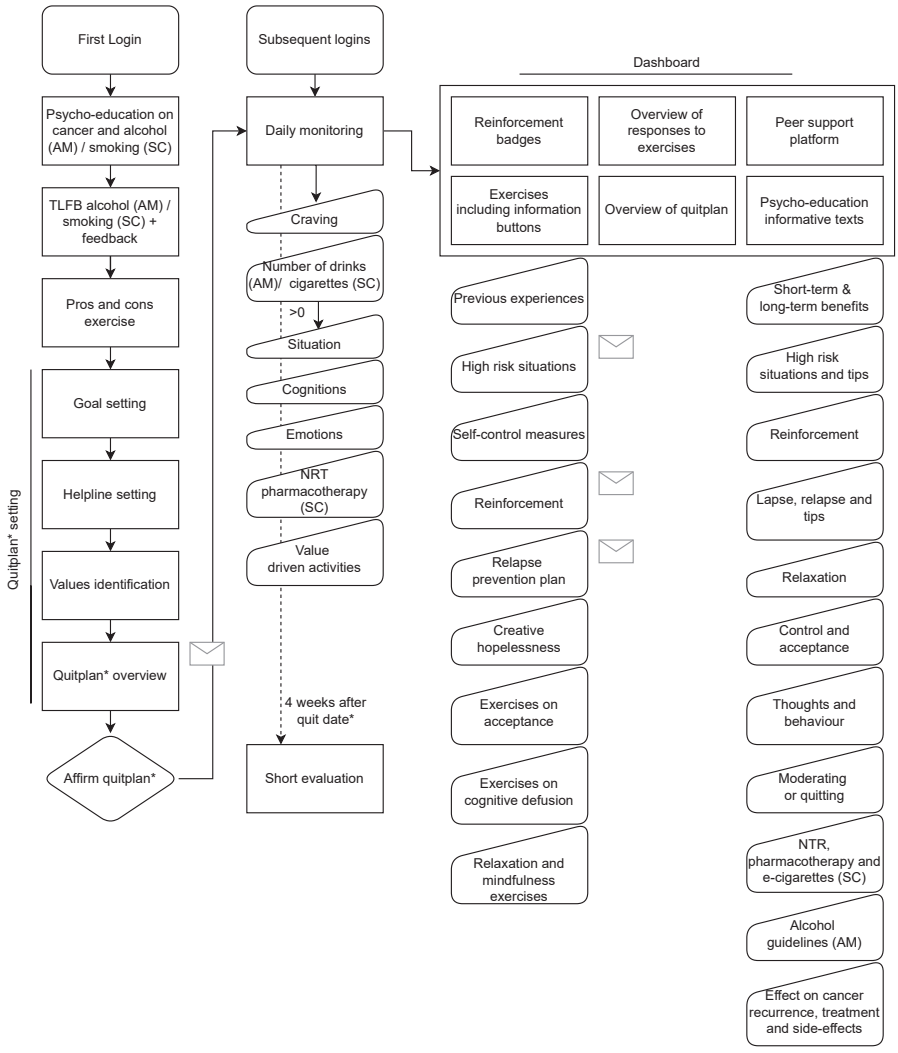
Both interventions are accessible through PC, tablet/iPad and smartphone. Length of the two interventions is equal. Participants are advised to use the intervention for 4 weeks after their set quit/moderation date, but they are free to quit whenever they want. After 4 weeks participants evaluate their goal achievement in the intervention. After this short evaluation all intervention components will remain available for at least 12 months. Table 1 shows descriptions of the main intervention elements, an overview of movement through these elements is shown in Figure 3.

Table 1. Main elements within new digital interventions MyCourse – Quit Smoking and MyCourse – Moderate Drinking

Main elements	Description
Goal setting	Participants set a quit plan (SC and AM RCT) or moderation plan (only AM RCT) including a quit date
Goal monitoring	Every day participants monitor their drinking or smoking behaviour, mood, cognitions, and contextual cues which have led them to drink or smoke. Feedback is provided in a personalized graph
Exercises based on CBT and ACT	Exercises help identify high risk situations for excessive drinking/smoking and self-management strategies. ACT-exercises help accept difficult feelings while keeping focused on the behaviour goal and help exercise self-compassion to prevent relapse
Psycho-education	Effect of alcohol/tobacco on cancer, cancer treatment and life after cancer
Reminders	Several automated email reminders to regularly log on, monitor behaviour and finish all exercises
Peer support platform	A moderated bulletin board, focused on sharing tips and experiences
Social support from social network	Semi-automated email functions throughout the program to send personalized, informing emails to a trusted person

Note. SC = smoking cessation, AM = alcohol moderation, RCT = randomised controlled trial, CBT = cognitive behavioural therapy, ACT = acceptance and commitment based therapy.

Figure 3. Structure of digital interventions MyCourse – Quit Smoking (SC) and MyCourse – Moderate Drinking (AM)



Note. Mail icons demonstrate semi-automatized email options to participants' own social network. * Moderation plan/moderation date is possible in MyCourse – Moderate Drinking.

At the first login, participants are prepared for action using motivational interviewing-based techniques. Advantages and disadvantages of drinking (in AM RCT) or smoking (in SC RCT) and moderation/quitting are assessed. Next, ACT's core process of committed action is targeted by having users apply their core values guiding quitting towards a personalized quit plan. Only for

AM RCT: If moderation is chosen as a goal, the maximum amount of alcohol consumed per day and per week is set. The participant is also asked to set a date to start working towards the new drinking (AM RCT) or smoking cessation (SC RCT) goals. The quit date is to be set within one week upon logging in for the first time.

The next stage is the behaviour change phase, based on CBT. Here, participants are asked to monitor their drinking (AM RCT) or smoking (SC RCT), their mood, their cognitions, and contextual cues which have led them to drink (AM RCT) or smoke (SC RCT). Based on the monitoring data they provide, feedback is generated in the form of a graph to show progress towards their goals at a glance. This monitoring screen is shown first upon subsequent logins. In line with ACT, participants also monitor whether they have acted on their values each day. This is phrased as having engaged in a positive activity, where participants can choose from the values they have selected when setting their Quit/Moderation plan.

A personalized dashboard shows the different intervention components. Exercises are provided to help participants gain better insight into their drinking behaviour, and ways to handle cravings and high risk situations. In the final stage, participants learn how to manage relapse, and how to maintain behaviour change. ACT's core processes of acceptance (preparedness to experience feelings or sensations), being present (staying connected with the here-and-now), cognitive reflection (watching the process of thinking), and self-as-context (awareness of the difference between one's self and one's thoughts) are targeted through a series of exercises designed to enhance these skills. Participants are invited to use these skills when they have urges, experience withdrawal symptoms or lapses [42].

On the peer support platform participants can provide and receive support from other participants during the intervention. Additionally they are encouraged to seek support from their own social network. Throughout the program, participants have the ability to share some of their answers with their partner or someone else who provides them support via semi-automatized emails. For example, they can share their quit plan or their high risk situations, thus helping their supportive social network in helping them by providing them with key information.

At any time, participants have quick access to an overview of their quit plan and finished exercises. To enhance adherence, emailed reminders are sent regularly after the participant has not logged in for several days, has not registered their drinking or smoking behaviour, or has not completed all exercises.

Throughout the interventions a sea faring ship is used as a metaphor. This is a means to help participants understand and experience the gist of ACT principles and foster continuity throughout the different intervention elements. Metaphors are used in ACT to loosen the grip of our cognitive thoughts on our feeling of self and on our behaviour. Using metaphors can

circumvent the inclination to verbally protest against, for example, the exercise that explains how trying to exert control all the time will most likely not benefit you [55].

Control conditions

The two control-condition interventions provide plain information on risks of alcohol (AM RCT) or smoking (SC RCT) in general and information specifically relevant for cancer survivors. Tips on how to reduce or quit alcohol use or quit smoking are also provided, but do not include the interactive elements that are part of the self-help interventions. Participants in the control groups can access the information page as often as they want by logging in on the website. However, the information on the information pages is static, does not change over time, and is not tailored to the individual participant. After completion of the study, 12 months post-randomization, these participants are also provided with access to the self-help interventions. All participants are free to seek additional support if needed, use of additional support will be assessed in follow-up measures.

Outcome measures

An overview of all measures and their measuring points is given in Table 2.

Primary measures

Alcohol and tobacco use – Main study parameters are Timeline Follow-Back (TLFB) reports on alcohol use (number of standard drinks) in the 7 days prior to the 6-month post-randomisation measurement wave (AM RCT) [56, 57] and tobacco abstinence measured by TLFB reports on tobacco use (number of cigarettes) in the 7 days prior to the 6-month post-randomisation measurement wave (SC RCT). TLFB reports yield information on frequency as well as patterns of substance use behaviour [57, 58]. Outcomes from online administrated TLFB reports are consistent with face-to-face or telephone administrated TLFB reports [57, 59]. An additional question is sent in the SC RCT about tobacco use in the 14 days prior to 4 weeks after the set quit date, to comply with the Russell Standard and thus make the study better comparable to international smoking cessation studies [60].

Secondary measures

Alcohol and nicotine dependence – Secondary measures include alcohol (AM RCT) or nicotine dependence (SC RCT) as measured by, respectively, the Alcohol Use Disorders Identification Test (AUDIT) [61] and Fagerstrom-test for Nicotine Dependence (FTND) [62]. AUDIT is a 10-item questionnaire on patterns of alcohol use and problems experienced due to alcohol use, to distinguish low-risk from high-risk drinkers. The AUDIT has been validated in 6 countries [61]. FTND is a 6-item questionnaire which has been shown to reliably assess nicotine dependence in a Dutch sample [63].

Table 2. Schematic representation of outcome measures and measurement waves

Assessments (number of items)	Baseline (t_0)	3-months post-randomisation (t_1)	6-months post-randomisation (t_2)[d]	1-year post-randomisation (t_3)
AAQ-II (7)	x	x	x	x
AUDIT (10)	x		x	x
Knowledge questionnaire (12)	x	x	x	
BSI-18 (22)	x		x	
EQ-5D (5+1)	x	x	x	x
Fagerstrom Test for Nicotine Dependence (6)	x	x	x	x
MCSDS (13)	x			
OCDS[a] (5)	x[a]	x[a]	x[a]	
Perceived partner support (1)	x	x	x	x
Self-efficacy measure (3)	x	x	x	x
SF36 (36)	x	x[c]	x	x[c]
Socio-demographics (24)	x			
TiC-P (31)	x	x	x	x
Timeline-Follow-Back (TLFB) for alcohol consumption (7)	x	x	x	x
Timeline-Follow-Back (TLFB) for tobacco consumption (7)	x	x	x	x
QSU-brief[b] (10)	x[b]	x[b]	x[b]	
ZUF-8 (8)		x		

Note. [a] only applied in the AM RCT.
[b] only applied in the SC RCT.
[c] only 11 items from the SF36 will be administered at 3 and 12 months post-randomisation (necessary to apply the Brazier algorithm).
[d] Primary endpoint for both the AM and SC RCT.

Treatment satisfaction – Treatment satisfaction is measured by Fragebogen zur Messung der Patientenzufriedenheit (ZUF-8) [64], a German version of the CSQ-8 which has shown good psychometric properties (translated in Dutch). Its eight items are scored on a 4-point scale, without a 'neutral' answer option.

Cost-effectiveness

Cost-data and quality of life – Cost-data are measured by the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [65]. Part 1 measures healthcare consumption through questions on frequency of contact with several health care providers. Part 2 of the TiC-P assesses health related productivity losses. This Dutch questionnaire showed good test-retest reliability and promising construct-validity for items concerning contact with health professionals [66]. Quality of life is assessed by EQ-5D (5L) [66–69] and MOS SF-36 [70]. Participants state the extent of problems experienced on five dimensions. EQ-5D (5L) improved discriminatory power compared to EQ-5L (3L) and showed good validity across several international patient groups [71]. MOS SF-36 consists of 36 items on 8 dimensions, with higher scores reflecting a higher level of well-being. A Dutch translation showed good psychometric properties [72].

Mediators and other measures

In addition, several hypothesised intervention effect mediators will be assessed through the following questionnaires: craving using OCDS [73] (AM RCT) and QSU-brief [74, 75] (SC RCT), symptoms of psychopathology BSI-18 [76], experiential avoidance using AAQ-II [77], obtained knowledge on CBT and ACT principles using a 12-item questionnaire [78], a single item on perceived partner support [79], a 3-item questionnaire on self-efficacy to moderate alcohol drinking (AM RCT) or quit smoking (SC RCT) [80, 81], and utilization variables (number of logins, time spent logged in, use of major content elements etc.) [82]. The Marlowe-Crowne Social Desirability Scale (MCSDS) will be included to evaluate the reliability of the self-reported questionnaire data [83]. Collected socio-demographic variables will include age, sex, education, marital status, living situation and cultural background.

Participants will furthermore be asked for permission to access their patient data in the Netherlands Cancer Registry, which is managed by IKNL (Netherlands Comprehensive Cancer Organisation) to obtain reliable data about their disease course. They are also asked for permission to access their healthcare cost-data registered by national statistics organization Statistics Netherlands (Centraal Bureau voor Statistiek (CBS)). Access to these data can be granted or denied by the participants by ticking boxes in the informed consent form.

Statistical analyses

Outcome data will be analysed using Generalized Linear Mixed Models (GLMM) with log link functions depending on the data types and distributions of the dependent variables (count or continuous data in case of alcohol use, dichotomous data in case of smoking cessation) will be applied to the primary and secondary outcome measures. Missing data will be handled using the multiple imputation package Amelia 2 in the software package R 3.0+, and with at least 1 other package as a comparison. In a benchmark study, this Amelia 2 package outperformed other conventional multiple imputation packages [84]. Analyses will be conducted on the entire randomised sample (i.e. intention to treat) and on the per protocol/ treatment completers sample. All analyses will be carried out using SPSS version 20+ and/or R version 3.0+. Covariates in the model will be the minimised variables (see section on randomisation), variables with a $p<.05$ difference at baseline and the MCSDS. In the above mentioned analyses, clustering of measurements (baseline, 3-, 6- and 12-months) within participants and related covariance has not been taken into consideration. Linear mixed modelling will be adopted if necessary.

The economic evaluation will be conducted alongside the randomised trial. The Dutch tariffs (utility weights) [84] and the MVH-A1 tariff by Dolan et al. [85] for the EQ-5D-5L will be used for computing the QALYs [86]; for the MOS SF-36, the Brazier scoring algorithm (SF-6D) will be used [87]. Using the area under the curve (AUC) method, the periods between the measurement waves will be weighted by the utility of the health state in that period. This allows the computation of quality adjusted life years (QALYs) over the entire trial period. In a similar vein, cumulative costs over the entire follow-up period will be obtained from the cost estimates at the various measurement waves. The cost-effectiveness evaluation will be performed in line with suggestions by Drummond et al. (2015) [88], i.e. in agreement with the intention-to-treat principle, with missing data addressed using imputation. The incremental cost-effectiveness ratio (ICER) will be calculated as follows: ICER = $(C_1–C_2)/(E_1–E_2)$, where C are costs, E effects, and subscripts ($_1$ and $_2$) refer to the two trial arms (experimental/self-help and control/ information brochure). Confidence intervals around the ICER will be calculated using a non-parametric bootstrap approach: 2,500 non-parametric bootstrapped samples will be extracted from each of the original datasets. For each of these bootstrapped samples, the incremental costs, incremental effects, and the incremental cost-effectiveness ratio (ICER) will be calculated. The resulting 2,500 ICERs per dataset will be used for further calculations and will be plotted on a cost-effectiveness plane. In addition, cost-effectiveness acceptability curves (CEACs) will plotted. One-way sensitivity analyses directed at uncertainty in the main cost drivers will be performed to gauge the robustness of our findings.

DISCUSSION

This paper describes the study protocol for assessing two digital self-help interventions aimed at supporting cancer survivors in their attempts to quit smoking or to moderate or quit their alcohol use. Two separate RCTs will determine the effectiveness and cost-effectiveness of MyCourse – Quit Smoking and MyCourse – Moderate Drinking, which have been developed in close collaboration with cancer survivors, and several experts on eHealth, smoking cessation, alcohol misuse and cancer survivors. Primary outcome measures are smoking abstinence (SC RCT) and number of drinks (AM RCT) at 6 months post-randomisation. Several possible mediators will be examined as well, to gain insight into active mechanisms in digital behavior change interventions.

In this study cancer survivors are described as individuals from the time of diagnosis [89], a definition also adopted by the National Cancer Institute in the USA [90] and the Dutch Cancer Registry (NKR) [91]. Both interventions are offered at any time after diagnosis. Cancer diagnosis is often referred to as a 'teachable moment' that could entail increased motivation to adopt health behaviors [36, 92]. But some might argue that only after treatment people can focus their energy on digital interventions. Correct timing of these interventions is yet to be studied, although a recent study suggests to offer SC support as soon as possible [93]. Cancer survivors' characteristics, preferences, and the ways in which the interventions have been adjusted to them, will be described in a different paper. Note that cancer survivors involved in this development process were mostly older, hence the interventions might not be as suitable for young adult cancer survivors. Digital interventions targeting SC in current scientific literature mostly target younger cancer survivors [31, 32]. However, for older cancer survivors digital interventions are also likely a suitable mode of delivery, as in 2016, over 89% of Dutch adults aged 45-75 has internet access, over 81% of Dutch adults aged 45-65 uses internet daily, 63% of 65-75 year olds use internet daily, and an additional 13% at least weekly [94]. Searching for health information is among their top internet activities.

The present study will improve the scientific knowledge regarding the effectiveness and cost-effectiveness of digital unguided self-help interventions to address cigarette use and alcohol misuse among cancer survivors. If found successful, they will be implemented and made available to all interested cancer survivors in the Netherlands. Accordingly, this study contributes to providing evidence-based and sustainable psycho-social oncological care to a growing population. Furthermore, by stimulating these health behaviors, recovery and quality of life after cancer treatment are expected to be improved and the incidence of second cancers to be reduced.

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CHAPTER 6

Effectiveness, cost-effectiveness and cost-utility of a digital smoking cessation intervention for cancer survivors:

health economic evaluation and outcomes of a pragmatic randomised controlled trial

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ABSTRACT

Background

Smoking cessation (SC) interventions may contribute to better treatment outcomes and the general wellbeing of cancer survivors. The aim of the present study was to evaluate the effectiveness, cost-effectiveness, and cost-utility of a digital interactive SC intervention compared to a noninteractive web-based information brochure for cancer survivors.

Methods

A health economic evaluation alongside a pragmatic two-arm parallel-group randomised controlled trial (RCT) with follow-ups at 3, 6 and 12 months comparing the SC intervention with the information brochure. The study was conducted in The Netherlands over the Internet, from November 2016 to September 2019. Participants were Dutch adult cancer survivors, current smokers with the intention to quit smoking. In total, 165 participants were included and analysed; 83 in the MyCourse group and 82 in the control group.

In the intervention group, participants had access to a newly developed, digital, minimally guided SC intervention "MyCourse-Quit Smoking". In the control group, participants received a noninteractive web-based information brochure on SC. Both groups received unrestricted access to usual care.

Primary outcome was self-reported 7-day smoking abstinence at 6-month follow-up. Secondary outcomes were quality adjusted life years (QALYs) gained, number of cigarettes smoked, nicotine dependence, and treatment satisfaction. For the health economic evaluation, intervention costs, healthcare costs, and costs stemming from productivity losses were assessed alongside the effects over a 12-month horizon.

Results

At the 6-month follow-up the quit rates were 27.7% (n=23) and 25.6% (n=21) in the MyCourse and control group, respectively (OR = 0.47, 95%CI 0.03 to 7.86, *P* = .60). In both groups nicotine dependence scores were reduced at 12 months and the number of smoked cigarettes was reduced roughly by half. The number of cigarettes decreased more over time and the MyCourse group demonstrated a significantly greater reduction at 12-month follow-up (IRR = 0.87, 95%CI 0.76 to 1.00, *P* = .04). Intervention costs were estimated at US$ 193 per participant for the MyCourse group and at US$ 74 for the control group. Mean per-participant societal costs were US$ 25,329 (SD = 29,137) and US$ 21,836 (SD = 25,792), respectively. In the cost-utility analysis, the MyCourse intervention was not preferred over the control group when taking the societal perspective. With actual smoking behaviour as the outcome, the MyCourse group led to marginally better results per reduced pack-year against higher societal costs, with a mean incremental cost-effectiveness ratio (ICER) of US$ 52,067 (95%CI 32,515 to 81,346).

Conclusions

At 6 months, there was no evidence found for a differential effect on cessation rates; both groups led to approximately a quarter of the cancer survivors quitting smoking. Number of cigarettes smoked was reduced by 50% in both groups. At 12 months, the MyCourse intervention led to a greater reduction of number of smoked cigarettes albeit at higher costs compared to the control group. No evidence was found for a differential effect on QALYs.

Trial registration number: The trial was registered in The Netherlands Trial Register (NTR): NTR6011, https://www.trialregister.nl/trial/5434 on 1 September 2016.

INTRODUCTION

In cancer survivors, continued tobacco use is one of the most important risk factors for development of secondary cancers, iatrogenic effects of cancer treatment and cancer mortality [1]. The prevalence of smoking among cancer survivors is nonetheless considerable, estimated at 11.8% for US cancer survivors in 2018 [2], with rates that tend to be higher among women, younger cancer survivors [3, 4] and those with low health-related quality of life [5]. In The Netherlands, no difference in smoking prevalence was found between cancer survivors and non-cancer survivors after adjusting for socio-demographic variables [6].

Many cancer centres in the United States have not implemented tobacco treatment services [7], less than half of cancer care providers routinely discuss smoking cessation (SC) medication with cancer survivors [8], and ultimately delivery of effective SC support to cancer survivors is currently lacking [9, 10]. In Europe, the general picture is comparable [11]. At the same time, cancer survivors are generally receptive towards discussion of SC with their healthcare professionals [3, 12, 13]. Among head and neck cancer patients receiving SC counselling, 26% higher SC rates were observed compared to control groups in a meta-analysis of 3 randomised controlled trials (RCTs) and 3 cohort studies [14]. Distance-based SC support was also found to be more effective to reduce smoking than a range of control conditions [15]. While Nayan et al. reported that SC interventions delivered in the peri-operative period lead to higher quit rates in cancer survivors (OR = 2.31), but found no effect of SC interventions delivered in the cancer clinic [16]. Also, when taking into account biochemically validated smoking status, no significant effect of SC interventions was found in cancer survivors [17]. An integrated tobacco treatment program in a cancer setting showed that high abstinence rates of 45.8% at 6 months can be achieved, as demonstrated in a cohort study of 3,245 patients (593 had no cancer history) [18], but this was a highly intensive treatment program consisting of in-person and telephone sessions spanning 8-12 weeks, which not only provided behavioural counselling for SC, but also pharmacotherapy and treatment of related mental health conditions. Overall, there is a paucity of literature on SC interventions specifically in cancer survivors and the relevant literature shows conflicting outcomes.

Even fewer studies have evaluated the cost-effectiveness of digital SC interventions within the population of cancer survivors. Digital interventions may have the benefit of being scalable, easy accessible and providing a cost-effective way to support the growing number of cancer survivors [19]. A pilot study demonstrated good acceptability of a digital SC intervention among cancer survivors [20]. A recent meta-analysis [15] indicated that few SC interventions for cancer survivors were digital interventions (2 out of 10), with most being delivered over the telephone. As yet, it is unclear how effective and cost-effective existing digital SC interventions over the internet become when specifically tailored to cancer survivors.

In this context, it was deemed timely and appropriate to launch a new study evaluating the effectiveness and cost-effectiveness of a recently developed digital intervention with minimal guidance aimed at supporting cancer survivors to quit smoking: MyCourse – Quit Smoking (in Dutch: MijnKoers – Stoppen met Roken). Details of how the intervention was developed are provided elsewhere [21]. In this study we aimed to answer the following research questions:

1. Is the digital interactive SC intervention "MyCourse – Quit Smoking" more effective than a web-based SC brochure to improve smoking cessation rates?
2. Is the digital interactive SC intervention "MyCourse – Quit Smoking" more cost-effective than a web-based SC brochure in terms of incremental costs per reduced pack year and incremental costs per quality adjusted life year (QALY) gained?

METHODS

Design

The effectiveness, cost-effectiveness and cost-utility of a digital SC intervention for cancer survivors was evaluated in an individually randomised controlled trial (RCT) with two parallel arms. The trial was conducted in The Netherlands between 2016 and 2019. The first inclusion was on November 4, 2016 and last inclusion on September 15, 2018; the last follow-up data was collected on the 24th of September, 2019. The study was prospectively registered in the Netherlands Trial register (NTR): NTR6011. For an extensive description of the study protocol see [21]. This study was part of a set of two separate RCTs on interventions for SC and alcohol moderation, both targeting cancer survivors. Results of the RCT on the alcohol moderation intervention (MyCourse – Moderate Drinking) will be published separately. Ethical approval was obtained from an accredited medical research and ethics committee in The Netherlands (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. NL55921.101.16).

Participants and recruitment

A dedicated website was created where participants could inform themselves about the study and apply for participation. Applicants for the trial were eligible when 18 years or older, diagnosed with any form of cancer in the past 10 years, had a PC/laptop and internet connection at home, had the ability and intention to participate in the 12-month study, smoked 5 or more cigarettes per day in the past 7 days, and had the intention to quit smoking cigarettes. Those who had insufficient mastery of the Dutch language, were pregnant or who self-reported suicidal ideation, acute psychosis, severe alcohol dependence, dementia or severe depression, were excluded. These criteria were assessed using the web-based screening questionnaire on the website. The same screening questionnaire was used for both trials to evaluate the SC and alcohol moderation intervention [21]. Some people were eligible for both the current SC trial and for the alcohol moderation trial; they were offered to participate in one trial of their own choosing. None of the participants were allowed to participate in both trials simultaneously.

Recruitment was conducted through web-based and offline strategies. Targeted web-based (social) media and search engine advertisements pointed to the website and web-based screening questionnaire. SC clinics, oncology departments and meeting centres for cancer survivors were contacted and offered promotional material (flyers, posters) to help refer cancer survivors to the website.

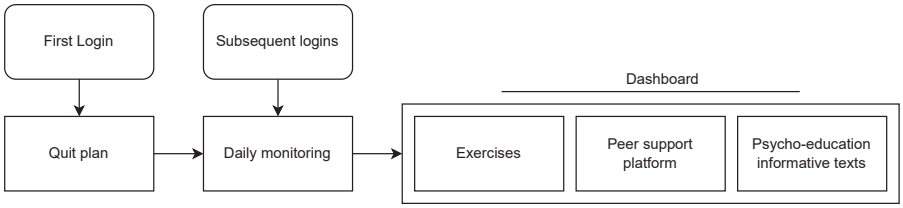
Procedure

After completing the screening questionnaire on the study's website, applicants were informed by a computer-generated email about their eligibility for study participation. Those eligible were sent an invitation email containing patient information, the informed consent form and a link to register. They then had 30 days to decide on their participation, during this time they could contact the research team or an independent physician with questions. Once the informed consent form was digitally signed, they could fill in the baseline questionnaire. Immediately after completion of the baseline measurement, participants were allocated to either the intervention or the control group arm in a 1:1 ratio through adaptive randomisation (minimisation of baseline imbalance with regard to age, sex and education level) performed automatically by a server-sided PHP script using a Mersenne twister random number generator. Participants received an email confirming their allocation and containing their username and instructions on how to log on. They were not blinded to the study group allocation. At 3, 6 and 12 months post randomisation, participants received a link to the web-based questionnaire by email. Non-responders received up to three reminder emails and, in case of continued non-response, were contacted by telephone. For each completed follow-up assessment, they were reimbursed approximately US$30. As this is was a pragmatic randomised controlled trial; in both groups, patients were allowed to use additional support (e.g., nicotine replacement therapy) if they felt they needed it.

Intervention

MyCourse – Quit Smoking is a newly developed, minimally-guided, digital intervention aimed at supporting SC in cancer survivors, based on well-established therapeutic approaches: motivational interviewing, cognitive behavioural therapy and acceptance and commitment therapy. These approaches have been incorporated into effective SC interventions in the general population [22–24]. Cancer survivors and professionals in eHealth, oncology and SC were involved throughout the development process. The intervention was accessible through PC, tablet and smartphone. At first login participants were guided in setting up a quit plan including a quit date, after which they gained access to 13 exercises, a web-based diary for self-monitoring of tobacco use and contextual cues, information on SC and cancer, and a peer support platform (see Figure 1 and Appendix 1). Participants could choose to use the intervention whenever they wanted for the duration of the study, but were encouraged to log in daily for at least four weeks. Elsewhere, we provide a more extensive description of the intervention and its development [21].

Figure 1. Intervention flow chart (adapted from [21])



Control group

Participants in the control group received access to a noninteractive web-based information brochure on the risks of smoking and tips on how to quit smoking, which they could access whenever they wanted by logging into the website. It contained both general SC information and information specifically relevant to cancer survivors. However, it did not contain any of the interactive elements of the MyCourse intervention.

Additional support

Participants in both groups were free to seek additional help if needed and were referred to the national SC information line (www.rokeninfo.nl) for more information. Use of additional support was retrospectively assessed at follow-up. At the end of the study, at 12 months post-randomisation, control group participants also received access to the digital intervention MyCourse – Quit Smoking.

Measures

Baseline

Socio-demographic characteristics and type of cancer were assessed. Tobacco use was assessed by using Timeline Follow-back (TLFB) self-reports [25] for the number of cigarettes smoked in the past 7 days. Nicotine dependence was assessed by the Fagerström Test for Nicotine Dependence (FTND) [26], a 6-item questionnaire. In participants reporting alcohol use, problematic alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT) [27], a 10-item questionnaire. The Marlowe-Crowne Social Desirability Scale (MCSDS) was used to assess reliability of the self-reported questionnaire data [28]. Quality adjusted life years (QALYs) were assessed by the 5-level EuroQol (EQ-5D-5L) [29]. In addition, the Medical Outcomes Study Short Form Survey-36 (MOS SF-36) was administered to calculate the Short Form 6-dimension (SF-6D) quality of life measure [30] using Brazier's algorithm [31].

Follow-up measurements

At all follow-up measurements we assessed tobacco and alcohol use by TLFB self-reports, nicotine dependence by FTND, productivity and healthcare costs, quality adjusted life years (QALYs) gained using EQ-5D-5L and MOS SF-36, and use of other SC support and e-cigarettes. Intervention use variables (eg, number of logins, use of major content elements etc.) were collected throughout the duration of the study. At 3 month follow-up treatment, satisfaction was assessed using the German adapted Client Satisfaction Questionnaire: Fragebogen zur Messung der Patientenzufriedenheit; ZUF-8, which was translated into Dutch [32].

Primary and secondary outcome measures

The primary predefined endpoint was 7-day smoking abstinence at 6-month follow-up, measured by TLFB self-reports. Those who reported not smoking at all in the past 7 days were considered abstinent smokers (yes/no). Secondary measures included number of smoked cigarettes in the past 7 days, nicotine dependence as measured by FTND (range 0-10), treatment satisfaction as measured by ZUF-8 (range 8-32), healthcare costs, productivity loss, and quality adjusted life years (QALYs).

Costs

Costs were calculated from a societal perspective for the year 2019. Intervention costs included depreciation costs (the estimated loss of value of an interactive website, as it needs to be updated regularly to keep up with technological advancements and prevent safety issues), costs for hosting the website, technical support and recruitment costs (which consisted of both advertising costs in on- and offline media as well as costs of printing promotional material) and these were allocated evenly to all participants regardless of intervention usage. Recruitment costs were included as they were considered an essential part of the intervention and control condition. Healthcare costs were calculated by multiplying all reported contacts with health services with the standard unit cost prices for the Netherlands [33]. Health service costs stemmed from contacts with specialised somatic and mental healthcare, plus patients' out of pocket costs for homecare, but travel costs were not included because in both groups the interventions were delivered over the Internet. Other healthcare costs included appointments for physiotherapy, alternative medicine and social work. Medication costs were valued by multiplying the reported dose of that drug with unit cost price [34]. Productivity loss included costs from absenteeism and presenteeism, calculated according to the friction cost method, meaning productivity losses were limited to a maximum of 85 days after which production losses cease to exist because the sick employee has been replaced by another and using an elasticity factor of 0.8 because there is not a strict 1 : 1 relation between days not worked and productivity losses. Cost-data related to healthcare use and productivity loss were assessed using the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [35]. Cumulative societal costs over the entire follow-up period of 12 months were calculated as the

sum of healthcare costs and productivity losses. Costs were converted from euros to US dollars using purchasing power parities (PPPs), for the reference year 2019.

Sample size

A study on an SC intervention among cancer survivors found a quit-rate of 30% in the active SC intervention group vs 15% in the SC control group, translating to a relative risk (RR) of 2.14 [36]. A pilot trial of an acceptance and commitment theory web-based SC intervention found a 23% quit rate in the experimental arm vs a 10% quit rate in the control arm, translating to RR = 2.20 [24]. Based on the average of these RRs, a RR = 2.1 was expected, translating into a 21% quit rate in the experimental arm, assuming a 10% quit rate in the control arm at 6-month follow-up. Based on the conventional statistical significance level (a ≤ 0.05), RR = 2.1 at 6-month follow-up, 204 participants would yield a power of .83 for one-sided tests or a power of .74 for two-sided tests.

Statistical Analyses

Imputation of missing data

All primary and secondary outcome measures were analysed in accordance with the intention-to-treat (ITT) principle, except for the ZUF-8 (treatment satisfaction). To that end, missing data for primary and secondary outcome measures, and costs, were imputed using the predictive mean matching method from the mice package in R [37]. Responses to ZUF-8 were not imputed. For the two deceased participants, smoking status and number of cigarettes smoked were left missing, and the quality of life (EQ-5D-5L) score and costs were set to 0.

Effect evaluation

Tobacco abstinence (binary yes/no outcome) was analysed using a Generalized Linear Mixed Model (GLMM) with a binomial distribution and log link function. While imputation of missing values is not always deemed necessary when running a GLMM, imputation of missing values before running a GLMM allowed us to consider all variables that could have impacted dropout, and not only the variables within a specific model. The number of cigarettes smoked (count data 0, 1, …, N) was analysed using a GLMM with a log link function and negative binomial distribution [38]. Included covariates were the minimized variables (gender, age and education) and the MCSDS (social desirability of responses). Model estimates, ORs, IRRs or Cohen d, 95% confidence intervals (CIs) and *P*-values are reported. The effect of time on number of cigarettes was explicated with an F-test. Differences between intervention and control group on FTND nicotine dependence and ZUF-8 patient satisfaction scores were analysed using a Linear Mixed Model for the Gaussian distribution with identity as the link function; estimates, 95% confidence intervals (CIs) and *P*-values are reported.

Cost-effectiveness analyses

An economic evaluation was conducted alongside this RCT following the approach by Drummond et al [39] and in concordance with the Consolidated Health Economic Evaluation Reporting Standards statement [40]. QALYs over the entire follow-up period were computed using the Dutch tariff (utility weights) [41] using the area under the curve (AUC) method, i.e. linear interpolation for cumulating the cost over the 12 months follow-up period. The incremental cost-effectiveness ratio (ICER) was calculated as follows: ICER = $(C_1 – C_0)/ (E_1 – E_0)$, where C are costs, E effects, and subscripts (1 and 0) refer to the MyCourse and control groups, respectively. We generated 2500 replicate samples by bootstrap and estimated corresponding incremental costs and effects for each replicate sample, which were then plotted on a cost-effectiveness plane. In addition to the ICER per QALY gained, the ICER per reduced pack-year was also calculated. Pack-years were calculated by multiplying cigarettes smoked in the past week by 52 (weeks in a year) and dividing by 20 (cigarettes per pack) and 365 (days in a year). We calculated ICERs from the following four perspectives: societal, healthcare, productivity loss and intervention cost-only. Cost-effectiveness acceptability curves (CEACs) were graphed to assess the likelihood that the intervention was deemed to be cost-effective given a series of willingness-to-pay (WTP) ceilings for gaining one quality adjusted life year (QALY).

Sensitivity analyses

The negative binomial and binomial analyses on the mice-imputed data constituted the main analyses.

We conducted several sensitivity analyses for the effectiveness and incremental cost-effectiveness analyses using QALYs based on the SF-6D (instead of the EQ-5D-5L), Winsorizing costs outliers, using the Amelia-2 package instead of the mice-package for imputations, considering a gradual decline in pack-years, and using different statistical models (see Appendix 1).

RESULTS

Sample characteristics

The participant flow and retention rates are presented in Figure 2. Of the 2,192 ineligible people, 1,684 had no diagnosis of cancer in the past 10 years. Of the 475 eligible cancer survivors, 268 (56.4%) declined to participate, 9 of whom chose to participate in our parallel RCT on MyCourse for alcohol moderation, and another 42 (18,9%) cancer survivors did not complete the baseline questionnaire and were therefore not randomised. Socio-demographic and other characteristics are reported in Table 1. Participants' mean age was 54.2 years (SD = 11.2), 17.6% (29/165) was male, approximately half was married or living together (93/165, 56.4%) and 30.3% (50/165) had a lower education level. On average, participants had smoked for 34.5 years (SD = 12.0) and smoked 100 cigarettes per week (SD = 51.2). Three participants quit smoking between screening and

completing the baseline questionnaire (see Table 2). Breast cancer (45.4%, 75/165), lung cancer (13.9%, 23/165), uterus cancer (11.5%, 19/165), and head and neck cancer (10.9%, 18/165) were most frequently reported. There was no difference in the proportion of missing data between groups at any of the time points ($\chi^2 = 0.09$, df = 1, $P = .77$; see Appendix 2).

Figure 2. CONSORT flowchart

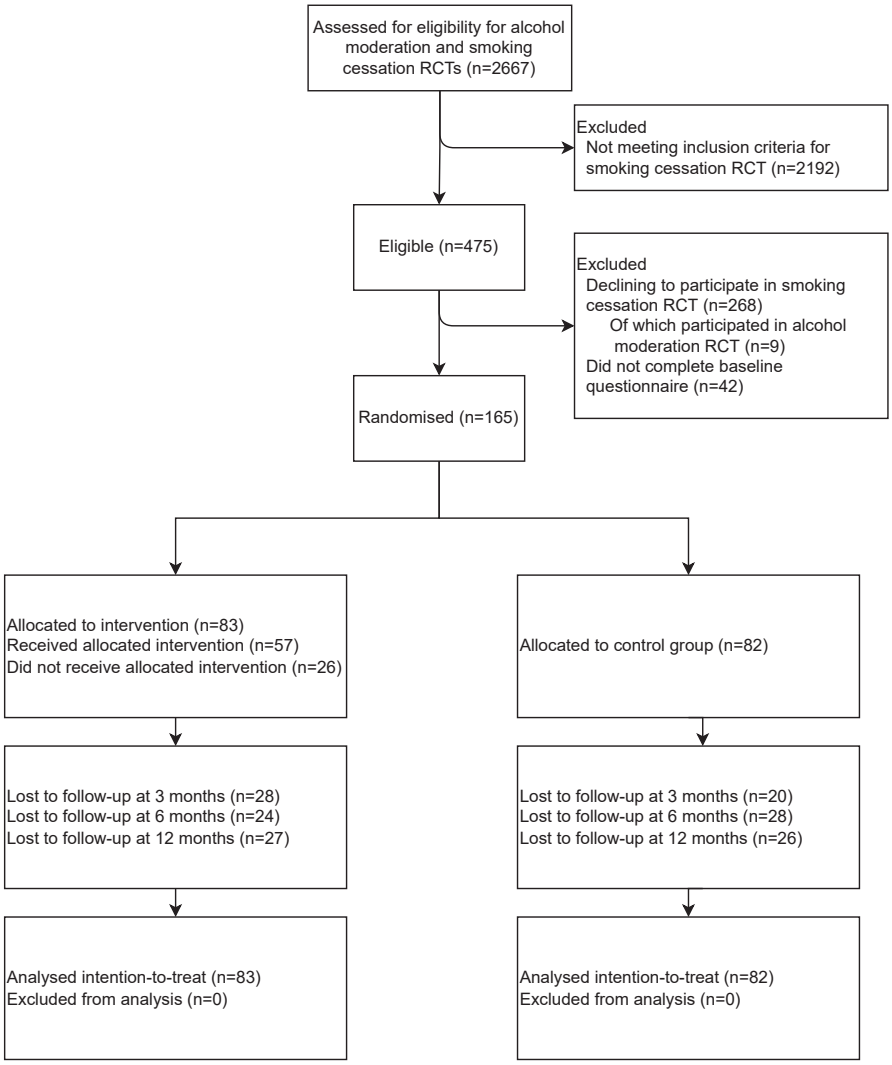


Table 1. Baseline characteristics[a]

	MyCourse (n = 83), n (%)	Control (n = 82), n (%)	Total (N = 165), n (%)
Gender			
Women	70 (84.3)	66 (80.5)	136 (82.4)
Men	13 (15.7)	16 (19.5)	29 (17.6)
Age, mean (SD)	55.0 (12.1)	53.3 (10.3)	54.2 (11.2)
Education			
Higher level	25 (30.1)	19 (23.2)	44 (26.7)
Mid-level	33 (39.8)	38 (46.3)	71 (43.0)
Lower level	25 (30.1)	25 (30.5)	50 (30.3)
Marital status			
Married or living together	47 (56.7)	46 (56.1)	93 (56.4)
Unmarried or living alone	15 (18.1)	11 (13.4)	26 (15.8)
Divorced	16 (19.3)	20 (24.4)	36 (21.8)
Widowed	5 (6.0)	5 (6.1)	10 (6.1)
Smoking behaviour			
Years smoked, mean (SD)	34.4 (11.8)	34.6 (12.2)	34.5 (12.0)
Number of cigarettes in past 7 days, mean (SD)	101.8 (54.3)	98.2 (48.2)	100 (51.2)
FTND, mean (SD)	4.9 (2.4)	4.9 (2.3)	4.9 (2.4)
Drinking behaviour			
Drank alcohol in last month	55 (66.3)	55 (67.1)	110 (66.7)
Number of drinks in past 7 days, mean (SD)	6.9 (13.1)	5.6 (8.7)	6.2 (11.2)
AUDIT[b], mean (SD)	3.7 (5.1)	3.6 (4.2)	3.6 (4.7)
Cancer diagnosis			
Breast	42 (50.6)	33 (40.2)	75 (45.4)
Lung	14 (16.9)	9 (11.0)	23 (13.9)
Uterus	7 (8.4)	12 (14.6)	19 (11.5)
Head and neck	10 (12.0)	8 (9.8)	18 (10.9)
Colon	5 (6.0)	5 (6.1)	10 (6.0)
Other (including bladder, lymphatic, melanoma, skin, kidney, prostate etc.)	5 (6.0)	26 (31.7)	20 (12.1)

Note. [a] Percentages may not add up to 100 due to rounding.
[b] AUDIT: Alcohol Use Disorders Identification Test.

Treatment uptake and satisfaction

Overall satisfaction with the SC intervention was highest in the MyCourse group (mean = 21.4, SD = 4.6) compared to the control group (mean = 17.3, SD = 6.1, d = .77, t = 4.13, *P* < .001). See Appendix 2. Majority of participants in the MyCourse group logged in at least once (68.7%, 57/83). Number of times participants logged in was skewed, with an average of 20.0 (SD = 61.2) and median of 3 (range 0-384). Time between the first and last login in those who logged in at least once was on average 105.2 days (SD = 157.5, median = 24). Most reported SC support in addition to MyCourse at 6-month follow-up was: nicotine replacement therapy (control group: 25/82, 30.5%, MyCourse group: 14/83, 16.9%) and contact with a healthcare professional (control group: 7/82, 8.5%, MyCourse group: 3/83, 3.6%). Use of nicotine replacement therapy was reported more often (18.1% vs 30.5% at 12 months) in the control group than in the MyCourse group (*P* = .02).

Adverse events

Two deaths occurred in the MyCourse group over the course of the study period, which was reported to the medical research and ethics committee. Cause of death was deemed to be unrelated to the study. No other adverse events were observed.

Incremental effects

Primary outcome

At 6-month follow-up, 27.7% (23/83) of smokers had quit smoking in the MyCourse group versus 25.6% (21/82) in the control group (see Table 2). No difference in 7-day abstinence was found between the two groups (OR_{adj} = 0.47 95%CI 0.03 to 7.86, *P* = .60) when controlling for social desirability, baseline number of cigarettes used in the last week, gender, age and education.

Secondary outcomes

Table 2 and Figure 3 present the effect estimates on the secondary outcomes. In brief, the number of cigarettes smoked in the past week was significantly reduced at all follow-ups and in both groups compared to baseline (F = 51.5, *P* < .001) (see Table 2 and Figure 3). At 12-month follow-up, number of cigarettes was reduced by about half in both the MyCourse group, showing an average reduction of 57 cigarettes (56%), and in the control group, showing an average reduction of 48 cigarettes (49%) (see Table 2 and Figure 4). At 12-month follow-up the reduction of number of cigarettes smoked was significantly greater in the MyCourse group than in the control group (IRR_{adj} = 0.87, 95%CI 0.76 to 1.00, *P* = .04). At 3 and 6-month follow-up the difference in number of cigarettes between groups was not significant.

FTND scores were significantly lower at all follow-ups in both groups compared to baseline scores, while the time x condition interaction was not significant (Cohen d = 0.03 95%CI –0.27 to 0.34, *P* = .95) indicating no significant difference between the groups over time.

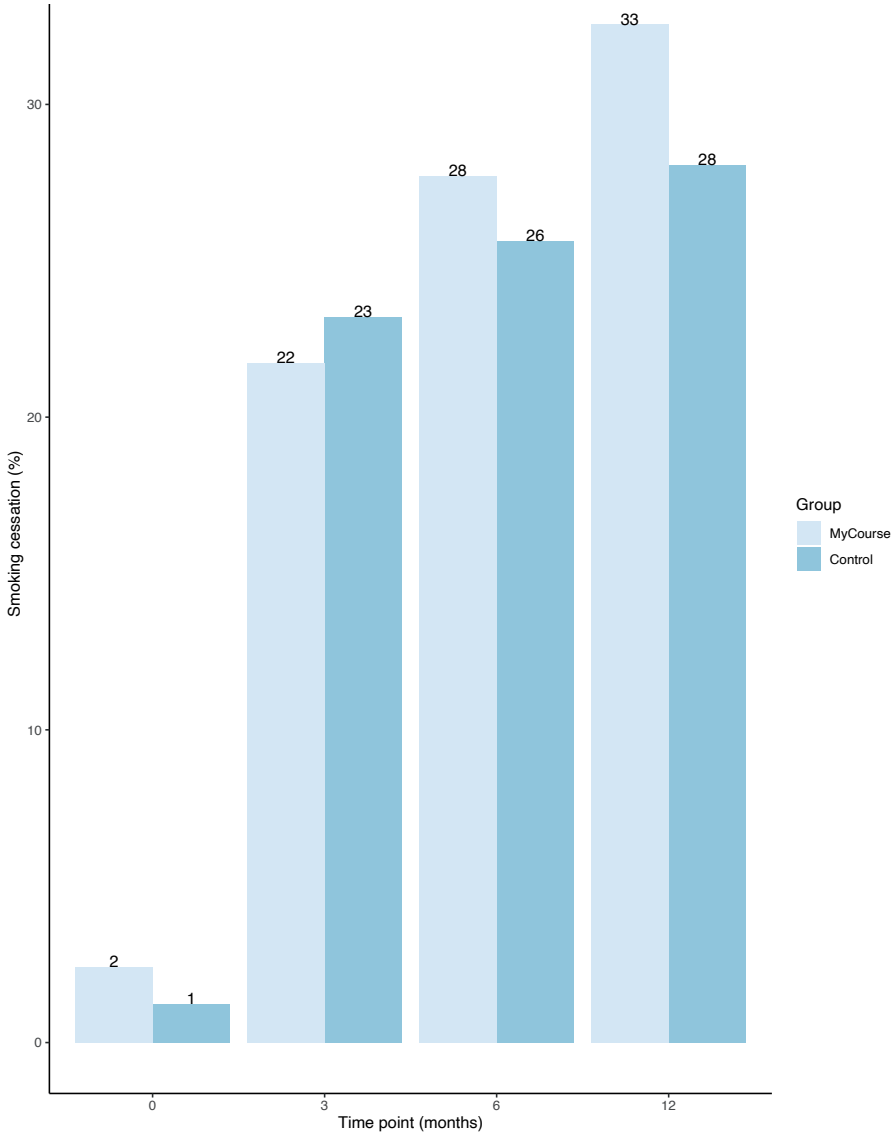
Mean EQ-5D-5L QALYs gained in the intervention group was 0.75 (SD = 0.18), and in the control group 0.78 (SD = 0.15). There was no significant effect of treatment on quality of life based on EQ-5D-5L scores (t =-1.1, *P* = .26).

Table 2. Smoking behaviour outcomes and treatment effects

Variable	MyCourse (n=83)	Control (n=82)	Effect size (95% CI)
Cessation, n (%)[a]			
Baseline	2 (2.4)	1 (1.2)	-
3 months	18 (21.7)	19 (23.2)	$OR_{adjusted}$ = 0.33 (0.02 to 5.44)
6 months	23 (27.7)	21 (25.6)	$OR_{adjusted}$ = 0.47 (0.03 to 7.86)
12 months	27 (32.6)	23 (28.1)	$OR_{adjusted}$ = 0.58 (0.03 to 9.78)
Number of cigarettes, mean (SD)[b]			
Baseline	101.8 (54.3)	98.2 (48.2)	-
3 months	54.3 (51.1)	54.2 (48.2)	$IRR_{adjusted}$ = 0.95 (0.85 to 1.06)
6 months	50.5 (50.5)	50.1 (47.5)	$IRR_{adjusted}$ = 0.96 (0.85 to 1.08)
12 months	45.4 (50.9)	49.6 (44.9)	$IRR_{adjusted}$ = 0.87 (0.76 to 1.00)[d]
FTND, mean (SD)[c]			
Baseline	4.9 (2.4)	4.9 (2.3)	-
3 months	2.9 (2.5)	2.8 (2.5)	Cohen d = 0.03 (−0.27 to 0.34)
6 months	2.6 (2.6)	2.8 (2.6)	Cohen d = 0.07 (−0.23 to 0.38)
12 months	2.4 (2.6)	2.7 (2.5)	Cohen d = 0.13 (−0.18 to 0.43)

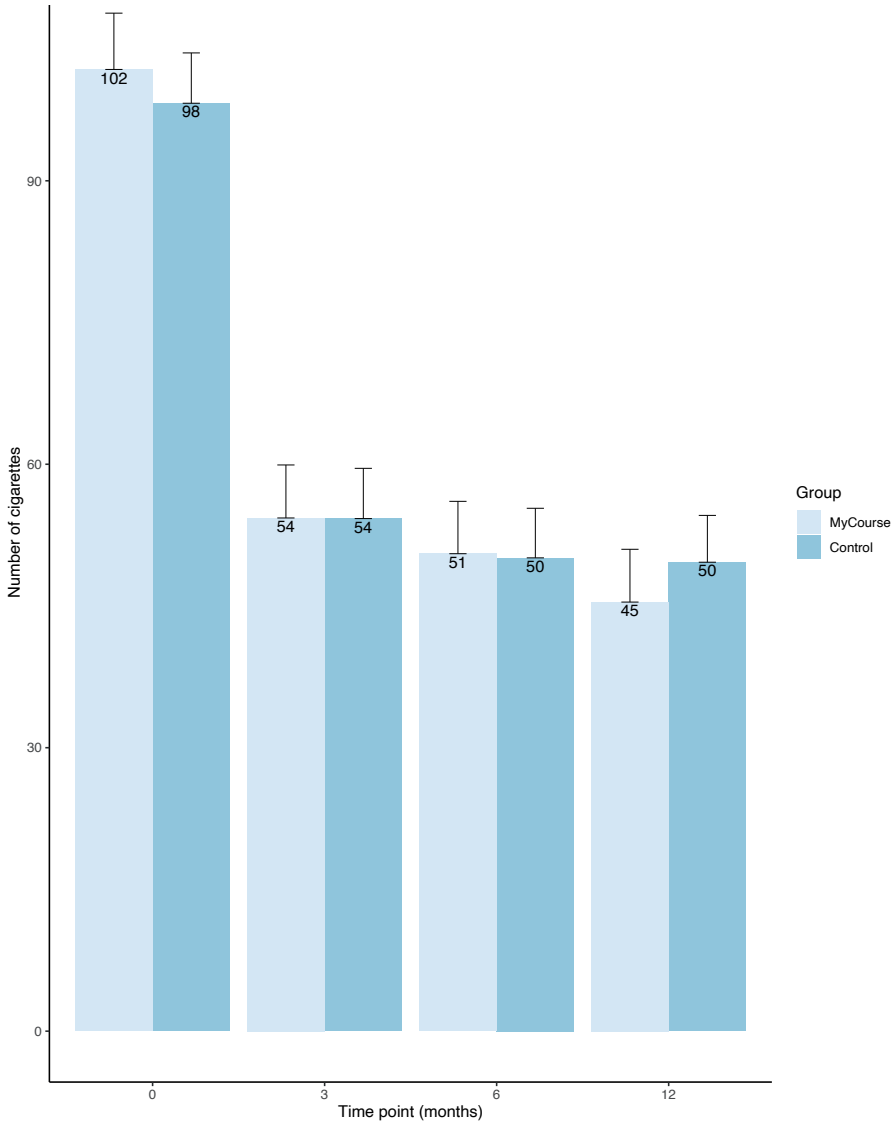
Note. Missing data were imputed. A total of three participants quitted smoking in the period between screening and completing the baseline questionnaire.
[a] Adjusted coefficients are based on a binomial mixed model with random intercept in which the outcome measure at follow-up is regressed on baseline number of cigarettes, covariates and condition.
[b] Adjusted coefficients are based on a negative binomial mixed model with random intercept in which the outcome measure at follow-up is regressed on baseline number of cigarettes, covariates and condition.
[c] Adjusted coefficients are based on a linear mixed model with random intercept in which the outcome measure at follow-up is regressed on baseline number of cigarettes, covariates and condition.
[d] *P*-value < .05 (*P* = .04).

Figure 3. Percentage of quitters in both groups at baseline and during the course of the study



Note. A total of three participants quitted smoking in the period between screening and completing the baseline questionnaire.

Figure 4. Mean number of cigarettes smoked in both groups at baseline and during the course of the study, including standard errors



Note. Error bars show standard errors of the mean.

Incremental costs

Table 3 presents the costs per group and the incremental costs (cost difference between MyCourse and control group) per cost item. The intervention costs were estimated at US$ 193 per participant in the MyCourse group and US$ 74 per participant in the control group. Average healthcare costs accumulated over the full 12 months follow-up time were US$ 14,416 (SD = 20,604) per participant in the MyCourse group and US$ 12,950 (SD = 17,704) per participant in the control group resulting in incremental healthcare costs of US$ 1,466 (SD = 27,165). Costs due to productivity losses were mainly driven by absenteeism at US$ 10,444 (SD = 17,277) in the MyCourse group and US$ 8,145 (SD = 15,750) in the control group, with high within-group variance. Incremental productivity costs per participant were on average US$ 1,908 (SD = 23,490). The average cumulative societal costs were US$ 3,493 (SD = 38,913) higher in the MyCourse group compared to the control group. See Table 3 for a detailed break-down of the main cost items and corresponding standard deviations.

Table 3. Mean cumulative costs (in US$) by group and incremental costs

Cost item	MyCourse (n = 83)		Control (n = 82)		Incremental costs[a] (n = 83)	
	Mean (US$)	SD	Mean (US$)	SD	Mean (US$)	SD
Healthcare costs	14416	20604	12950	17704	1466	27165
Specialized somatic	8418	11792	7180	10674	1238	15906
Specialized psychiatric	2151	10143	1380	5441	771	11510
Patient and family costs	1310	10034	1954	9252	−644	13648
Other	1533	2671	1411	2518	122	3671
Medication	1358	3901	1023	3254	335	5080
Productivity loss	10720	17345	8812	15841	1908	23490
Presenteeism	231	733	332	864	−101	1133
Absenteeism	10444	17277	8145	15750	2299	23379
Unpaid work	451	1048	474	1007	−23	1453
Intervention costs	193	0	74	0	119	0
Total societal costs	25329	29137	21836	25792	3493	38913

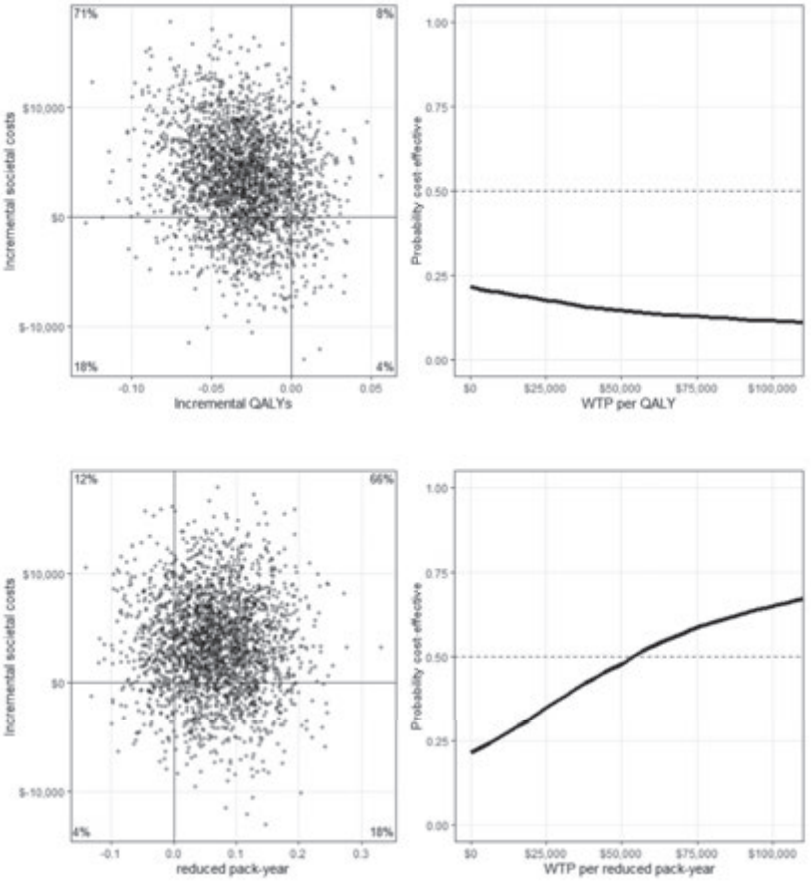
Note. [a] Costs in the MyCourse group minus costs in the control group.

Cost-utility

Participants in the MyCourse group gained fewer QALYs than participants in the control group (0.75 vs 0.78). In addition, the societal costs in the MyCourse group were higher than those in the control group (US$ 25,329 vs US$ 21,836). In other words, fewer QALYs were gained against

higher costs, which rendered the control group as the preferred option as seen from a cost-effectiveness viewpoint. The cost-effectiveness plane in Figure 5 shows there is a 71% likelihood that MyCourse is dominated by the control group.

Figure 5. Cost-effectiveness planes and cost-effectiveness acceptability curves in dollars



Note. Each quadrant in the cost-effectiveness planes represents a different association between the incremental costs (y-axis) and the incremental effects (x-axis) of the MyCourse group compared to the control group. When ICERs fall in the upper-right quadrant, this represents more effect at higher costs. When ICERs fall in the upper-left quadrant, this represents less effect at higher costs, meaning the MyCourse group is dominated by the control group. ICERs in the lower-right quadrant represent more effect at lower costs: the dominant quadrant. ICERs in the lower-left quadrant represent less effect at lower costs. QALY: quality-adjusted life-year. WTP: willingness to pay.

Cost-effectiveness

Participants in the MyCourse group reduced pack-years more compared to the control group (0.41 vs 0.34) against higher societal costs (US$ 25,329 vs US$ 21,836). Comparing the difference in total societal costs to the difference in pack-years yielded an ICER of US$ 52,067 per reduced pack-year (95%CI US$ 32,515 to US$ 81,346). There is a 66% chance that the intervention leads to more reduced pack-years, at a higher cost (see Figure 5). The CEAC based on the societal cost perspective presented in Figure 5 indicates that the intervention will be preferred over the control group when the willingness to pay per reduced pack-years is more than US$ 50,000. From an intervention-cost only perspective ICER per pack-year was calculated to be US$ 1,772 (95%CI US$ 1,384 to US$ 2,502). See Table 4 for a breakdown by perspective.

Table 4. Incremental cost-effectiveness ratios between baseline and 12-month follow-up[a]

Perspective	Incremental costs per reduced pack-year (95% CI)		
	Mean (US$)	Lower CI	Upper CI
Healthcare perspective	21851	9179	38920
Productivity loss perspective	28444	16832	44749
Intervention cost-only perspective	1772	1384	2502
Societal perspective	52067	32515	81346

Note. [a] The incremental cost-effectiveness ratios were calculated as follows: $(C_1–C_0)$ / $(E_1–E_0)$, where C refers to costs, E refers to effects, and the subscripts 0 and 1 refer to the experimental and control arms, respectively.

Sensitivity analyses

Sensitivity analysis on the Amelia 2-imputed data (OR_{adj} = 3.16, 95%CI 0.17 to 57.80, *P* = .44) and completers only (i.e., those who completed the questionnaires, without imputation) (OR_{adj} = 2.89, 95%CI 0.16 to 53.18, *P* = .47) showed similar results on the effect of treatment group on tobacco abstinence rates. The Poisson model with correction for overdispersion showed similar results on the effect of treatment on cigarettes smoked at 12 month follow-up (B_{adj} = –0.c55, 95%CI –1.05 to –0.04, *P* = .03). Sensitivity analyses on the Amelia-2 imputed data also showed a large effect of time, but found no effect of treatment group at 12-month follow-up (IRR_{adj} = 0.997, 95%CI 0.82 to 1.22, *P* = .97). The completers only sensitivity analysis, showed a greater reduction of number of cigarettes in the control group at 6 months (IRR_{adj} = 1.08, 95%CI 1.01 to 1.15, *P* = .03), but at 12 months a greater reduction in the MyCourse group (IRR_{adj} = 0.88, 95%CI 0.82 to 0.94, *P* < .001). For number of cigarettes smoked, social desirability score was a significant predictor in the Poisson model, but not in the negative binomial model. When QALYs were based on SF-6D scores, results of the economic evaluation remained similar.

When Winsorization of extreme costs was applied at the 95th percentile, the cost-effectiveness planes and CEAC curves remained similar, but ICER per pack-year was lower at US$ 31,342 (95%CI US$ 17,912 to US$ 50,007). When the gradual decline in number of pack-years was accounted for, ICER per pack-year was higher (US$ 68,267, 95%CI 42,293 to 111,044) and the cost-effectiveness planes comparable, see Appendix 3. All in all, the sensitivity analyses attested to the robustness of the findings in the main analysis.

DISCUSSION

Principal findings

This study evaluated the (cost-)effectiveness of MyCourse, a digital smoking cessation (SC) intervention tailored to cancer survivors, versus a web-based noninteractive information brochure. In the MyCourse group, 27.7% of the participants quit smoking after six months. In the control group, 25.6% quit smoking. The number of cigarettes smoked in the past 7 days was reduced by over half in both groups. At 12 months follow-up, MyCourse participants showed significantly larger reductions in the number of smoked cigarettes than participants in the control group. However, no statistically significant difference was found in SC rates between the intervention group and control group. Nicotine dependence as measured by FTND was also significantly reduced at all time points in both groups, but no difference was found between groups. Participants in the MyCourse group had significantly higher treatment satisfaction scores than those in the control group. From a societal perspective, the MyCourse intervention was dominated by the control group in the cost-utility analysis. In the cost-effectiveness analysis, MyCourse led to marginally better results against higher costs, with a mean ICER of US$ 52,067 per reduced pack-year. Cessation rates were high in the MyCourse and control groups.

Wider context

We found no difference in SC rates between the MyCourse and control group. In previous literature, digital SC interventions have shown superior effectiveness over non-active control groups (including both usual care and printed self-help materials), among the general population as well as other target groups [42, 43]. There is evidence that among cancer survivors, distance-based SC interventions (including digital interventions) also show greater effectiveness than control groups [15]. At the same time, cessation rates in the MyCourse group found in the current study are comparable with cessation rates found in two previous studies on digital SC interventions for (childhood) cancer survivors [20, 44], but cessation rates in our control group were higher than in these previous studies.

Our study did not find an effect on QALYs; a longer follow-up period may be necessary to detect improvements in quality of life among cancer survivors, as their quality of life may be more directly influenced by factors pertaining to the cancer diagnosis [45]. There are also some differences in the ICERs we found compared to previous literature. A systematic review in the Netherlands

showed greater cost-utility (< € 20 000 per QALY per year) of intensive SC counselling and pharmacotherapy over care as usual in another patient population: COPD patients [46]. A similar study on a digital SC intervention among the general population showed an ICER of about € 3000 per abstinent smoker [47]. The large ICER per reduced pack-year in the current study can partly be explained by the relatively small difference in effect on reduced number of cigarettes between the intervention and control group and the high healthcare and productivity costs in this population. Benefits or costs due to changes in tax-revenue are not included in a cost-effectiveness analysis, but could be a topic of interest in social cost-benefit analyses.

Cessation rates in our control group were higher than in the studies referenced for the power-analysis. This might be due to differences in target groups between the studies: we studied cancer survivors, whereas the referenced studies either focused on the general population [24] or cancer survivors suffering from comorbid problem drinking and/or depression [36]. The similar effect on SC of the MyCourse and the control group might be due to several factors. Notably, twice as many participants in the control group reported use of nicotine replacement therapy, suggesting this might have influenced SC rates. Control group participants may have had increased need for additional support. As this was a pragmatic trial, both groups were provided with the contact details of a free national telephone helpline (in Dutch: Rokeninfo-lijn), which could help find participants additional support if the current intervention was deemed insufficient. Furthermore, to recruit participants, a dedicated website and social media campaign was in place, aimed at informing cancer survivors of the short-term benefits of SC after a cancer diagnosis, emphasizing an accepting tone to reduce possible feelings of guilt and ultimately guiding them to participate in the study. Other contributing factors might have been related to the fact that over the course of the study period, participants have received multiple reminder emails and telephone calls from the researchers to fill out the survey at the respective follow-up measurement waves. Although these calls were kept as short as possible, some participants might have experienced those as part of the intervention, feeling supported by them, which could have influenced SC rates. To summarize, the low-threshold provision of psychoeducation, offered in an accepting manner and encouragement to seek support provided in recruitment materials and the information brochure, repeated reminders and increased use of nicotine replacement therapy may have been sufficient to support many participants in their SC efforts. This should be evaluated in future research.

To considerably increase SC rates among cancer survivors compared to control groups, intensive and well-implemented programs might be needed. It is possible that cancer survivors require digital interventions with more guidance, as suggested by a meta-analysis which found that only nurse-delivered SC interventions moderated effectiveness among cancer survivors [17]. Guidance might also help improve adherence, as the median number of logins (median = 3) was lower than the recommended (almost) daily use of the intervention over the course of four weeks. The period between first and last login did come close to usage as intended with a median of 24 days.

Strengths and limitations

The findings of this study should be interpreted in light of its strengths and limitations. A strength of this study is that the evaluation was conducted in a real-world setting: recruitment was done both through offline and web-based channels which will also be used for the intervention's future implementation. The difference in the number of people who completed the screening questionnaire and those who were eligible might seem to show a large selection, but this could be due to our web-based recruitment strategies which attracted many interested people with no history of cancer to the website as well. This study recruited cancer survivors from a range of cancer types. Several sensitivity analyses have been used to corroborate the findings. Missing data were dealt with using multiple imputation We attempted to control for possible social desirability of reported smoking behaviour by including MCSDS-scores in our models.. Limitations include that participants were not blinded to their intervention allocation. Majority of the participants were women (82.6%), therefore, these results might not be generalizable to men. Self-report smoking status was not biochemically verified in this study, and although self-reports in the general population generally show good validity, two studies among cancer survivors found falsification rates of 48% [48] and 80% [49], while a third (substantially smaller study) among thoracic cancer survivors showed relatively good agreement between self-reported and biochemically validated smoking status [50]. Adherence was a limitation in this study and might have influenced effects in the MyCourse group. Effects were limited in size and our final sample size was somewhat lower than anticipated. As for any RCT, it remains possible that a true effect was not found in this study (Type II-error). Both the main outcome measure (SC during a single week) and the length of follow-up time (a single year) may have masked the possible longer-term impact of sustained cessation on longer-term healthcare usage and productivity losses. Now it remains for future studies to evaluate if sustained SC over several years would have contributed to a reduction in healthcare and societal costs in the long run.

Conclusions

There was no evidence that at 6 months, the digital MyCourse intervention had a differential effect on cessation rates among cancer survivors compared to a web-based noninteractive information brochure; both conditions led to approximately a quarter of the cancer survivors quitting smoking. Number of cigarettes smoked was reduced by 50% in both groups. At 12 months, assignment to the MyCourse group was associated with a greater reduction of number of smoked cigarettes at higher costs, and higher satisfaction scores compared to the control group. It should be further investigated how to achieve considerably higher quit rates, but this study provides an indication that it is possible to achieve somewhat higher cigarette reduction rates with the help of a digital SC intervention. Although both interventions were low-cost, the noninteractive information brochure was more likely to be economically sustainable.

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APPENDICES

Appendix 1

Additional information on Methods

Intervention

The peer support platform was a moderated bulletin board where participants could provide tips and share experiences on SC with other participants. Participants could choose to use the intervention whenever they wanted for the duration of the study, but were encouraged to log in daily for at least four weeks, e.g. using automated intervention reminder emails. They were also encouraged to engage their own social network through semi-automated email options throughout the program, for example sharing their quit plan or sharing their answers to an exercise about ways in which the participant would like to be supported by their social network in their SC efforts. Questions about the intervention could be directed at the research staff through email or telephone, but for information on more intensive/guided SC support participants were referred to the national SC information line (www.Rokeninfo.nl).

Sensitivity Analyses

Missing data for primary and secondary outcome measures were imputed using a second package: the Amelia 2-package. Inspection of the distributions of the imputed data showed that the mice-package predictive mean matching method outperformed the Amelia 2-package. This is not surprising as the Amelia 2-package can only handle multivariate normally distributed data, while tobacco use variables can be considered a form of count data and usually do not approach a multivariate normal distribution. We repeated the main analyses on both the Amelia 2-imputed data and the respondent only data (i.e., data without imputation). For evaluation of number of cigarettes we also conducted a Poisson regression with correction for overdispersion, this is another recommended approach for substance use data [38]. For the incremental costs analyses we winsorized the most extreme healthcare costs at the 95th percentile in a sensitivity analysis and based QALYs on SF6D scores instead of the EQ-5D-5L. For the cost-effectiveness analyses, we performed an alternative calculation of the reduction in pack-years by taking into account the reduction at 3, 6 and 12 months and not only at 12 months.

Appendix 2

Table S5. Attrition and satisfaction with the intervention

Measures	Primary and secondary meausures	Total (N=165)	Intervention (n=83)	Control (n=82)
3 month follow-up				
missing, n (%)				
	cessation	48 (29.1)	28 (33.7)	20 (24.3)
	number of cigarettes	48 (29.1)	28 (33.7)	20 (24.3)
	Fagerstrom	49 (29.7)	28 (33.7)	21 (25.6)
follow-up period, mean days (SD)		101.6 (15.1)	100.3 (11.7)	102.8 (17.7)
ZUF score		-	21.4 (4.61)	17.3 (6.11)
6 month follow-up				
missing, n (%)				
	cessation	52 (31.5)	24 (28.9)	28 (34.1)
	number of cigarettes	52 (31.5)	24 (28.9)	28 (34.1)
	Fagerstrom	54 (32.7)	26 (31.3)	28 (34.1)
follow-up period in days, mean (SD)		195.6 (21.9)	197.0 (21.8)	194.0 (22.0)
12 month follow-up				
missing, n (%)				
	cessation	53 (32.1)	27 (32.5)	26 (31.7)
	number of cigarettes	53 (32.1)	27 (32.5)	26 (31.7)
	Fagerstrom	56 (33.9)	29 (34.9)	27 (32.9)
follow-up period in days, mean (SD)		374.1 (24.3)	375.9 (17.3)	372.3 (29.8)

Appendix 3

Cost-effectiveness planes and cost-effectiveness acceptability curves after winsorization and after taking into account a gradual decline in pack-years

Figure S1. Cost-effectiveness planes and cost-effectiveness acceptability curves after winsorization of costs

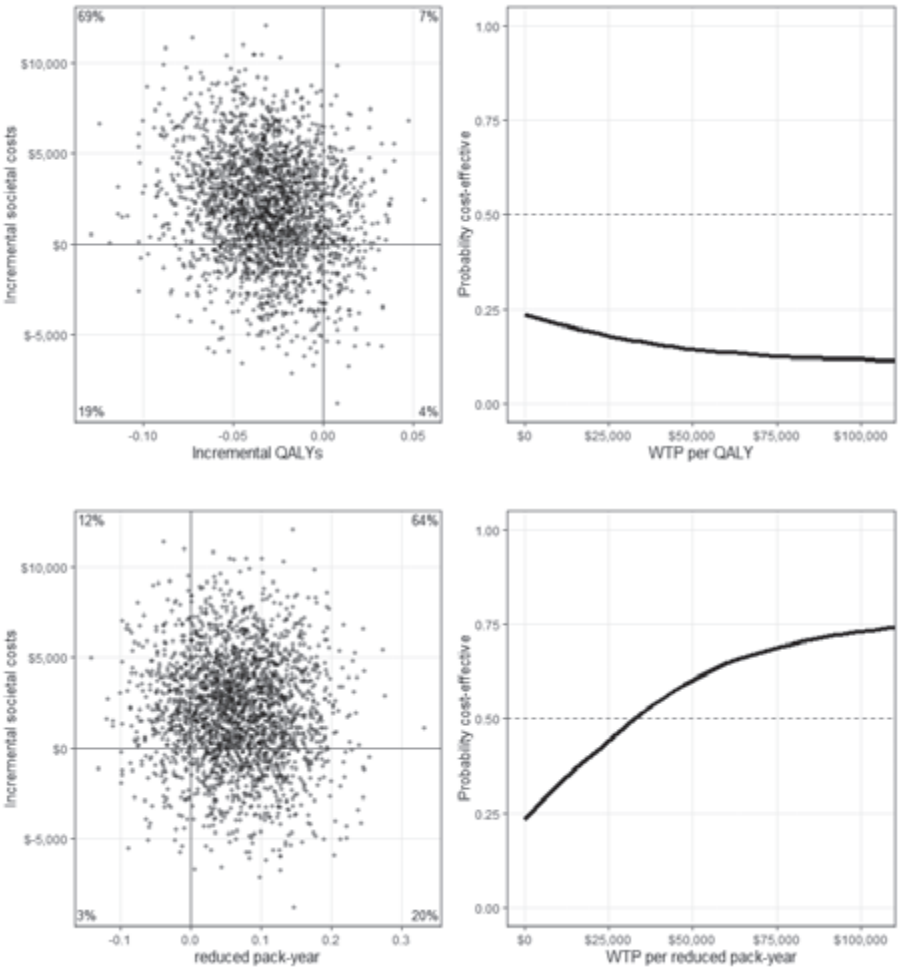
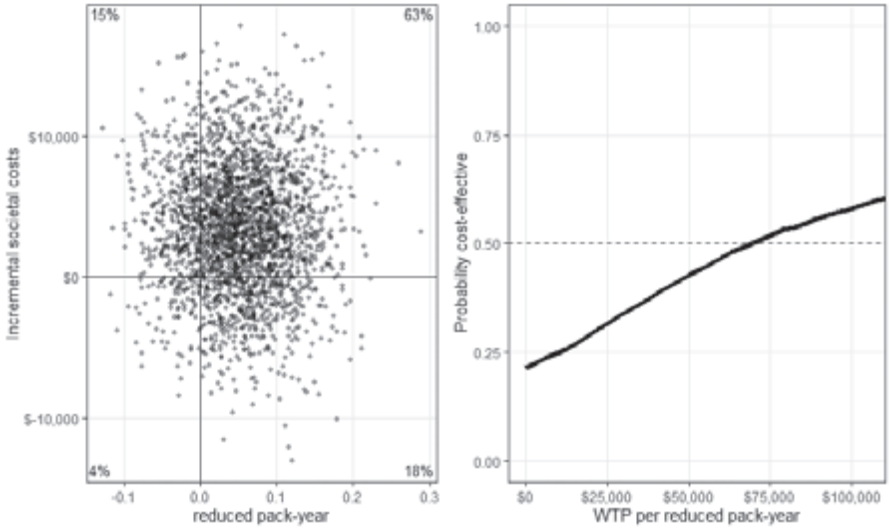


Figure S2. Cost-effectiveness planes and cost-effectiveness acceptability curves after taking into account a gradual decline in pack-years



CHAPTER 7

Effectiveness, cost-effectiveness and cost-utility of a digital alcohol moderation intervention for cancer survivors:

health economic evaluation and outcomes of a pragmatic randomised controlled trial

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ABSTRACT

Background

Alcohol moderation (AM) interventions may contribute to better treatment outcomes and the general wellbeing of cancer survivors. The aim of this study was to evaluate the effectiveness, cost-effectiveness and cost-utility of MyCourse, a digital AM intervention, compared with a non-interactive web-based information brochure for cancer survivors.

Methods

A health economic evaluation alongside a pragmatic two-arm parallel-group randomised controlled trial (RCT) was conducted with follow-ups at 3, 6 and 12 months after randomisation. The study was conducted on the web in the Netherlands, from 2016 to 2019. Participants were adult 10-year cancer survivors drinking over the Dutch recommended drinking guidelines (≤ 7 standard units [10 g of alcohol] per week) with the intention to moderate or quit drinking. In total, 103 participants were randomised and analysed; 53 in the MyCourse group and 50 in the control group.

In the MyCourse group, participants had access to a newly developed, digital, minimally guided AM intervention "MyCourse – Moderate Drinking".

The primary outcome was the self-reported number of standard drinks (10 g of ethanol) in the past 7 days at the 6-month follow-up. The secondary outcome measures were alcohol-related problems as measured by the Alcohol Use Disorders Identification Test (AUDIT) and treatment satisfaction at all follow-ups. For the health economic evaluation, healthcare costs, costs because of productivity losses and intervention costs were assessed over a 12-month horizon.

Results

Alcohol use at the 6-month follow-up decreased by 38% in the MyCourse group and by 33% in the control group. No difference in 7-day alcohol use was found between groups (B = 2.1, 95%CI −7.6 to 3.1, *P* = .22) at any of the follow-ups. AUDIT scores for alcohol-related problems decreased over time in both groups, showing no significant difference between the groups (Cohen d = 0.3; 95%CI −0.1 to 0.6; *P* = .21). Intervention costs per participant were estimated at US $279 for the MyCourse group and US $74 for the control group. The mean societal costs were US $18,092 (SD 25,662) and US $23,496 (SD 34,327), respectively. The MyCourse group led to fewer gained quality-adjusted life years at lower societal costs in the cost-utility analysis. In the cost-effectiveness analysis, the MyCourse group led to a larger reduction in drinking units over time at lower societal costs (incremental cost-effectiveness ratio per reduced drink: US $ −1158; 95% CI −1609 to −781).

Conclusions

At 6 months, alcohol use was reduced by approximately one-third in both groups, with no significant differences between the digital interactive intervention MyCourse and a noninteractive web-based brochure. At 12 months, cost-effectiveness analyses showed that MyCourse led to a larger reduction in drinking units over time at lower societal costs. The MyCourse group led to marginally fewer gained quality-adjusted life years also at lower societal costs.

Trial registration number: The trial was prospectively registered in The Netherlands Trial Register (NTR): NTR6010, https://www.trialregister.nl/trial/5433 on 1 September 2016.

INTRODUCTION

Alcohol use is one of the main lifestyle factors influencing cancer development and there is also evidence that it negatively affects the development of new malignancies [1], cancer treatment success [2] and mortality rates [3]. Therefore, it is recommended that cancer survivors quit or minimize their alcohol use [4]. Currently, drinking rates among cancer survivors are comparable with drinking rates among the general population, with estimates that 5.1% of cancer survivors are heavy drinkers (>2 drinks per day for men; >1 drink per day for women) vs 6% of the general population [5].

Studies evaluating alcohol moderation (AM) interventions in cancer survivors are scarce. AM interventions offer support in reducing or quitting alcohol use and can range from brief face-to-face interventions by healthcare providers to smartphone apps. A 2018 review on smoking and alcohol cessation interventions in people with head and neck cancer and oral dysplasia [6] found no randomised controlled trials (RCTs) evaluating AM interventions for head and neck cancer survivors and neither did a recent meta-analysis on AM distance-based interventions for cancer survivors of all cancer types [7]. The latter review identified a few studies that incorporated AM as a module in a broader lifestyle program and found insufficient evidence of their effectiveness on AM. A qualitative study assessed patients' experiences with a face-to-face alcohol cessation program in bladder cancer survivors undergoing surgery; results indicated that major bladder surgery was a useful cue for motivating patients with cancer to reconsider the consequences of risky drinking and the alcohol intervention was seen as a relevant offer around the time of surgery [8]. Facilitating access to AM interventions for cancer survivors via distance-based interventions, particularly digital ones, might be an effective and highly accessible means to provide the growing population of cancer survivors with AM support [9].

Studies among the general population have shown that brief face-to-face and digital interventions can be effective in reducing alcohol consumption. An individual patient data meta-analysis comparing guided and unguided low-intensity Internet interventions for AM found that participants in both types of interventions used on average 50 g less ethanol per week than the controls (5.02 standard units of 10 g of ethanol, 95%CI −7.57 to −2.48) [10]. A conventional meta-analysis evaluating brief AM interventions delivered in a primary care setting found that participants used on average 20 g (95% CI −28 to −12) of ethanol per week less than the controls [11]. A meta-analysis of personalized digital interventions found similar results when comparing the interventions to non-intervention control groups (23 g of ethanol, 95% CI 15 to 30, based on 41 studies), and found no difference in reduction of alcohol consumption in personalized digital interventions compared with face-to-face interventions, based on five studies [12].

Brief alcohol interventions in primary care settings have been found to be cost-effective for the general population [13]. Referral to a digital AM intervention was a cost-effective strategy in three

European countries [14]. A game with tailored feedback on alcohol awareness was found to be cost-effective from the societal perspective in reducing number of drinks in subgroups (older, lower educational level) of adolescents [15]. We found no studies on the cost-effectiveness of digital AM interventions for cancer survivors, but cost-effectiveness is a key element in the knowledge base needed for policy decisions around implementation and financing of digital interventions [16, 17]. It is unknown what results in (cost-)effectiveness are to be obtained from a digital AM intervention tailored to cancer survivors, as they have increased feelings of distress, symptoms of anxiety and depression [18, 19], and they could have additional benefits of AM (e.g., in terms of treatment outcomes) [20].

Therefore, it was deemed necessary to evaluate both the effectiveness and cost-effectiveness of a minimally guided digital intervention aimed at supporting cancer survivors to moderate their alcohol use: MyCourse – Moderate Drinking (in Dutch: MijnKoers – Minderen met Drinken). The development process and detailed intervention description are provided elsewhere [21]. In this study we aim to answer the following research questions:

1. Is the digital, interactive, minimally guided AM intervention "MyCourse – Moderate Drinking" more effective than a web-based AM brochure to moderate alcohol use?
2. From a societal perspective, is the digital, interactive, minimally guided AM intervention "MyCourse – Moderate Drinking" more cost-effective than a web-based AM brochure in terms of incremental costs per reduced weekly drink and incremental costs per quality-adjusted life year (QALY) gained?

We expect the MyCourse intervention to be both more effective and more cost-effective than a web-based brochure on AM.

METHODS

Design

In a two-arm individually randomised controlled trial (RCT) conducted in the Netherlands between 2016 and 2019, the effectiveness and cost-effectiveness of the MyCourse – Moderate Drinking intervention for cancer survivors was evaluated. First inclusion was on November 28, 2016 and the last inclusion was on September 3, 2018; the last follow-up measurement was collected on September 30, 2019. The study was prospectively registered in the Netherlands Trial register (NTR6010). The planned inclusion period was extended by several months, in order to recruit as many participants as possible. For an extensive description of the study protocol see Mujcic et al [21]. This study was part of a set of two separate RCTs on digital interventions for AM and smoking cessation in cancer survivors. Results of the RCT on the smoking cessation intervention (MyCourse – Quit Smoking) will be published separately. Ethical approval was obtained from an accredited medical research and ethics committee in The Netherlands (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. NL55921.101.16).

Participants and recruitment

Participants could find out about the study and apply for participation via a web-based screening questionnaire on a dedicated website that was created for the study. Participants were eligible if they were aged ≥18 years, had been diagnosed with any form of cancer in the past 10 years, had a personal computer or laptop and internet connection at home, had the ability and intention to participate in the study for 12 months, used alcohol more than recommended by Dutch guidelines (operationalised as drinking >7 European standard units of alcohol [70 g of ethanol] per week), and had the intention to reduce their alcohol use. The exclusion criteria were insufficient mastery of the Dutch language, pregnancy or self-reported suicidal ideation, acute psychosis, severe alcohol dependence, dementia or severe depression at times of screening. The same screening questionnaire procedure was used for both the current trial and the similar parallel trial evaluating a smoking cessation intervention (Mujcic et al. 2018). Some people were eligible for both trials; if so, they were allowed to participate in only one of the trials, based on their own choice.

Both web-based and offline strategies were employed for the recruitment of participants. Targeted web-based advertisements on social and other media as well as on search engines, referred those interested to the website and the web-based screening questionnaire. Patient organisations, oncology departments in hospitals and meeting centres for cancer survivors were contacted and offered promotional material (flyers, posters) to help refer cancer survivors to the website.

Procedure

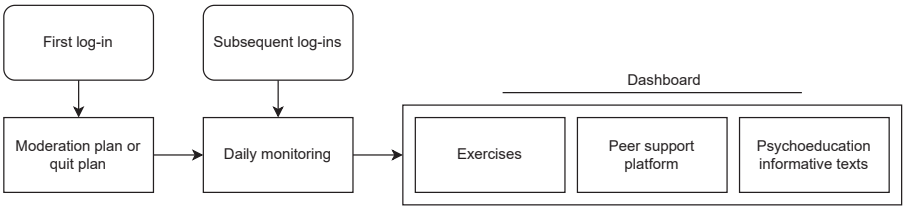
After filling out the screening questionnaire on the study website, applicants were informed by a computer-generated email about their eligibility for study participation. Those eligible were sent an invitation email containing all relevant patient information, the informed consent form and a link to register. Eligible cancer survivors had up to 30 days to decide about their participation, and during this period they could contact the research team or an independent physician with questions. After they had digitally signed the informed consent form, they were sent the baseline questionnaire. Immediately after completion of the baseline measurement, participants were automatically allocated to either the MyCourse or the control group arm in a 1:1 ratio through adaptive randomisation (minimisation of baseline imbalances with regard to age, sex and education level) by a server-sided PHP script using a Mersenne twister random number generator. Participants received an email confirming their allocation and containing their username and instructions on how to log on. They were not blinded to study condition allocation (the participants were not explicitly told about their allocation, but recruitment material included a video showing interactive elements of MyCourse, making it plausible that participants knew they were not allocated to the experimental condition. Thus, we cannot consider the participants blinded). At 3, 6 and 12 months after randomisation, the participants

received a link to the web-based questionnaire by email. via email. The nonresponders received up to 3 reminder emails, and in case of continued nonresponse they were contacted by telephone. For each completed follow-up assessment, they were reimbursed with €25 (approximately US $30). As this was a pragmatic RCT, patients in both groups were not asked to refrain from using additional support if they wanted to.

MyCourse group

MyCourse – Moderate Drinking is a newly developed, minimally-guided, digital intervention aimed at supporting AM in cancer survivors. It is based on well-established therapeutic approaches: motivational interviewing, cognitive behavioural therapy, and acceptance and commitment therapy, as well as a Dutch digital AM intervention previously found to be effective in the general population [22]. Throughout the development process cancer survivors and professional experts in e-Health, oncology and substance use disorders were involved through a series of interviews and focus groups. The intervention was accessible through personal computer, tablet and smartphone. At first login participants were guided by website prompts in either setting up a quit plan or a moderation plan, including a quit date or moderation date, after which they would gain access to several exercises, a web-based diary for self-monitoring of alcohol use and contextual cues, and a peer support platform (Figure 1 adapted from Mujcic et al [21] and Appendix 1). MyCourse could be used by the participants whenever they chose to, but they were encouraged to log in daily for at least four weeks. The intervention and its development process have been extensively described elsewhere [21].

Figure 1. Intervention flow chart (adapted from [21])



Control group

The control group consisted of a noninteractive web-based static information brochure on the risks of (increased) alcohol use and tips on how to moderate or quit drinking. It was accessible to the participants at any time by logging into the website. The brochure contained both general information on AM and information specifically relevant to cancer survivors. However, no interactive elements of the MyCourse condition were present and the participants did not receive reminders.

Additional support

Both groups were provided with the contact details of the national AM information line (in Dutch: Alcoholinfo-lijn), which could help refer participants to additional support if they deemed the received intervention to be insufficient. At the end of the study, at 12 months after randomisation, the participants in the control group received access to the digital intervention, MyCourse – Moderate Drinking, which was offered to the MyCourse group.

Measures

Baseline

At baseline we assessed the sociodemographic characteristics and type of cancer. Alcohol use was assessed using Timeline Follow-back (TLFB) self-reports [23] (number of standard drinks consumed in the past 7 days, ie, 7-day alcohol use). Problematic alcohol use was assessed using the 10-item Alcohol Use Disorders Identification Test (AUDIT) questionnaire. In participants reporting smoking, we assessed tobacco use with TLFB self-reports and nicotine dependence using the 6-item questionnaire Fagerstrom Nicotine Dependence Test (FTND) questionnaire [24]. Socially desirable answering tendencies which may have affected the reliability of the self-reported questionnaire data were assessed using the Marlowe-Crowne Social Desirability Scale (MCSDS) [25]. We used the 5-level EuroQol 5 dimensional (EQ-5D-5L) [26] tool to measure Quality Adjusted Life Years (QALYs). The Medical Outcomes Study Short Form (MOS SF-36) [27] was used to calculate the Short Form 6-dimension (SF6D) quality of life measure using the Brazier algorithm [28].

Follow-up measurements

At all follow-up measurements, we assessed alcohol use with TLFB self-reports, quality of life using the EQ-5D-5L and the Medical Outcomes Study Short Form, productivity and health care costs, and use of other AM support. Intervention use variables (eg, number of log-ins and use of major content elements) were collected automatically. The AUDIT questionnaire was administered at the 6- and 12-month follow-ups. At the 3-month follow-up, treatment satisfaction was assessed using a Dutch translation of the German adapted Client Satisfaction Questionnaire (Fragebogen zur Messung der Patientenzufriedenheit; Patient Satisfaction Questionnaire [ZUF-8]) [29]. The use of additional support for AM was retrospectively assessed at follow-up.

Primary and secondary outcome measures

The primary outcome measure was 7-day alcohol use (number of standard drinks; 1 standard drink=10 g of ethanol) at the 6-month follow-up measured by TLFB self-reports. The 6-month assessment was the primary end point, as the studies that formed the basis of our power analysis were based on outcomes at the 6-month follow-up and it is a common end point in alcohol trials [30]. Those who reported no drinking at all in the past 7 days were considered abstinent (0/1). Secondary outcome measures were AUDIT problematic alcohol use (0-40), ZUF-8 treatment satisfaction (8-32), EQ-5D-5L quality of life (0-1), healthcare costs and productivity loss.

Costs

Costs were calculated from a societal perspective for the index year 2019. Intervention costs included intervention depreciation costs, costs for hosting the website, technical support and recruitment costs (which consisted of both advertising costs in on- and offline media as well as printing costs of promotional material). Recruitment costs were included as they were considered an essential part of the MyCourse and control groups. Healthcare costs were calculated by multiplying all reported contacts with healthcare professionals with the standard unit cost prices for the Netherlands [31]. Health service costs stemmed from contacts with specialised somatic and mental healthcare, plus the patients' out-of-pocket costs for homecare, but travel costs were not included because in both groups the interventions were delivered over the internet. Other healthcare costs included appointments for physiotherapy, alternative medicine and social work. Medication costs were calculated by multiplying the reported dose of a drug with its unit cost price [32].

Productivity loss included costs from absenteeism and presenteeism, calculated according to the friction cost method, meaning productivity losses were limited to a maximum of 85 days after which production losses cease to exist because the sick employee has been replaced by another and calculated using an elasticity factor of 0.8 as there is no strict 1-to-1 relation between days not worked and productivity losses. Cost data related to healthcare use and productivity loss were assessed using the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) [33] at all follow-up assessments. Cumulative societal costs over the entire follow-up period of 12 months were calculated from the sum of healthcare costs and productivity losses. Costs were converted from euros to US dollars using purchasing power parities, for the reference year 2019. No discount rate was applied as the follow-up period was 12 months.

Sample size

The sample size was based on conventional levels of statistical significance ($a \leq 0.05$). On the basis of the average of 2 previous RCTs on very similar self-help interventions in the Netherlands versus a control group (see Riper 2008 and Blankers 2011 in [30], a Cohen d effect size of $d = 0.40$ was expected. Using the power calculation package "pwr" for R 3.0.1 [34], we calculated that a sample size of 2 x 57 participants in the case of one-sided testing led to a power of 0.77, or a power of 0.66 in the case of two-sided testing. The choice for one-sided testing was discussed in the previously published protocol paper [21].

Statistical Analyses

Imputation of missing data

Except for the ZUF-8 (treatment satisfaction) questionnaire, all primary and secondary outcome measures were analysed in accordance with the intention-to-treat principle. To that end, missing data for primary and secondary outcome measures and costs were multiple-imputed using the predictive mean matching method from the mice-package in R [35]. For each missing observation, 50 imputations were created. The responses on the ZUF-8 questionnaire were not imputed.

Effect evaluation

Alcohol use in the past 7 days (count data 0, 1, …, N) was analysed using robust estimation of generalized linear mixed models (GLMM) from the robustlmm package in R [36], as the data did not fit well into any of the commonly supported distributions. Imputation of missing values before running a generalized linear mixed allowed us to consider all variables that could have affected the dropout. Covariates in the model were the minimized variables (gender, age, and education) and the MCSDS (to statistically account for any social desirability of responses). Model estimates, Cohen d, 95% CIs and *P* values were reported. Differences over time and between the groups on AUDIT problematic alcohol use and ZUF-8 patient satisfaction scores were analysed using a linear mixed model in the lme4 package in R [37]. We used one-sided testing and an α of .05 as described in the study protocol [21].

Cost-effectiveness analyses

An economic evaluation was conducted alongside the RCT in concordance with the Consolidated Health Economic Evaluation Reporting Standards Statement statement [38] and following the approach by Drummond et al [39]. QALYs over the entire follow-up period were computed using the Dutch tariff (utility weights) [40] and the area under the curve method. The incremental cost-effectiveness ratio (ICER) was calculated as follows: ICER = $(C_1 – C_0)/ (E_1 – E_0)$, where C refers to costs, E refers to effects, and the subscripts (0 and 1) refer to the MyCourse and control arms, respectively. We generated 2500 nonparametric bootstrapped samples and plotted the corresponding incremental costs and incremental effects on a cost-effectiveness plane. Both ICER per QALY and ICER per reduced weekly drink were calculated from the following four perspectives: societal, healthcare, productivity loss and intervention cost only. Cost-effectiveness acceptability curves (CEACs) were also drawn to assess the likelihood that the experimental intervention will be deemed to be cost-effective given a series of willingness-to-pay (WTP) ceilings.

Sensitivity analyses

The robust regression on the mice-imputed data was the main analysis. We conducted several sensitivity analyses to assess for effectiveness and cost-effectiveness using QALYs based on the SF-6D (instead of the EQ-5D-5L), imputation using the Amelia II-package instead of the mice-package, Winsorization of costs, and different statistical models (see Appendix 1).

RESULTS

Sample characteristics

The participant flow and retention rates are shown in Figure 2. Of the 2346 ineligible people, 1684 (71.78%) had had no diagnosis of cancer in the past 10 years. A total of 321 cancer survivors were eligible for participation in the study, of whom 206 (64.2%) declined to participate, and 34 (10.6%) participated in the study on smoking cessation instead. Of 115, 10 (8.7%) cancer survivors did not complete the baseline questionnaire and were therefore not randomized, and 2 (1.7%) cancer survivors withdrew during the course of the study. This resulted in a study sample of 103 participants; of whom, 53 (51.5%) were randomized into the experimental MyCourse group and 50 (48.5%) were randomized into the control group. Table 1 presents the sociodemographic and other characteristics of the sample. In summary, the mean age of the participants was 54.6 (SD 11) years, 16.5% (17/103) were men, most were married or living with a significant other (70/103, 68%), and 31.3% (32/103) had a middle or low educational level. Breast cancer was the most frequently reported type of cancer (65/103, 63.1%). Problematic alcohol use as measured by the AUDIT was significantly higher in the MyCourse group than in the control group as calculated using the Welch 2-sample *t* test (2-tailed) for continuous variables ($t_{100.9}$=2.03; *P*=.02). No difference was found in the proportion of missing data between the groups (χ^2_1=2.5 *P*=.11; see Appendix 2 for details). Data were missing because of loss to follow-up (participants who did not respond after several reminders by email and telephone).

Figure 2. CONSORT flowchart

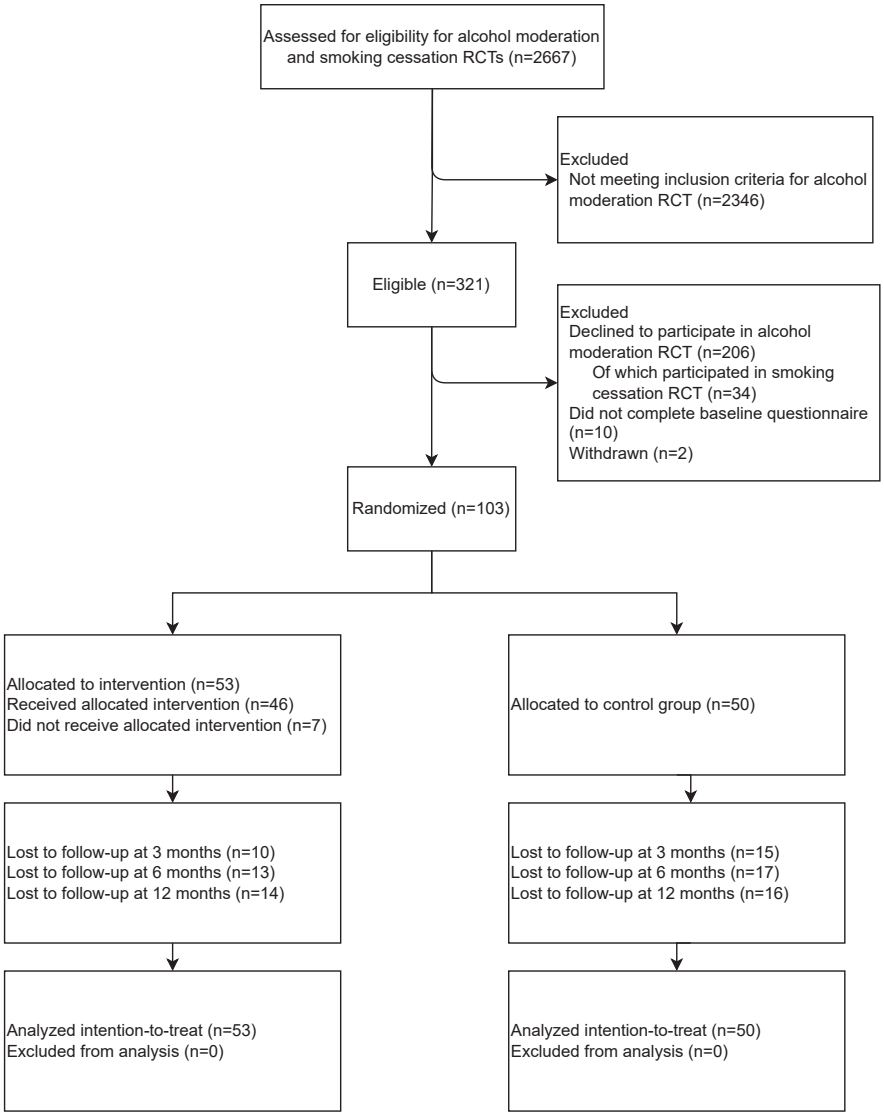


Table 1. Baseline characteristics[a]

Characteristic	MyCourse (n = 53), n (%)	Control (n = 50), n (%)	Total (N = 103), n (%)
Gender			
Women	46 (86.8)	40 (80.0)	86 (83.4)
Men	7 (13.2)	10 (20.0)	17 (16.5)
Age (years), mean (SD)	54.5 (12.1)	54.6 (9.9)	54.6 (11.0)
Education			
Higher level	34 (64.2)	37 (74.0)	71 (68.9)
Midlevel	11 (20.8)	11 (22.0)	22 (21.4)
Lower level	8 (15.1)	2 (4.0)	10 (9.7)
Marital status			
Married or living together	34 (64.2)	36 (72.0)	70 (68.0)
Unmarried or living alone	6 (11.3)	8 (16.0)	14 (13.6)
Divorced	10 (18.9)	4 (8.0)	14 (13.6)
Widowed	3 (5.7)	2 (4.0)	5 (4.9)
Drinking behaviour			
Number of drinks in past 7 days (mean, SD)	26.8 (19.0)	20.7 (14.7)	23.8 (17.2)
AUDIT[b] (mean, SD)	14.5 (6.0)	12.2 (5.4)	13.3 (5.8)
Smoking behaviour			
Smoked in last month (n, %)	10 (18.9)	6 (12.0)	16 (15.6)
Number of cigarettes in past 7 days among smokers (mean, SD)	87.9 (52.6)	81.6 (68.5)	85.3 (56.8)
Nicotine dependence (mean, SD)	0.6 (1.7)	0.3 (1.3)	0.5 (1.5)
Cancer diagnosis			
Breast	38 (71.7)	27 (54.0)	65 (63.1)
Uterus	4 (7.5)	2 (4.0)	6 (5.8)
Head and neck	1 (1.9)	4 (8.0)	5 (4.9)
Colon	2 (3.8)	3 (6.0)	5 (4.9)
Lung	1 (1.9)	2 (4.0)	3 (2.9)
Other (including bladder, lymphatic, melanoma, skin, prostate etc.)	7 (13.2)	12 (24.0)	19 (18.4)

Note. [a] Percentages may not add up to 100 due to rounding.
[b] AUDIT: Alcohol Use Disorders Identification Test.

Treatment uptake and satisfaction

Overall, patients were most satisfied in the MyCourse group (Cohen d=0.81; $t_{61.5}$=3.42; P<.001; see Appendix 2 for the mean scores). Most participants logged in at least once (46/53, 87%). The average number of times the participants logged in was 31.4 (SD 50.5), with a median of 8 (range 0-254). For those who logged in at least once, the period between the first and last log-in was on average 105.6 (SD 125.6) days with a median of 45 days. There was little use of AM support besides MyCourse; no support was reported most often (control group: 26/50, 52%; MyCourse group: 26/53, 49%) and some connected with others who were also moderating their drinking (control group: 4/50, 8%; MyCourse group: 5/53, 9%). Of 103 participants, only 1 (0.9%) reported having had contact with a health care professional about AM.

Incremental effects

Primary outcome

Despite the randomization, there was an apparent, although nonsignificant, difference between the groups in baseline alcohol use (Table 1). The number of drinks consumed in the past week at the 6-month follow-up decreased by 38% in the MyCourse group and by 33% in the control group and even more at the 12-month follow-up—by 48% in the MyCourse group and 38% in the control group (Table 2). No difference in 7-day alcohol use was found between the groups (unstandardized regression coefficient, B=−2.1, 95% CI −7.6 to 3.1; P=.22; Table 3) at 6 months—or at any of the other follow-up assessments—when controlling for MCSDS score, baseline alcohol use, gender, age, and education.

Secondary outcomes

AUDIT scores decreased over time in both groups (Table 2 and Figure 3), but there was no difference between the groups (Cohen d=0.3; 95% CI −0.1 to 0.6; P=.21; Table 3) at 6 months. The mean EQ-5D-5L QALYs score in the MyCourse group was 0.82 (SD 0.12) and in the control group 0.84 (SD 0.10). There was no significant effect of the treatment on the quality of life based on EQ-5D-5L scores ($B_{adjusted}$=0.003; SE 0.01; P=.39).

Table 2. Drinking behaviour outcomes at 3, 6 and 12-month follow-ups (N=103)[a]

Variable	MyCourse (n=53)	Control (n=50)
Number of drinks in past 7 days, mean (SD)[b]		
Baseline	26.8 (19.0)	20.7 (14.7)
3-month follow-up	17.3 (15.8)	15.1 (11.9)
6-month follow-up	16.6 (15.2)	13.8 (11.4)
12-month follow-up	13.9 (11.0)	12.9 (10.7)
Change in number of drinks in past 7 days, mean (SD)[c]		
3-month follow-up	−8.5 (12.0)	−5.2 (13.5)
6-month follow-up	−9.4 (15.0)	−6.4 (16.4)
12-month follow-up	−12.1 (16.3)	−7.4 (13.3)
AUDIT[d], mean (SD)		
Baseline	14.5 (6.0)	12.2 (5.4)
6-month follow-up	11.3 (6.2)	9.9 (5.1)
12-month follow-up	10.0 (6.0)	9.3 (5.1)
Abstinence, n (%)		
3-month follow-up	6 (11.4)	7 (14.0)
6-month follow-up	6 (11.3)	8 (16.1)
12-month follow-up	5 (9.6)	7 (14.1)

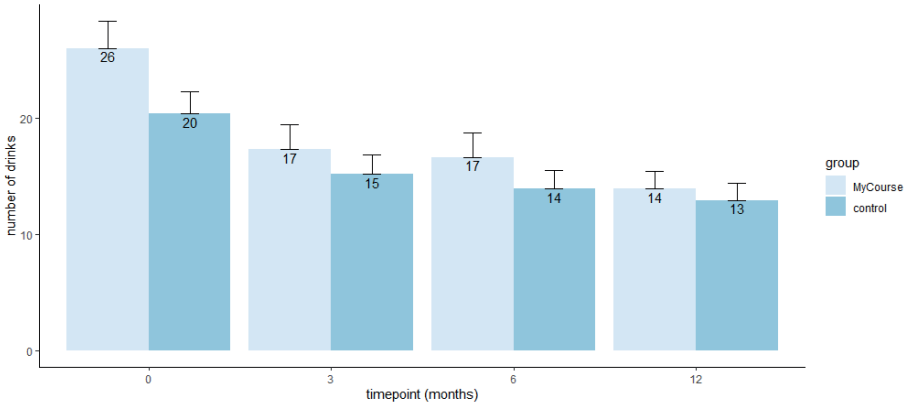
Note. [a] Missing data were imputed.
[b] The number of drinks per day was maximized at 11 units in the follow-up measurements for the imputation of missing data, meaning that 77 was the maximum number of drinks in the past 7 days.
[c] Mean number of drinks at follow-up minus the mean number of drinks at baseline.
[d] AUDIT: Alcohol Use Disorders Identification Test.

Table 3. Treatment effects on drinking behaviour at 3, 6 and 12-month follow-ups[a]

Outcome measure	Treatment effect $B_{adjusted}$ (SE; 95%CI)	*P* value	Cohen d (95% CI)
Number of drinks in past 7 days[b]			
3 months	−3.2 (2.6; −8.5 to 1.9)	.11	N/A[c]
6 months	−2.1 (2.7; −7.6 to 3.1)	.22	N/A
12 months	−3.7 (2.7; −8.9 to 1.6)	.09	N/A
AUDIT[d]			
6 months	−0.9 (1.0)[e]	.21	0.3 (−0.1 to 0.6)[d]
12 months	−1.6 (1.0)[e]	.06	0.1 (−0.2 to 0.5)

Note. [a] Missing data were imputed.
[b] Adjusted coefficients are based on a robust regression mixed model with random intercept and fixed slope in which the outcome measure at follow-up is regressed upon baseline number of drinks, covariates, and group.
[c] N/A: not applicable.
[d] AUDIT: Alcohol Use Disorders Identification Test (adjusted coefficients are based on a linear mixed model with random intercept and fixed slope in which the outcome measure at follow-up is regressed upon baseline number of drinks, covariates, and group).
[e] 95% CI value is not available.

Figure 3. Mean number of drinks in the past 7 days in both groups at baseline and during the course of the study, including standard errors



Incremental costs

Table 4 presents the costs per group and the incremental costs (cost difference between the MyCourse and control groups) per cost item. The intervention was costed at US $279 per participant in the MyCourse group and US $74 per participant in the control group. The average healthcare costs accumulated over the full 12-month follow-up time were US $7840 (SD 11,767) per participant in the MyCourse group and US $8233 (SD 15,077) per participant in the control group, and the incremental healthcare costs were US $−393. Costs owing to productivity losses were mainly driven by absenteeism: US $9532 (SD 19,389) per participant in the MyCourse group and US $14,799 (SD 23,364) per participant in the control group, with high within-group variance. Incremental productivity costs per participant were on average US $−5217 (SD 26,378). The average cumulative societal costs were US $5404 (SD 42,859) lower in the MyCourse group compared with the control group.

Table 4. Mean cumulative costs (in US$) by group and incremental costs

Cost item	MyCourse (n = 53)		Control (n = 50)		Incremental costs[a] (n = 53)	
	Mean (US$)	SD	Mean (US$)	SD	Mean (US$)	SD
Healthcare costs	7840	11767	8233	15077	−393	19125
Specialized somatic	3819	5772	3627	6463	192	8665
Specialized psychiatric	1209	3878	688	1906	521	4321
Patient and family costs	953	5517	178	1811	775	5807
Other	907	1142	1126	1434	−219	1833
Medication	953	5479	2613	10521	−1660	11862
Productivity loss	9972	1934	15189	26307	−5217	26378
Presenteeism	153	319	210	408	−57	518
Absenteeism	9532	19389	14799	26364	−5267	32726
Unpaid work	452	1049	474	1007	−22	1454
Intervention costs	279	0	74	0	205	0
Total societal costs	18092	25662	23496	34327	−5404	42859

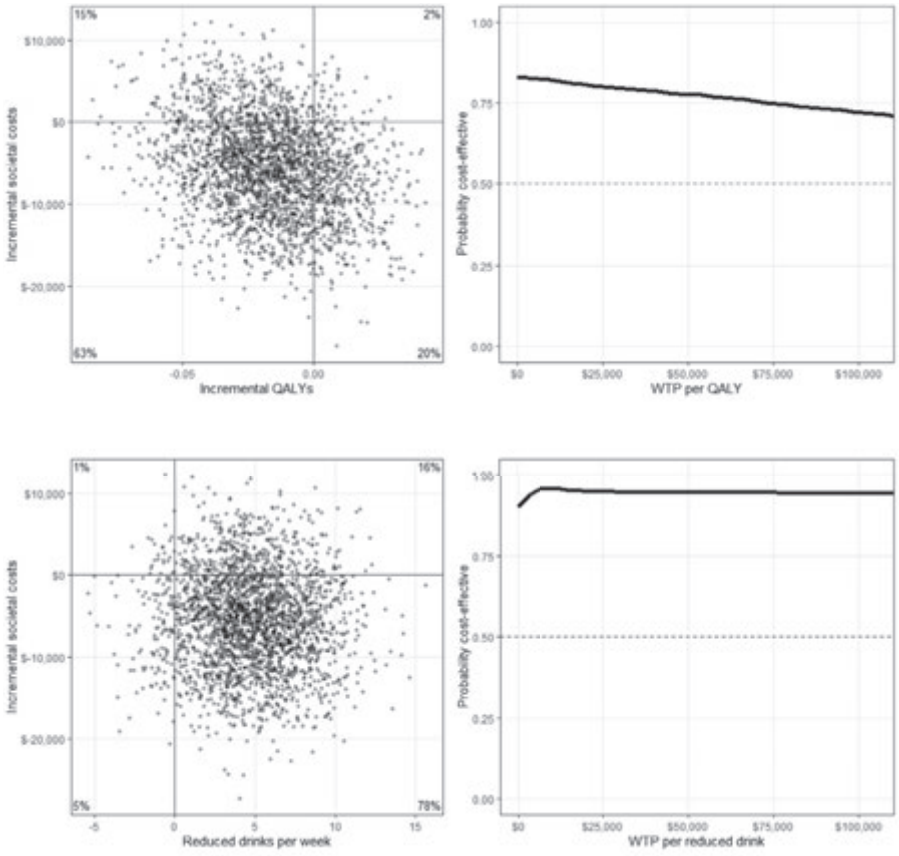
Note. [a] Costs in the MyCourse group minus costs in the control group.

Cost-utility

With QALY as the outcome, the ICER was US $314,606 (95% CI 186,201 to 553,552). The cost-effectiveness plane (Figure 4) shows that there is a 63% chance that the MyCourse intervention will lead to fewer QALYs gained at lower societal costs and a 15% chance that it will lead to more QALYs gained at lower societal costs. The relatively high ICERs are mostly a result of a difference in productivity costs (Table 4) and a very small differential effect on QALYs.

Assuming an intervention-cost-only perspective, the ICER per QALY gained became negative (US $–11,930; 95% CI –18,440 to –8912), indicating that intervention costs were higher and the QALY gains were lower in the MyCourse group compared with the control group.

Figure 4. Cost-effectiveness planes and cost-effectiveness acceptability curves in dollars



Note. Each quadrant in the cost-effectiveness planes represents a different association between the incremental costs (y-axis) and the incremental effects (x-axis) of the MyCourse group compared with the control group. When incremental cost-effectiveness ratios (ICERs) fall in the upper-right quadrant, this represents more effect at higher costs. When ICERs fall in the upper-left quadrant, this represents less effect at higher costs, meaning the MyCourse group is dominated by the control group. ICERs in the lower-right quadrant represent more effect at lower costs: the dominant quadrant. ICERs in the lower-left quadrant represent less effect at lower costs. QALY: quality-adjusted life year; WTP: Willingness to pay.

Cost-effectiveness

The MyCourse group reduced their number of weekly drinks more on average (mean 12.1, SD 16.3 drinks) than the control group (mean 7.4, SD 13.3 drinks) over a 12-month period and at lower societal costs. ICER per reduced drink was calculated at US $−1158 (95% CI −1609 to −781), meaning that compared with the control group each additional reduced drink in the MyCourse group was associated with a societal cost reduction. There is a 78% chance that the MyCourse intervention will lead to more weekly reduced drinks at lower societal costs and a 16% chance that it will lead to more weekly reduced drinks at higher costs (Figure 4). MyCourse will be preferred over the control group at any willingness-to-pay level (see Figure 4 for the CEAC curve). Assuming an intervention-cost-only perspective, a reduction of 1 additional weekly drink would cost an additional US $44 (95% CI 38-53) in the MyCourse group compared with the control group. Table 5 shows a breakdown by perspective.

Table 5. Incremental cost-effectiveness ratios between baseline and 12-month follow-up[a]

Perspective	Incremental costs per QALY[b] (95% CI)			Incremental costs per reduced drink (95% CI)		
	Mean (US$)	Lower CI	Upper CI	Mean (US$)	Lower CI	Upper CI
Healthcare perspective	22859	−18584	78705	−84	−242	74
Productivity loss perspective	303677	198917	516624	−1118	−1497	−823
Intervention cost-only perspective	−11930	−18440	−8912	44	38	53
Societal perspective	314606	186201	553552	−1158	−1609	−781

Note. [a] The incremental cost-effectiveness ratios were calculated as follows: $(C_1–C_0)$ / $(E_1–E_0)$, where C refers to costs, E refers to effects, and the subscripts 0 and 1 refer to the experimental and control arms, respectively.
[b] QALY: quality-adjusted life year (as measured by the 5-level EuroQol 5 Dimension).

Sensitivity analyses

Sensitivity analyses of the Amelia II-imputed data ($B_{adjusted}$=2.1; SE 1.8; *P*=.12) and completers-only data ($B_{adjusted}$=1.7; SE 1.4; *P*=.12) as well as a negative binomial mixed model on the mice-imputed data (incidence rate ratio=1.05; 95% CI 0.79-1.4; *P*=.38) corroborated the main findings and showed no effect of treatment on the number of drinks in the past week. All sensitivity analyses showed a decrease in alcohol use in both groups. Because of the apparent, although nonsignificant difference, between the groups in baseline alcohol use, we also modeled the individual change scores in alcohol use in a robust regression. Although the average reduction in alcohol use at 6 and 12 months was larger in the MyCourse group, the difference was not statistically significant, yielding the same results ($B_{adjusted}$=−2.1; SE 1.8; *P*=.12; Table 2). When

QALYs were based on SF-6D scores, results of the economic evaluation remained similar. When Winsorization of extreme costs was applied at the 95th percentile, the cost-effectiveness planes and CEAC curves remained similar (Appendix 3), but ICER per EQ-5D-5L QALY was US $118,287 (95% CI 51,324-235,817), and ICER per reduced drink became less extreme (US $−435; 95% CI −680 to −219). Overall, the sensitivity analyses attested to the robustness of the findings in the main analysis.

DISCUSSION

Principal findings

We evaluated the effectiveness and cost-effectiveness of *MyCourse–Moderate Drinking*, a digital interactive AM intervention for cancer survivors vs a web-based noninteractive information brochure. At the 6-month follow-up, the number of drinks in the past 7 days was reduced by 38% in the MyCourse group (mean −9.4, SD 15.0 standard units) and by 33% in the control group (mean −6.4, SD 16.4 standard units) and even further at the 12-month follow-up (MyCourse group: mean −12.1, SD 16.3 standard units; control group: mean −7.4, SD 13.3 standard units). No significant difference in 7-day alcohol use was found between the groups at any of the follow-up points. AUDIT scores decreased over time in both groups, but there was no statistically significant difference between the MyCourse group and the control group. Importantly, the participants were more satisfied in the MyCourse group.

In the cost-effectiveness analyses, the MyCourse group led to fewer QALYs and more reduced drinks, both at lower societal costs. Thus, MyCourse has shown to be more effective and cost-saving for number of reduced drinks.

From a societal perspective, the MyCourse group gained fewer QALYs at lower societal costs. The MyCourse intervention itself was associated with higher intervention costs than the noninteractive information brochure. Both ICERs reflected only marginally higher QALY gains in the control group. This study did not find any effect of MyCourse on QALYs. It could be hypothesized that a longer follow-up period would have been necessary for improvements in quality of life to take place in a population of cancer survivors, as their quality of life may be more directly influenced by factors pertaining to the cancer diagnosis (eg, invasiveness of cancer treatment, disease stage, cancer-related physical symptoms and comorbidities) [41]. Therefore, we conclude that the MyCourse intervention seems more economically sustainable from a societal perspective than the noninteractive information brochure in reducing the number of drinks over a 12-month time horizon, whereas to find evidence of possible cost-utility of a digital AM intervention, a longer follow-up period might be needed.

The difference in baseline alcohol use might be a possible explanation for the seemingly different conclusions between the incremental effect analysis and the cost-effectiveness analysis on the

greater reduction of 7-day alcohol use in the MyCourse group. Even though the participants were randomized, at baseline, the participants in the MyCourse group had higher AUDIT scores and consumed more drinks on average than the control group (although the difference between the groups was not significant). At the 3-, 6-, and 12-month follow-ups, there was no significant difference in the number of drinks consumed in the past week or the AUDIT scores between the 2 groups. Thus, the larger nominal reduction in the number of drinks in the MyCourse group does not reflect a difference in the number of drinks at any of the follow-up assessments but rather a difference at baseline. This baseline difference translates differently in the incremental effect analysis, assessing differences at discrete time points, compared with the cost-effectiveness analysis, assessing differences over a period (12 months). It is also possible that, because of insufficient power, no significant difference was found in the incremental effect analysis, whereas, in the cost-effectiveness analysis, this was of lesser influence.

Wider context

Meta-analyses of brief AM interventions [11] and AM internet interventions [10] among the general population have found that alcohol use in the past 7 days in the intervention group was reduced by approximately 20-50 g more than in the control group. Although this study did not find a significant effect on the AM rates of the MyCourse intervention over the control condition, we did find considerable reductions of approximately 70 g of ethanol at the 12-month follow-up in the control group and 120 g in the MyCourse group. These increasing reductions at longer follow-up assessments were also found in a previous digital AM intervention study [42]. In line with limited previous studies on brief and digital AM interventions [13–15], this study showed that a digital AM intervention can be cost-effective among cancer survivors. Unfortunately, because of a lack of literature, no comparisons could be made to other dedicated AM interventions for cancer survivors. A study on a telephone-counselling, combined alcohol, smoking and depression intervention for head and neck cancer survivors also found a decrease in AUDIT scores after 6 months in both groups and no differential effect between the experimental intervention and the control group receiving only the nurse-delivered face-to-face 45 minute assessment including a handout with referrals for further care (which the experimental group received as well) [43].

The lack of difference in alcohol use in the past 7 days between the MyCourse group and the control group might be due to several study aspects. It is also possible that, because of the inclusion criterion of having the intention to reduce one's alcohol use, participants in both groups were highly motivated to change their alcohol use and that this obscured any effect of the MyCourse group. In addition, during this study, great efforts were made to recruit participants. At the time of recruitment in 2016-2018, AM discussion and support for cancer survivors was not well-implemented in many oncology settings; therefore, the researchers invested in informing oncology department staff on the importance and benefits of addressing AM in cancer survivors. Recruitment efforts were not only aimed at professionals; a dedicated

website and a social media campaign were also in place, aiming to inform cancer survivors about the short-term benefits of AM after a cancer diagnosis while emphasizing an accepting tone to reduce possible feelings of guilt and ultimately guiding survivors to participate in the study. These recruitment efforts alone might have served as an intervention by focusing attention on AM. For cancer survivors not yet considering AM, the first step would be to address the knowledge gap on the adverse health effects of alcohol [44, 45].

Second, the assessment load in this study was substantial, and the participants received multiple reminder emails and telephone calls from the researchers to fill out the survey at the respective follow-up measurement waves. Although these calls were kept as short as possible, some participants might have experienced them as part of the intervention; thus, possibly contributing to an intervention effect and making participants think regularly about their drinking behavior and feel supported [46, 47]. This minimal guidance could thus have increased AM rates in the control group. Future research should evaluate whether addressing AM in an accepting manner and with multiple repeated short reminders can encourage AM in cancer survivors.

It is possible that a true effect was not found in this study because the sample size was smaller than intended (103 instead of 114 participants). It is unlikely that the use of additional support explains the reduction of alcohol use in the control group, as very few people used any additional support. Low use of additional support was also found in a previous Dutch study on digital AM support [48]. Although the control group was as effective as the MyCourse group in reducing alcohol use in the incremental effect analyses, considering the significantly higher satisfaction rates and better economic sustainability in the MyCourse group, it would be preferable to offer the MyCourse group.

Strengths and limitations

An important strength of this study is that the evaluation was conducted in a real-world setting; recruitment was done through both offline and web-based channels, which could plausibly be used in case of future implementation. This study succeeded in recruiting cancer survivors from a range of cancer types. The median number of times participants logged into MyCourse was high (8). Several sensitivity analyses have attested to the robustness of the findings. The long-term follow-up of this study showed that AM is sustained over a long period. The results should be interpreted in light of the limitations of the study. Most of this study's sample were women (86/103, 83.4%); thus, cautioning the generalization of the results to men. The participants were not blinded to their intervention allocation. Not all participants complied with the advised daily use of MyCourse for 4 weeks, and this might have influenced effects in the MyCourse group. A follow-up period of >12 months might be needed to find evidence of possible cost-utility of a digital AM intervention in cancer survivors.

Conclusions

To the best of our knowledge, this is the first study on a digital AM intervention for cancer survivors, and it showed that alcohol use was reduced by one-third in both the MyCourse and control groups and that this effect was sustained over 12 months. No significant differential effect on alcohol use between the MyCourse group and the control group was observed at the follow-ups, although cancer survivors were more satisfied in the MyCourse group. From a societal perspective, the MyCourse group seems economically more sustainable for reducing the number of drinks, as a greater reduction in the number of drinks over time was observed against lower societal costs.

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APPENDICES

Appendix 1

Additional information on Methods

Intervention

The intervention could be used whenever the participants wanted to, for the duration of the study, but they were encouraged to login (almost) daily for at least four weeks. This encouragement happened for example through automated intervention reminder emails. The intervention also encouraged participants to engage their own social network through semi-automated email options throughout the program. Participants could for example share their moderation plan or answers to an exercise about high-risk situations for alcohol use. The peer support platform was a moderated bulletin board where participants could provide tips and share experiences on AM with other participants. Questions about the intervention could be directed at the research staff through email or telephone, but for information on more intensive/guided AM support possibilities participants were referred to the national AM information line (www.Alcoholinfo.nl).

Sensitivity Analyses

Missing data for primary and secondary outcome measures were imputed using a second package: the Amelia 2-package. Inspection of the distributions of the imputed data showed that the mice-package predictive mean matching method outperformed the Amelia 2-package. This is not surprising as the Amelia 2-package can only handle multivariate normally distributed data, while alcohol use variables can be considered a form of count data and usually do not approach a multivariate normal distribution. We repeated the main analyses on both the Amelia 2-imputed data and the respondent only data (i.e., data without imputation).

For evaluation of number of drinks we also conducted a GLMM with log link function and a negative binomial distribution on the mice imputed data, a recommended approach for analysing substance use data [49]. For the incremental costs analyses we winsorized the most extreme healthcare costs at the 95th percentile in a sensitivity analysis and based QALYs on SF6D scores instead of the EQ-5D-5L.

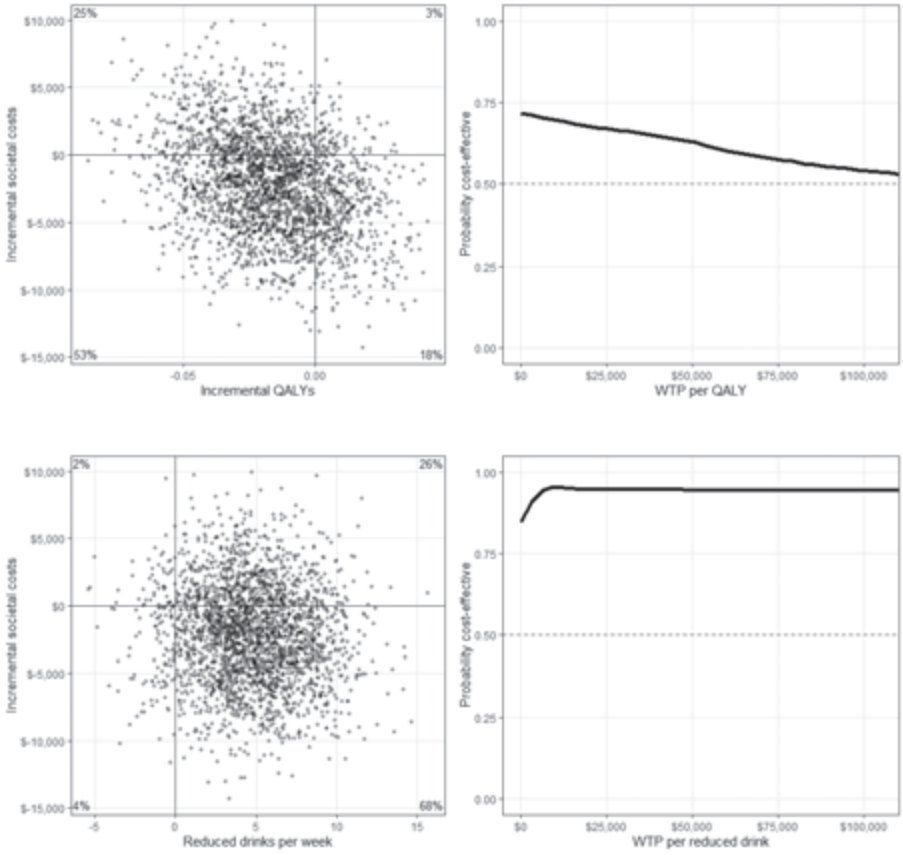
Appendix 2

Table S5. Attrition and satisfaction with the intervention

Measures	Primary and secondary measures	Total (N=103)	MyCourse (n=53)	Control (n=50)
3 month follow-up				
missing, n (%)				
	number of drinks	25 (24.3)	10 (18.9)	15 (30.0)
follow-up period in days, mean (SD)		104.0 (15.9)	101.9 (14.0)	106.5 (17.9)
ZUF score, mean (SD)			21.6 (4.5)	17.7 (4.9)
6 month follow-up				
missing, n (%)				
	number of drinks	30 (29.1)	13 (24.5)	17 (34.0)
	AUDIT	32 (31.1)	13 (24.5)	19 (38.0)
follow-up period in days, mean (SD)		201.1 (33.6)	197.5 (23.6)	205.6 (43.2)
12 month follow-up				
missing, n (%)				
	number of drinks	30 (29.1)	14 (26.4)	16 (32.0)
	AUDIT	31 (30.1)	15 (28.3)	16 (32.0)
follow-up period in days, mean (SD)		375.7 (15.8)	376.7 (18.2)	374.6 (12.7)

Appendix 3

Figure S1. Cost-effectiveness planes and cost-effectiveness acceptability curves after winsorization



CHAPTER 8

Evaluation of two digital alcohol and tobacco interventions for cancer survivors using the RE-AIM framework

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Submitted

ABSTRACT

Background

Smoking cessation and alcohol moderation can lead to better oncological outcomes for cancer survivors. The aim of this study was to evaluate digital smoking cessation and alcohol moderation interventions (MyCourse) for cancer survivors using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework and advise on their broader implementation.

Methods

Data were collected for each construct of the RE-AIM framework, using mixed methods. We used data from two randomised controlled trials among cancer survivors (reach and effectiveness), data from a pre-post observational study (reach), interviews with 6 trial participants (reach, implementation and maintenance on the individual level), interviews with 4 healthcare professionals (adoption, implementation on the institutional level) and 8 experts in eHealth, healthcare communication and healthcare marketing (maintenance on the institutional level). In addition, costs of recruitment and reactions to online recruitment strategies were analysed.

Results

Reach: The total participation rate for both interventions was 38.2% (268/701) among cancer survivors. Most reported referral method were Facebook ads (28%, 76/268). *Effectiveness:* The smoking cessation intervention led to marginally more reduced pack-years against higher societal costs, the AM intervention led to more reduced drinks at lower societal costs. *Adoption:* Hospitals were most often interested in promotional material for the MyCourse interventions (45%, 13/29), followed by smoking cessation clinics (36%, 5/14) and meeting centres for cancer survivors (32%, 24/75). *Implementation:* Healthcare professionals thought of the interventions as a good addition to their routine procedure in advising healthy lifestyle behaviours. Participants would appreciate more flexibility in setting up a moderation plan within the interventions and more guidance/contact during difficult moments. *Maintenance:* Healthcare professionals were willing to keep recommending the interventions, if proven effective.

Conclusions

The MyCourse interventions provide a low threshold to support in reducing alcohol and tobacco use, but were not convincingly more effective than an online information brochure. They were deemed useful tools that were easily incorporated into routine clinical practice by healthcare professionals. Reach of digital interventions can benefit from more structured health marketing by health organizations. Care should be taken when targeting cancer survivors through online recruitment strategies.

INTRODUCTION

Smoking cessation (SC) and alcohol moderation (AM) are among the main cancer prevention strategies [1], but are also recommended to people already diagnosed with cancer [2, 3], as smoking and alcohol use are associated with worse oncological outcomes [4, 5]. Digital interventions for SC and AM have shown their effectiveness among the general population. There is however a translational gap between the development of effective interventions and their implementation. Many cancer survivors do not receive SC support [6, 7] and studies on AM support for cancer survivors are scarce [8, 9].

One way to address this gap is by evaluating interventions using the RE-AIM framework. The RE-AIM framework is widely applied in the public health domain [10]. Its use is recommended to evaluate the relevance of health interventions in real-world settings and to stimulate translational impact of research [11]. The RE-AIM framework consists of five dimensions, that expand evaluation beyond the question of effectiveness and help improve sustainable implementation: 1) reach of the target population, 2) effectiveness in impacting an important outcome, 3) adoption by the target population or institutions, 4) implementation of the delivery of the intervention, and lastly 5) maintenance of reach and effectiveness over time.

Digital SC and AM interventions have shown effectiveness over different control groups among the general population [12–15], but there are few studies evaluating SC or AM support interventions for cancer survivors, even fewer evaluated digital interventions and – to our knowledge – none that has used the RE-AIM framework. However, RE-AIM evaluations of tobacco cessation programmes in healthcare settings are available [16–18]. One evaluation focused on comprehensive evidence-based cessation programs in three cancer centres [16], which included the implementation of modified workflows, referral methods, and the provision of face-to-face or telehealth counselling. The centres received funding to implement their programs. Reach of smokers, defined as the proportion of smokers who received at least one treatment, ranged from 7-43%. All three programmes showed high adoption rates (proportion of providers willing to deliver/advise the program) and implementation rates were at around 50%, although operationalized differently in all instances. Maintenance goals were formulated for each program, describing the expansion of telehealth services, removal of patient barriers such as costs and transportation, and low-burden support tools for clinicians.

As for AM, we found one RE-AIM evaluation of a training program for alcohol screening and a brief intervention for nurses [19] and another RE-AIM evaluation of educational resources on prenatal alcohol exposure in pregnant women for healthcare professionals [20]. Neither described the dimensions for alcohol users, but focused instead on healthcare professionals. The latter found that wallet cards describing possible effects of drinking alcohol during pregnancy were used by half of professionals and five years after first implementation there was a 31% increase of healthcare professionals who routinely provided information on consequences of alcohol use to pregnant women.

MyCourse – Quit Smoking and MyCourse – Moderate Drinking are two digital minimally guided interventions, supporting AM and SC in cancer survivors. They were developed simultaneously and evaluated in two similar randomised controlled trials (RCTs) [21]. Their effectiveness is described extensively elsewhere [22, 23] and is summarized in short in the present paper. We aimed to evaluate the MyCourse interventions on:

1. Reach: What is the participation rate and what are the characteristics of participants? How were recruitment materials appreciated?
2. Effectiveness: Are SC and AM rates higher in the MyCourse groups than in non-interactive online information groups?
3. Adoption: Are hospitals, SC clinics, revalidation centres and cancer patient organisations willing to refer cancer survivors to the MyCourse interventions?
4. Implementation: What are barriers and facilitators for healthcare professionals to refer cancer survivors to the MyCourse interventions (institutional level)? How are MyCourse interventions used by participants and what are reasons for drop-out (individual level)?
5. Maintenance: How can these digital interventions be disseminated and maintained (institutional level) after the study period? What are long-term effects (12-months) on SC and AM of the MyCourse interventions (individual level)?

METHODS

Ethical approval

Ethical approval for the RCTs was obtained from an accredited medical research and ethics committee in The Netherlands (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. NL55921.101.16). The internal ethics committee at the Trimbos Institute provided additional approval for the observational study (201612_41-1515).

Design

Pragmatic randomised controlled trials

The effectiveness, cost-effectiveness and cost-utility among cancer survivors of two digital interventions, MyCourse – Quit Smoking and MyCourse – Moderate Drinking, were assessed in two separate pragmatic RCTs. Both RCTs were two-armed, the control conditions consisted of a non-interactive online information brochure on SC or AM, respectively. Some participants were eligible for both RCTs; they were offered to participate in one RCT of their own choosing. No one was allowed to participate in both trials simultaneously. Participants were followed up at 3, 6, and 12 months post-baseline and they received €25 reimbursement for each completed follow-up questionnaire. An extensive description of the design, procedures and measurements can be found elsewhere [9].

Observational study

Many people without a history of cancer showed interest in the study. Therefore, people who were not eligible for participation in one of the RCTs were offered to participate in the observational single arm pre-post observational study. Every participant in this study received access to the intervention of their choosing: MyCourse – Quit Smoking or MyCourse – Moderate Drinking. A disclaimer was shown, informing participants that the interventions were designed for and most suited to cancer survivors. Participants were also informed that in case they were pregnant or reported psychiatric conditions, they were advised to seek more formal ways of support and they were provided with help lines to help them find more support. Participants in the observational study received no reimbursement for completing a questionnaire, these participants took part in a raffle for one €200 gift voucher. The goal of including this specific sample in the current analysis is to verify whether the content and marketing of the MyCourse interventions should be cancer specific.

Procedures

RCTs and observational study

Recruitment efforts were directed towards cancer survivors. Eligibility for both RCTs and the observational study was assessed through an online screening questionnaire on a dedicated website. As these were pragmatic RCTs and an observational study, participants were allowed to use additional support (e.g., nicotine replacement therapy), if they felt they needed it. The first inclusion was on November 4, 2016 for the RCTs and on April 14, 2017 for the observational study. The last follow-up data was collected on September 30, 2019. For a more extensive description see [9].

Interviews

Semi-structured interviews with RCT participants (cancer survivors), healthcare professionals and experts were conducted in January and February 2019, after participant inclusion to the RCTs had ended. Topic guides are provided in the appendix (Appendix 1). We recruited 3 participants who were predominantly positive about MyCourse and 3 participants who were predominantly negative, based on two questions from the patient satisfaction questionnaire ZUF [24]. Healthcare professionals who had advised MyCourse to their patients were interviewed. Experts were purposively recruited for their expertise: health communication, health marketing and implementation of eHealth programs, including financial sustainability. Health communication and health marketing were focused on because of the relatively new route of implementation through online advertisements, described under ‘Reach’.

Cancer survivors were recruited by inviting them for an interview during the reminder phone call or e-mail for the 12-month follow-up assessment. The healthcare professionals and experts were invited via e-mail or telephone. The interviewees were informed about the recording and the goal of the interview before providing written informed consent. Except for one face-to-face interview, all interviews were carried out by telephone and the audio files were recorded and transcribed.

Interviews with cancer survivors and healthcare professionals focused on their experience using and referring to the interventions. Interviews with experts focused on long term maintenance strategies and considerations when disseminating eHealth interventions.

Sample

Trial participants

Applicants for the RCTs were eligible when 18 years or older, diagnosed with any form of cancer in the past 10 years, had a PC/laptop and internet connection at home, and had the ability and intention to participate in the 12-month study. For participation in the tobacco RCT, participants had to have smoked 5 or more cigarettes per day in the past 7 days, and have the intention to quit smoking cigarettes. For participation in the alcohol RCT, participants had to have drank more than 7 standard units of alcohol (70 g ethanol) in the past 7 days and have the intention to moderate or quit their alcohol use. Those who had insufficient mastery of the Dutch language, were pregnant, or who self-reported suicidal ideation, acute psychosis, severe alcohol dependence, dementia or severe depression, were excluded.

The alcohol RCT sample consisted of 103 participants; 53 were randomized to the intervention group and 50 to the control group. The tobacco RCT sample consisted of 165 participants; 83 were randomized to the intervention group and 82 to the control group. Mean age across all RCT participants was 54.3 years (SD = 11.1), 17.2% (n = 46) was male and the majority was married or living together (60.8%). Breast cancer was the most frequently reported type of cancer in both RCTs (52.2%, n = 150). See Table 1 for the baseline characteristics of RCT participants.

The observational study included a total of 271 participants: 117 for MyCourse – Moderate Drinking and 154 for MyCourse – Quit Smoking. The observational study samples were similar to the RCT samples, with a mean age of 50.6 years (SD = 13.8) and 28% was male. As in the RCT samples, most people in the alcohol sample were highly educated whereas in the tobacco sample most had mid-level education. Majority of participants in the observational study had no cancer diagnosis (81.2%, n = 220). Further sample characteristics can be found in the supplementary material (Appendix 2).

Interviewees

In total, 6 RCT participants (4 from the SC RCT and 2 from the AM RCT), 4 healthcare professionals (a program manager, 2 specialized head and neck-oncology nurses and 1 specialized radiology nurse), and 8 experts were interviewed (1 eHealth specialist, 1 professor in health communication, 3 editors of oncological publications, 2 health marketing specialists and 1 advertising code expert). All approached interviewees accepted the invitation for an interview. None received a remuneration for their participation.

Table 1. Baseline sample characteristics of participating cancer survivors

	Alcohol RCT (N = 103), n (%)	Tobacco RCT (N = 165), n (%)	Total (N = 268), n (%)
Gender			
female	86 (83.5)	136 (82.4)	222 (82.8)
male	17 (16.5)	29 (17.6)	46 (17.2)
Age, mean (SD)	54.6 (11.0)	54.2 (11.2)	54.3 (11.1)
Education			
Higher level	71 (68.9)	44 (26.7)	115 (42.9)
Mid-level	22 (21.4)	71 (43.0)	93 (34.7)
Lower level	10 (9.7)	50 (30.3)	60 (22.4)
Marital status			
Married or living together	70 (68.0)	93 (56.4)	163 (60.8)
Unmarried or living alone	14 (13.6)	26 (15.8)	40 (14.9)
Divorced	14 (13.6)	36 (21.8)	50 (18.7)
Widowed	5 (4.9)	10 (6.1)	15 (5.6)
Smoking behaviour			
Smoked in last month (n, %)	16 (15.6)	165 (100)	181 (67.5)
Number of cigarettes in past 7 days, mean (SD)	9.9 (33.2)[a] 85.3 (56.8)[b]	100 (51.2)	65.4 (62.9)[a] 99.0 (51.6)[b]
Nicotine dependence, mean (SD)	0.5 (1.5)	4.9 (2.4)	3.2 (3.0)
Drinking behaviour			
drank alcohol in last month	103 (100)	110 (66.7)	213 (79.5)
number of drinks in past 7 days, mean (SD)[c]	23.8 (17.2)	6.2 (11.2)	13.0 (16.2)
AUDIT, mean (SD)	13.3 (5.8)	3.6 (4.7)	7.4 (7.0)
Cancer type			
breast	65 (63.1)	75 (45.4)	150 (52.2)
lung	3 (2.9)	23 (13.9)	26 (9.7)
uterus	6 (5.8)	19 (11.5)	25 (9.3)
head and neck	5 (4.9)	18 (10.9)	23 (8.6)
colon	5 (4.9)	10 (6.0)	15 (5.6)
other (including bladder, lymphatic, melanoma, skin, kidney, prostate etc.)	19 (18.4)	20 (12.1)	39 (14.6)

Note. [a] Including participants who did not smoke in the past 7 days.
[b] Only including participants from the alcohol RCT who smoked in the past 7 days. [c] Including participants who did not drink in the past 7 days.

Intervention description

MyCourse – Quit Smoking and MyCourse – Moderate Drinking are minimally-guided, digital self-help interventions aimed at supporting SC and AM in cancer survivors. The interventions are highly similar, both being based on well-established therapeutic approaches of motivational interviewing, cognitive behavioural therapy and acceptance and commitment therapy. Both interventions were accessible through PC, tablet and smartphone. A notable difference was that MyCourse – Quit Smoking only provided participants with the option to set a quit goal, whereas MyCourse – Moderate Drinking also allowed a moderation goal (reduced number of drinks).

The interventions were freely available and interested people could register themselves online. These low-burden interventions ensure that healthcare professionals needed little time and effort to refer patients to the interventions. Participants could choose to use the intervention whenever they wanted for the duration of the study, but were encouraged to log in daily for at least four weeks. An extensive description of the interventions is given elsewhere (Mujcic et al., 2018).

Measures

Reach of the MyCourse interventions was assessed by calculating participation rates (number of participants/those eligible for participation) for the RCTs and the observational study. Socio-demographic characteristics were assessed by baseline questionnaires. Costs of recruitment efforts are reported. Number of people referred by each recruitment channel was assessed by the question 'How did you find out about MyCourse?' In the observational study, this question was asked at baseline, for the cancer survivor sample this question was asked at the 6-month follow-up. Reasons for non-participation to the study were extracted from reminder calls or reminder emails to complete the baseline questionnaire and registration. Thoughts on the online advertisements targeted at cancer survivors (Facebook/Google Ads) were extracted from interviews and reactions to Facebook advertisements.

Effectiveness of the AM intervention was assessed by self-reported 7-day alcohol use at 6-month follow-up. Effectiveness of the SC intervention was assessed by self-reported smoking cessation at 6-month follow-up (primary endpoint) and self-reported 7-day tobacco use. Cost-effectiveness was assessed by incremental cost-effectiveness ratio (ICER) per reduced pack-year (SC), per reduced drink (AM) and per QALY (AM and SC).

Adoption was assessed by number of approached healthcare organizations and those who reported an interest in online or offline promotional material for the MyCourse interventions.

Implementation on the institutional level was assessed by reported barriers and facilitators for implementation of digital AM and SC interventions from interviews with healthcare professionals. Implementation on the individual level was assessed by intervention use variables (number of logins, login period) for cancer survivors, collected during the RCTs. Reasons for drop-out were noted during the collection of follow-up measurements (log data).

Maintenance on the institutional level was evaluated by discussion of dissemination and financial sustainability of digital (AM and SC) interventions in interviews with healthcare professionals and experts. Maintenance on the individual level was addressed by evaluation of long-term effectiveness of the MyCourse interventions.

Analyses

Reach was addressed by descriptive analyses of sample characteristics, participant flow and costs of recruitment. Effectiveness, cost-utility and cost-effectiveness analyses were based on the RCT samples. A detailed description of these analyses is available elsewhere for the alcohol RCT [23] and tobacco RCT [22]. For the observational study, only baseline characteristics are presented because of very low retention rates at 3-month follow-up.

Qualitative data from the structured interviews were independently analysed by two authors, DK and AM, by means of selective coding, using an earlier created codebook. Additional codes were created during the analyses when necessary. The RE-AIM dimensions of implementation and maintenance were assessed qualitatively for several reasons [25]. By assessing these dimensions qualitatively, we were able to gain insight into key contextual factors, as little is yet known on digital SC and AM interventions for cancer survivors. Another reason is that the institutional level (healthcare professionals) was not planned to have a huge role in recruitment and more emphasis was put on online recruitment strategies in the current study, making it difficult to quantify the institutional level of these dimensions.

RESULTS

Reach

Recruitment

Costs For the recruitment of participants to the digital MyCourse interventions, different online and offline advertisement strategies were used. As cancer survivors were self-referred to the study, efforts were mostly directed at referring cancer survivors directly to the dedicated MyCourse websites. Offline strategies included contacting SC clinics, oncology departments in hospitals, and meeting centres for cancer survivors and offering them promotional material to help refer cancer survivors to the website. Offline recruitment costs totaled €7,479 and included costs of promotional material (flyers, posters, animated videos, as well as advertisements in printed media, i.e. newspapers and magazines). Personnel costs of the researchers who contacted the organizations were not included.

We started with a limited budget for Facebook ads, Google ads, and newspaper advertisements and only after determining that traffic on the website for the great majority came through Facebook ads, it was decided to increase the budget for Facebook ads. The total cost of online recruitment was €15,501, of which €8,128 was spent on Facebook ads and €2,149 on Google Adwords. An online marketing company set up the online advertisement strategy (€4,190), but the advertisements were mostly monitored by the research team. The remainder was spent on ads on Dutch health-related websites (€1,017). Most reported referral methods in the RCTs sample and in the observational study sample were Facebook (RCTs: 76/268, observational study: 103/271) and online search engines (RCTs: 45/271, observational study: sample: 87/271). Healthcare professionals or printed promotional material were rarely mentioned as sources of referral, suggesting that Facebook and online search engines were the most effective referral methods.

Participation After the inclusion period of nearly 2 years (22 months), 2,667 screening questionnaires had been entered online. For the RCTs among cancer survivors, 701 cancer survivors were eligible for at least one of the trials (tobacco or alcohol), of those 95 were eligible for both. Total participation rate for both trials was 38.2% (268/701) among cancer survivors, for the alcohol trial the rate was 32.1% (103/321), and for tobacco 34.7% (165/475) participated. Among those who filled out the screening questionnaire, 73.7% (1966/2667) was not eligible for either of the trials. Of those who were ineligible for the trials, 271 participated in the observational study. The samples were not representative for the registered cancer patients in the Netherlands in 2019: there was an overrepresentation of women, breast cancer survivors and younger cancer survivors (<60 years old) (IKNL, 2019). See Table 1 and Appendix 2 for detailed sample characteristics.

Reported reasons for not finishing the study registration were: they found another way to quit smoking, they believed they would not succeed in quitting smoking, they reduced their

alcohol intake on their own, they were too sick to quit smoking, they did not want to quit smoking, or unknown reasons. The interviews showed that people registered for the MyCourse interventions because it was free, online, easily accessible, and without any obligations to log on at certain times or complete specific exercises.

Interviewed participants did not find the online advertisements patronizing and they experienced the recruitment as non-judgmental, but they disliked that the advertisement was somewhat frightening and confrontational because of the explicit connection to cancer. Disapproving reactions on Facebook were also related to the connection between cancer patients and smoking tobacco or drinking alcohol: *"(…) There are more things that can cause cancer, not only smoking tobacco"* and *"(…) I know a lot of people who never smoked, but did die because of cancer unfortunately. So, when do people stop making this comparison?".* Some people also thought of the advertisement as yet another imposed patronizing rule of conduct, mostly concerning the advertisement for MyCourse – Moderate Drinking. *"Geez, is that also no longer allowed?"* was one of the reactions on the advertisement on Facebook. Positive reactions included expressions of the willingness to try MyCourse or recounting SC attempts. Some voiced their appreciation of the attention on the alcohol and cancer relationship, stating it was under addressed in healthcare.

Effectiveness

Although no significant differences on SC rates or number of drinks were found between the MyCourse groups and control groups receiving non-interactive online information brochures [22, 23], at 6 and 12-months follow-up the number of quitters and reduced number of drinks was considerable. Participants were also more satisfied with the MyCourse interventions than with the information brochures.

Cessation rates were relatively high in both the group receiving MyCourse – Quit Smoking (27.7%) and the control group (25.6%) at 6 months follow-up, but there was no between-group difference [22]. At 12 months follow-up, MyCourse participants showed significantly larger reductions in the number of smoked cigarettes than participants in the control group. MyCourse – Quit Smoking led to marginally more reduced pack-years against higher societal costs, with a mean incremental cost-effectiveness ratio (ICER) of US$ 52,067 per reduced pack-year.

Number of drinks at 6-month follow-up was reduced by a third in both the group receiving MyCourse – Moderate Drinking (–9.4, SD = 15.0) and the group receiving non-interactive online information (–6.4, SD = 16.4) but there was no between-group difference in 7-day alcohol use [23]. At 12 month follow up, the MyCourse intervention led to more reduced drinks at lower societal costs (ICER per reduced drink: € –1158, 95%CI € –1609 to € –781).

Adoption

After contacting one of the researchers (AM, DK), interested organizations received promotional material or posted information on their social media and websites regarding the MyCourse interventions. Hospitals were most often interested (45%, 13/29), followed by SC clinics (36%, 5/14) and meeting centers for cancer survivors (32%, 24/75). Cancer patient organizations were least inclined to distribute information about alcohol or smoking or the MyCourse interventions to its members (25%, 3/12). Researchers emphasized that the recruitment for the MyCourse interventions involved little effort from the healthcare professional, meaning there was no obligation to recruit participants, they did not have to screen the participants or help the participants enroll for the MyCourse interventions.

Several difficulties arose while contacting organizations. Often there was no single person specifically appointed to provide lifestyle advice to cancer survivors and each oncology department had its own organizational structure, making it difficult to contact the healthcare professional who could refer cancer survivors to the MyCourse interventions. It is noteworthy that contacted healthcare professionals who were unsure whether to advice MyCourse to their patients, were so because they believed smoking and alcohol use were personal lifestyle choices, especially concerning referral to the AM intervention.

Implementation

Institutional level

All four interviewed healthcare professionals advised MyCourse to their patients. They often directed their patients to the MyCourse website and reported that they tried to maintain neutral, positive, and convincing in their advice. The healthcare professionals advised the MyCourse intervention to their patients in the first consult, often because they only saw the patients once. Reasons for recommending MyCourse included that they thought it was a good tool that did not cost them much extra effort and it was a good addition to their regular procedure in advising to quit smoking or drink less alcohol: *"MyCourse complements the way I usually advise smoking cessation and it did not take up more time or actions than usual to advise MyCourse and hand out the flyer."* (ZV2, woman, nursing consultant radiotherapy). Reasons for not recommending MyCourse interventions included that it was hard to identify which patients drank too much alcohol, that some patients did not speak Dutch fluently, or were thought not to be computer literate enough to successfully use the digital MyCourse interventions.

Individual level

The majority of cancer survivors in the RCTs logged in at least once (tobacco RCT: 68.7%, N = 57, alcohol RCT: 86.8%, N = 46). Number of times participants logged in was skewed, with an average of 20.0 (SD = 61.2) and median of 3 (range 0-384) for the tobacco trial and average of average 31.4 (SD = 50.5), with a median of 8 (range 0-254) for the alcohol trial. Time between

the first and last login in those who logged in at least once was on average 105.2 days (SD = 157.5, median = 24) in the tobacco trial, and for the alcohol trial 105.6 days (SD = 125.6, median = 45). The AM intervention was used for a longer period than the SC intervention.

For most dropouts, no reasons were provided. Nevertheless, some people provided insight into their reasons for dropping out: they were too sick, found a different way to quit smoking, had difficulties with the usability of the intervention or did not want to quit smoking or drink less alcohol anymore. Some of the participants used MyCourse in combination with other methods to quit smoking, most often medication, according to the follow-up calls with the RCT participants. Few participants of the MyCourse – Moderate Drinking intervention used additional help. Participants valued MyCourse because it was flexible, easily accessible, and it focused on the short-term benefits of SC and AM.

> *"You can use it whenever it suits you best." (P2, woman, RCT participant)*
>
> *"Usually you hear people say that after a year you can experience the benefits, but now you can think about benefits you get within weeks or months. Those small steps were very pleasant."(P6, woman, RCT participant)*

The participants also experienced the intervention as non-judgmental. *"The intervention came across as very neutral, it was not judgmental"* (P3, woman, RCT participant). Participants missed more practical tips, a personal approach in the texts, more flexibility in setting up the quit plans, and direct help during critical moments. *"During a relapse I really needed a hand, someone who I could call who could help me through that moment"* (P4, woman, RCT participant). Addressing these shortcomings could improve the MyCourse intervention according to the participants. A few participants mentioned that the date they wanted to quit smoking did not fit in the format of MyCourse – Quit Smoking (which only provided the possibility to set a quit date within the next 7 days) or that their desired drinking pattern did not fit the format of MyCourse – Moderate Drinking, which did not allow for different drinking limits on specific days, for example a distinction between working days and weekends.

Maintenance

Institutional level

Regarding the offline recruitment strategy, healthcare professionals were of the opinion that MyCourse was a useful tool to address AM and SC in cancer survivors. Whether they would advise MyCourse in the future would depend mostly on the needs of the patient and whether the intervention is found to be effective. *"I'm very content with MyCourse and I'm convinced that it's effective. I will keep advising MyCourse to my patients, depending on their needs of course."* (ZV1, woman, manager of oncology department)

Regarding the online recruitment strategy, we found that according to experts in the health communication and marketing field, health organizations often have small budgets for (online) marketing and lack a marketing department or even a marketing employee. Despite organisational difficulties, the strengths of health organisations are durable content, authenticity, trustworthiness and sharing expert knowledge. This can be used in the advantage of health organisations with small budgets for online marketing. It was also noted that it is important to align the health message as much as possible to the opinion of the target group, for example a health message suggesting a maximum of zero units of alcohol per day, will not cause any health behavior change for people who do not experience any negative influence from drinking alcohol. *"Don't remove yourself too much from your target group. This makes it less believable and creates resistance. People have to want it themselves."* (E1, man, expert health communication). In order to increase the effect of a health message, it should focus on a small target group rather than try to appeal to the whole population.

Targeting a specific group online, in this case cancer survivors, might evoke an uneasy feeling, be perceived as patronizing, and cause resistance. This could be linked to the increased awareness of online privacy. In particular, the introduction of the new General Data Protection Regulation Act in 2018 in the European Union [26] led to more attention regarding this subject in media and society. In addition, it is important to be as transparent as possible, for example being clear about the organization distributing the health message.

The experts noted that the way of financing the (eHealth) care system is changing. It is possible that in the near future, financing of eHealth will depend less on health insurance companies and more on the willingness of the users to pay for it, be it through subscriptions to additional insurance packages or prevention programs from employers. Important to note is that we found that MyCourse being free was one of the main aspects that lowered the threshold to participate.

Individual level

Results from the RCT showed that SC, reduction of number of cigarettes and reduction of number of drinks were sustained at 12 months in both the MyCourse groups and the control groups.

DISCUSSION

Using mixed methods and the RE-AIM framework, the public health impact of two SC and AM interventions was assessed and considerations for durable long-term implementation were explored. Effectiveness and cost-effectiveness of the interventions is discussed extensively elsewhere [22, 23]. Based on the RE-AIM framework, the MyCourse interventions have shown that cancer survivors can be reached by using online recruitment strategies, but that online strategies as part of an implementation strategy need extra consideration for privacy concerns and stigmatisation. Oncology healthcare professionals are also an important part of any

implementation strategy for AM and SC support in cancer survivors. This RE-AIM evaluation showed that the MyCourse interventions have succeeded in being a low-threshold support for cancer survivors and low-burden tool for healthcare professionals. However, the effectiveness and long-term sustainability of the interventions warrant attention.

Participation rates for both interventions was around 32-35% among cancer survivors, because some were eligible for both, the combined participation rate was somewhat higher at 38.2%. Participation rates for cancer survivors in the RCTs may be lower than in real-life settings as the study load and possibility of randomization to the control group might have posed a barrier. There was a similar participation rate among the general population in the observational study (38.5%), showing that – at least in terms of reach – the interventions can be implemented among both cancer survivors and the general population. It remains unclear whether effectiveness and satisfaction with the intervention are the same in the general population. Social media channel Facebook was the most reported recruitment channel, both among cancer survivors and the general population. Social media has previously been noted as a successful recruitment strategy, especially among hard-to-reach target groups [27]. Nevertheless, this does not mean that referrals by healthcare professionals did not play an important part in reaching the target population; cancer survivors might have heard or read about the intervention in a healthcare setting, but decided to register after seeing an online ad or using a search engine. Employment of online recruitment strategies by healthcare organisations entails some difficulties, including lack of a dedicated marketing department and small budgets (compared to commercial organisations), but can be promising when emphasizing transparency, trustworthiness and sharing of expert knowledge. Targeting hard-to-reach groups online should be done carefully, because of concerns about privacy and possible stigmatisation. One way to reduce stigma and prevent resistance caused by a specific health message, is to disseminate an intervention not explicitly targeted at a specific subgroup, but focus the dissemination on the intended target group. This has two advantages: it is offered to the general population as well and it can lead to less resistance for being stigmatic or patronizing.

The interventions were successfully perceived as easily accessible to participants and a useful tool for healthcare professionals that can be easily integrated into routine healthcare. However, participants have a need for increased support in difficult moments of AM or SC, for example in the form of enhanced guidance by a support coach. The effectiveness might thus be improved by intensifying the intervention through enhancing regular use of the digital interventions by more cancer survivors, for example by offering more flexibility in setting up the moderation plan (e.g., desired patterns of drinking or start dates for SC) and increased guidance [12, 28], for example in the form of blended support. Effectiveness is an important aspect for healthcare professionals in deciding whether to continue to advise MyCourse to their patients.

About half of contacted hospital healthcare professionals were interested in MyCourse interventions. Healthcare professionals have a strong need for training, resources and knowledge to deliver advice on alcohol moderation and smoking cessation to patients [29, 30]. In addition, barriers to address these behaviours are a lack of time and perceived lack of interest of the patient [31]. The low-burden promotial material of MyCourse is therefore suitable, but attention should be focused on training of healthcare professionals as well. Further complicating the addressing of lifestyle behaviours in a hospital setting were the large differences between hospitals in who was responsible for provision of advice on alcohol and tobacco use to patients. A more clear or uniform structure within hospitals would be helpful for the implementation of any AM or SC support, including digital interventions. Researchers have noted the ease of recruitment via the internet and the growing amount of online social support for health behaviour change for cancer survivors [32], as we also found in the current study although we do identify some concerns.

The AM intervention differed in several ways from the SC intervention on the RE-AIM dimensions. Healthcare professionals were more hesitant to advise MyCourse – Moderate Drinking, finding it more difficult to address AM and recognize to whom it would be appropriate to address AM. Cancer survivors and the general population had more questions about the need for AM in relation to cancer. These differences might be attributed to the generally accepted view that smoking is detrimental to health and causally related to cancer, whereas alcohol use is more often seen as a personal lifestyle choice that is not to be interfered with unless it clearly leads to problems. Also, alcohol's link to cancer is less well-known. Furthermore, healthcare personnel and other cancer organisations were not always conscious of this relationship either or were not well equipped to address alcohol use in their patients. These findings might implicate a need among the general population for increased awareness of detrimental effects of alcohol, its relationship to cancer and ways to recognize problematic alcohol use. Addressing this knowledge gap might be the first step towards successful AM interventions for cancer survivors.

Strengths and limitations

This is one of the few studies evaluating the potential impact of digital SC and AM interventions beyond their (cost-)effectiveness, especially among cancer survivors. The use of mixed methods and focus on various target groups yielded a wide-ranging understanding of the use of the interventions by participants (both cancer survivors and the general population), of its usefulness for healthcare professionals, and of strategies for broad implementation. Furthermore, the study was not limited to a specific cancer type. The present findings should be considered in the light of the study's limitations. A great majority of participants were women and only women cancer survivors agreed to be interviewed, limiting generalizability to men. Participants from the general population sample were not interviewed because of the study scope and we did not interview cancer survivors who declined participation. We only interviewed healthcare professionals who had agreed to recommend MyCourse to their

patients. For healthcare professionals who did not agree to receive promotional material and cancer survivors who declined participation, reasons (if provided) were analysed, but most did not respond. We did not assess how often healthcare professionals recommended MyCourse. This was decided in light of the emphasis on the low-burden properties of these interventions. Interviews provided valuable information on MyCourse's utility to healthcare professionals. However, as concerns exist about the lack of addressing SC and AM by healthcare professionals [33, 34], further studies into the addressing of these behaviours are warranted.

Conclusion

To our knowledge, this is the first evaluation of digital alcohol and tobacco interventions for cancer survivors using the RE-AIM framework. Online recruitment strategies (through search engines and online advertisements) played an important role in achieving good reach of the digital self-help MyCourse interventions, and generally succeeded in achieving a non-judgemental tone. The MyCourse interventions provide low threshold alcohol and tobacco support for cancer survivors and are low-burden, useful tools for healthcare professionals, showing good adoption, but resources and training could further encourage addressing of AM and SC. Increased effectiveness and long-term successful implementation on the individual level may be achieved by adjustments to the interventions, including additional guidance and increased flexibility. Long-term maintenance of digital interventions disseminated online could benefit from comprehensive (online) health marketing strategies, supported by a dedicated health marketing department within the organisation. The RE-AIM framework provided valuable insights for improving implementation of digital alcohol and tobacco support in cancer survivors. The mixed method approach allowed for insight on RE-AIM dimensions for which no adequate quantitative data were available.

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APPENDICES

Appendix 1

Topic guides interviews

Participants

1. Recruitment
   - Opinion on the way of recruitment and advertising (specifically for cancer survivors)
   - Introduction with MyCourse through a healthcare professional
2. Usability of MyCourse
   - Opinion on the look, feel and usability of MyCourse
   - Aspects of MyCourse that were evaluated positive
   - Aspects of MyCourse that were evaluated negative
   - Frequency of use
3. Overall opinion of MyCourse program
   - Aspects of MyCourse participants would like to keep
   - Reason for participating
   - Reasons for quitting
   - Other recommendations

Healthcare professionals

1. Background
   - Organisation and department
   - Experience and function
2. Approach
   - Way of discussing AM or SC
   - Way of tailoring your approach to the participant
   - Possible barriers for discussing AM or SC
3. Implementation
   - Use of materials (flyers, posters etc.) for MyCourse
   - MyCourse's fit with regular was of discussing AM or SC
   - Possible barriers for implementing MyCourse
   - Aspects for future implementation
4. Patient
   - Barriers for AM or SC for the patient
   - Effect of MyCourse on the patient
5. Alternative support for AM or SC (besides online)
   - Overall opinion
   - Positive aspects of MyCourse

- Reasons to keep implementing MyCourse
- Negative aspects of MyCourse
- Reasons not to implement MyCourse
- Possible improvements for MyCourse

Health marketing experts

Interview topic guide for experts in the relatively new field of online ads for healthcare programs

1. Background
   - Organisation and function
   - Experience with online ads for health promotion
   - Trends in online ads for health promotion
2. Recruitment through online ads for health promotion
   - Targeting
   - Benefits of recruiting with online ads
   - Barriers and pitfalls when recruiting with online ads
   - Budget tips and sustainability
3. Future role of online ads for health promotion
   - Opportunities for better use of online ads
   - Additional value

Appendix 2

Table S1. Sample characteristics observational study

	Alcohol (n = 117), n (%)	Tobacco (n = 154), n (%)	Total (N = 271), n (%)
Gender			
female	79 (67.5)	112 (72.7)	191 (70.5)
male	35 (29.9)	41 (26.6)	76 (28.0)
No response	3 (2.5)	1 (0.6)	4 (1.5)
Age, mean (SD)	51.1 (15.3)	50.2 (12.5)	50.6 (13.8)
Education			
Higher level	67 (57.3)	47 (30.5)	114 (42.1)
Mid-level	33 (28.2)	57 (37.0)	90 (33.2)
Lower level	10 (8.5)	45 (29.2)	55 (20.3)
No response	7 (5.6)	5 (3.2)	12 (44.3)
Marital status			
Married or living together	59 (50.4)	70 (45.5)	129 (47.6)
Unmarried or living alone	29 (24.8)	52 (33.8)	81 (29.9)
Divorced	17 (14.5)	22 (14.3)	39 (14.4)
Widowed	5 (4.3)	6 (3.9)	11 (4.1)
No response	7 (6.0)	4 (2.6)	11 (4.1)
Cancer diagnosis			
Yes	14 (12.0)	25 (16.2)	39 (14.4)
No	95 (81.2)	125 (81.2)	220 (81.2)
No response	8 (6.8)	4 (2.6)	12 (4.4)

CHAPTER 9

Summary and general discussion

Ajla Mujčić

SUMMARY AND GENERAL DISCUSSION

Alcohol moderation and smoking cessation can lead to health benefits for all, yet for cancer survivors these behaviour changes can additionally contribute to more beneficial treatment outcomes and wellbeing [1, 2]. However, targeted support in changing alcohol and tobacco use among cancer survivors is often lacking [3, 4]. Digital interventions might be able to fill this gap. This thesis describes the development and evaluation of two digital alcohol moderation and smoking cessation interventions for cancer survivors, and elucidates the role that digital interventions might play in supporting cancer survivors in their alcohol moderation and smoking cessation efforts.

Summary of the main findings

Chapter 2 presented a systematic review and meta-analyses of distance-based (i.e. digital, telephone and print) alcohol and tobacco interventions for cancer survivors. We included 17 studies (12 randomised controlled trials (RCTs) and 4 non-randomised studies) in the qualitative synthesis, of which 15 were included in the meta-analysis with a total of 3,796 participants. The meta-analysis on smoking cessation interventions resulted in higher cessation rates for distance-based interventions among cancer survivors with an odds ratio (OR) of 1.56 (95%CI 1.13-2.15), based on 10 studies that compared a distance-based intervention with a control condition after 6 months (or the follow-up closest to that period). Control conditions ranged from a waiting list to printed information brochures or active counselling. Results did not change when including only the RCTs or when applying the missing=smoking procedure to appropriate studies. There was no indication of publication bias. However, heterogeneity was high and all studies had at least some concerns regarding bias.

For alcohol moderation, the evidence that distance-based interventions led to higher moderation rates than control conditions in cancer survivors was insufficient. Important to note is that no single-behaviour interventions were found that only targeted alcohol moderation. Instead, we only found 3 studies of interventions that targeted multiple lifestyle behaviours simultaneously including alcohol.

Subgroup analyses showed indications that single-behaviour interventions might be more effective than multiple-behaviour interventions in encouraging smoking cessation, based on within-group meta-analyses comparing pre- and post-treatment smoking rates. This was not found in the meta-analysis comparing experimental to control groups, which has lower risk of bias. Furthermore, in **Chapter 2**, we showed that few alcohol and tobacco interventions for cancer survivors were digital, while the majority was telephone-based.

In **Chapter 3** we zoomed in on the use of a digital alcohol intervention for the general population in The United Kingdom: Down Your Drink. This unguided, self-management intervention in

which participants could participate on their own pace and choose which elements to interact with, was based on motivational interviewing (MI) techniques and cognitive behavioural therapy (CBT). It contained many interactive elements and opportunities for free text responses, enabling an analysis on the presence of change and sustain talk, as well as an analysis of the use of other key MI and CBT elements.

Two independent coders assessed the presence of change and sustain talk from the participant's responses within the intervention using the Client Language EAsy Rating (CLEAR) coding system, as well as the use of several key MI and CBT components. It was found that Down Your Drink was able to elicit change and sustain talk in free text responses. For most participants, more instances of change talk than of sustain talk were reported. One third of users (34.4% of those who logged in at least once) made use of what are considered other active ingredients in brief alcohol interventions: self-monitoring of their alcohol use and making a relapse plan.

In an exploratory secondary data-analysis, it was found that the number of listed high-risk situations was robustly associated with lower alcohol use at 3-month follow-up (B_{adj} −2.15, 95% CI −3.92 to −0.38, *P*=.02), even after controlling for number of words entered as a proxy for total activity within the intervention. Findings were inconsistent on the associations between alcohol use and the presence of change talk, sustain talk, and the number of listed strategies to deal with high-risk situations. These components could potentially contribute to an effective digital alcohol intervention, but studies with a pre-registered analyses plan should confirm this.

To further inform the development of digital interventions for alcohol moderation and smoking cessation, we explored Dutch cancer survivors' views on digital support for these health behaviours in **Chapter 4**, using a multi-method approach. We conducted an online survey (n=240), four focus groups (n=15) and semi-structured interviews with cancer survivors (n=8). An expert meeting (n=7) and interviews (n=6) with experts on eHealth for cancer survivors and experts on supporting alcohol moderation or smoking cessation were organised as well. One of the main findings was that there are large differences within the population of cancer survivors. In most survivors, the cancer diagnosis has impacted their daily lives, albeit to different degrees. Many would however not necessarily identify themselves as cancer survivors. Autonomy was an important theme that translated into several different preferences for the tone and content of the interventions, which was in line with previous research on smoking cessation support for cancer survivors. Digital alcohol moderation and smoking cessation interventions for cancer survivors were seen as a valuable solution, provided that they incorporate a positive, non-judgemental and non-patronizing tone-of-voice and address concerns especially relevant to cancer survivors, while avoiding stigmatization. Still, some would prefer face-to-face contact. We also found that in order to encourage alcohol moderation in cancer survivors, problem recognition and the awareness of the benefits of alcohol moderation could be improved. Healthcare professional's advice was generally valued highly and oncology healthcare professionals might be encouraged to address alcohol and tobacco use in cancer survivors more routinely.

In **Chapter 5**, it is described how the findings of the previous chapters shaped our development of the digital interventions MyCourse – Moderate Drinking and MyCourse – Quit Smoking. In this chapter we provide an extensive description of the two interventions and the study protocol of the two separate -but similar- pragmatic RCTs that were performed to evaluate them. MI, CBT and acceptance and commitment therapy made up the theoretical base for both interventions. The interventions were completely digital, minimally guided (except for technical assistance) and contained interactive components. Participants were guided to set-up a moderation or quit plan, after which they could engage in different exercises, a diary to monitor alcohol or tobacco use, a library with informative texts on alcohol moderation or tobacco cessation, and a peer-support platform.

The RCTs were prospectively registered in The Netherlands Trial Register (alcohol RCT: NTR6010; tobacco RCT: NTR6011). Both RCTs were conducted completely online with follow up assessments at 3, 6 and 12 months. The primary outcome measure in the alcohol RCT was 7-day alcohol use, for the tobacco RCT it was smoking cessation operationalised as 7-day smoking abstinence, both were assessed at the 6-month follow-up. Participants were randomised to either the newly developed MyCourse intervention or to a control group that received a static online information brochure without any interactive elements. For the analysis of the data, we followed the intention-to-treat approach and imputed any missing data using a multiple imputation method.

In this chapter we also present the protocol for the health economic evaluations alongside the RCTs. We calculated incremental cost-effectiveness ratios (ICER) to evaluate cost-effectiveness and cost-utility of both interventions. We assessed intervention costs, healthcare costs, and costs stemming from productivity losses over the full 12-month study horizon. The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) was used to assess self-reported healthcare costs and costs due to productivity losses, while quality of life years (QALYs) gained were assessed using the EQ-5D and SF-36.

In **Chapter 6 and 7** we present the effectiveness, cost-effectiveness and cost-utility of the MyCourse interventions for cancer survivors as assessed in two pragmatic RCTs in a real-world setting. In the alcohol RCT, 103 participants were included and analysed. In the tobacco RCT, we included 271 participants.

MyCourse – Moderate Drinking and MyCourse – Quit Smoking reduced alcohol use and increased tobacco cessation, respectively, in the long term, but were not more effective than the control groups, with the exception that at 12-month follow-up, MyCourse – Quit Smoking led to a greater reduction of cigarettes compared to the control group.

The health economic evaluation showed that the costs of offering the MyCourse interventions are low; per participant the costs were US$ 193 for MyCourse – Quit Smoking and US$ 279 for MyCourse – Moderate Drinking.

MyCourse – Moderate Drinking led to a larger reduction of alcohol use against lower societal costs compared to the control group, indicating its cost-effectiveness; mean incremental per-participant societal costs per reduced drink were US$ –1,158 (95% CI –1,609 to –781) for the MyCourse intervention.

MyCourse – Quit Smoking led to a larger reduction of pack-years, but against higher societal costs, therefore the control condition (consisting of a non-interactive information brochure) might be more likely to be economically sustainable. Mean incremental per-participant societal costs per prevented pack year were US$ 52,067 (95%CI US$ 32,515 to US$ 81,346) for the MyCourse intervention.

The societal costs were US$ 5,404 (SD = 42,859) lower in the MyCourse – Moderate Drinking group compared to the control group, and they were US$ 3,493 (SD = 38,913) higher in the MyCourse – Quit Smoking group compared to the control group. The main source of the cost-differences between the MyCourse and control groups were healthcare costs and costs due to productivity loss, but within-group variation of these costs was high as well, possibly reflecting the high heterogeneity in healthcare use among cancer survivors. To determine the source of the cost-differences, more studies are needed.

Both MyCourse interventions led to marginally lower gains in QALYs in the economic evaluation, there was no significant effect in the effect evaluations. For the alcohol intervention, less QALYs were gained at lower costs, for the tobacco intervention less QALYs were gained at higher costs.

Both MyCourse interventions led to higher satisfaction scores than the control groups. It is possible that the relatively heavy assessment load masked a contrast on the primary outcomes between the groups. In addition, the 12-month follow-up period might have been too short to notice an effect on quality of life in the population of cancer survivors.

Finally, we evaluated the MyCourse interventions from a broader perspective to inform future implementation. **Chapter 8** describes the use of a mixed method approach for the evaluation of the interventions according to the RE-AIM framework, which entails an evaluation on five dimensions: reach, effectiveness, adoption, implementation and maintenance. We used both offline and online recruitment strategies for the interventions. Online recruitment strategies, especially through social media, succeeded in reaching cancer survivors, but the highly specific online targeting possibilities can invoke unease and thus extra care should be taken to respect privacy and avoid stigmatization. Participation rates were reasonable at 32-35%, but might be higher outside of a study setting because of the study load. We briefly described an observational study in which those who were not eligible for the RCTs, mostly because they were not diagnosed with cancer, had direct access to the interventions, after they filled out a short questionnaire. We found adoption rates comparable to those in cancer survivors,

suggesting the MyCourse interventions might be adjusted and subsequently offered to the general population as well. The interventions were perceived as having a low threshold and being low-burden by cancer survivors and healthcare professionals. The focus on short-term benefits was valued by cancer survivors. To continue use of the intervention, cancer survivors suggested adjustments to the interventions (e.g., increased guidance and flexibility, technical improvements), while for healthcare professionals continued use would depend on the interventions proving to be effective. We again found, as in **Chapter 4**, that addressing alcohol and tobacco use by healthcare professionals should be encouraged. We additionally found that in many oncology departments it was not clear who was appointed to provide lifestyle advice to patients and that this was further complicated by the variety in organizational structures between departments and hospitals.

Reflections on the main findings in the context of previous literature

We found no difference on alcohol moderation or smoking cessation between the MyCourse groups and control groups. Studies on similar digital interventions aimed at the general population did find an effect on alcohol use in the past 7 days [5]. We found a reduction of about 90 g of ethanol (SD = 15.0) in the MyCourse group and 60 g (SD = 16.4) in the control group after 6 months, which increased to about 120 g and 70 g, respectively, after 12 months. However, no significant difference was found between groups. A meta-analysis of digital interventions among the general population showed that digital interventions (guided and unguided) reduced alcohol consumption by 50 g more than control group participants [5]. This meta-analysis included guided interventions, but also among unguided interventions a significant intervention effect was found of about a 30 g greater reduction compared to control groups. Guided digital interventions reduced alcohol consumption by about 100 g more than control groups. Outcomes differed by type of control group; when compared to waitlist control groups, digital intervention effects were higher than when compared to assessment-only or minimal intervention control groups. Follow-up periods in the meta-analysis ranged from 1 to 6 months and did not impact outcomes [5]. To the best of our knowledge, there is no meta-analysis or study on a dedicated digital intervention for alcohol moderation among cancer survivors. The effect on alcohol moderation in the MyCourse intervention group is smaller than in previous studies on digital alcohol interventions among the general population.

We found that smoking cessation rates after 6 months were 27.7% in the MyCourse group and 25.6% in the control group, with no difference between the two groups. Among the general population, a meta-analysis on digital smoking cessation interventions showed significantly higher cessation rates of 14.8% in digital intervention groups compared to 12.9% in non-active control groups (e.g., usual care or self-help guides) (Relative risk [RR] = 1.15, 95% Confidence interval [CI] 1.01 to 1.30) [6], but when digital interventions were compared to an active control group (e.g., telephone counselling), cessation rates did not differ significantly between groups (RR = 0.92, 95%CI 0.78 to 1.09). Among cancer survivors, we showed higher cessation rates for

distance-based interventions compared to any control group in **Chapter 2** (OR = 1.56; 95% CI, 1.13-2.15) [7]; this meta-analysis included both active and inactive control groups. Compared to our RCT, the studies referenced in the power-analysis showed comparable (23% [8]) or higher (30% [9]) cessation rates in the experimental group, but interestingly much lower cessation rates in the control groups at 15% [9] and 10% [8], versus 25.6% in our study. Control groups consisted of usual care, including a referral to resources for support [9] or a national smoking cessation website [8]. A more recent pilot study on a smoking cessation application for cancer survivors found preliminary smoking cessation rates (based on complete cases) of 20% in the experimental group and 7% in the control group, which also received an evidence-based smoking cessation smartphone application, but not tailored to cancer survivors [10].

To summarize, the effects on alcohol moderation and smoking cessation in the MyCourse intervention groups are smaller than in previous studies on digital alcohol interventions and somewhat comparable to what is found in other digital tobacco interventions. At the same time, the effects we found in the control groups are higher than what is generally found in the literature.

We propose several explanations for finding few differences between the MyCourse and control groups. As the study load was substantial (12 months including multiple follow-up assessments) and participants self-registered into the study, it is possible that study participants were a selection of highly motivated individuals, thus increasing effects in the control groups. It is also possible that participating cancer survivors are even more motivated than the general population, as few studies have focused on this target group specifically. The high assessment load and multiple reminders might have functioned as intervention elements in the control group, as they urged participants to think about their alcohol or tobacco use regularly. Participants in the smoking cessation control group used more nicotine replacement therapy, possibly explaining the relatively high cessation rates. Both alcohol moderation groups rarely used additional support. Outside a research setting, with no more assessments and reminders present, the control condition might still have an effect on alcohol moderation and smoking cessation. In research on psychotherapy, improvement occurred in some people immediately after making a first appointment, before commencing actual treatment [11]. Positive expectations about the treatment partly explain this effect [12, 13]. For our study in particular, the promotional material for the interventions and the information brochure in the control condition focused clearly on positively addressing alcohol and tobacco use, which **Chapter 4** showed to be an important precondition for acceptance in cancer survivors. Furthermore, Trimbos Institute, a renowned institute, was the sender of these messages. It is therefore plausible that the control condition had an intervention effect based on positive expectations. This 'placebo effect' is currently understudied in psychological treatment, but once understood, has the potential to improve evaluation of psychological interventions [13].

The interventions were based on ACT, CBT and MI. Interventions and components based on these theories have been found to be effective in previous studies [14–16]. Yet, the effects observed in this thesis lead to the conclusion that the components based on these theories were not powerful enough to achieve increased effectiveness over an information brochure. Engagement with the intervention might need to be encouraged more for these components to take effect. Findings across disciplines might inform these optimizations [17].

Based on the reflections on our main findings and our RE-AIM analysis in **Chapter 8**, we suggest that the following adjustments to the intervention might increase engagement with and effectiveness of the MyCourse interventions: addition of guidance by a healthcare professional, preferably on-demand guidance in difficult moments, increased flexibility when setting and changing goals, more encouragement of nicotine replacement therapy, and improved usability.

Lastly, by choosing a different study design, we might have gained a better understanding of which components should be maintained, added or removed to optimize effectiveness. We will touch upon this further in the section on Methodological considerations.

Limitations of the present thesis and directions for future research

Several limitations need to be considered when interpreting the results of this thesis.

In the RCTs, women were substantially overrepresented. In the alcohol RCT they made up 83.4% of participants, in the tobacco RCT this was 82.4%. This might partly be related to the relatively large group of breast cancer survivors that participated (alcohol RCT: 63.1%, tobacco RCT: 45.4%). Previous studies have shown that women more often look for health information online than men [18, 19], similar findings have been reported for breast cancer survivors compared to other types of cancer, while prostate cancer survivors searched less health information online [20]. It is suggested that women are more engaged in online searches for health information than men and have greater awareness of their health and nutrition [21]. As the recruitment for the present RCTs mainly took place online, this might explain the overrepresentation of women. The results from the RCTs and economic evaluation should therefore be cautiously generalized to men. Furthermore, men are not only less inclined to seek informal help, but also less inclined to seek formal (offline) help [22]. At the same time, men use apps more often (in general and for health information purposes [21]), indicating digital interventions might have value for them. Future studies should therefore look into how to better reach men or male cancer survivors with digital interventions.

The sample sizes for the RCTs were smaller than anticipated, as inclusion was more difficult than expected. For the alcohol RCT, we calculated that a sample size of 114 participants in case of one-sided testing and a Cohen's d effect size of d = 0.40, would lead to a power of 0.77. For the tobacco RCT, we calculated that based on a ≤ 0.05, RR = 2.1 at 6-month follow-up, 204

participants would yield a power of .83 for one-sided tests. However, less participants were included (alcohol RCT: 103, tobacco RCT: 165). As always, it remains possible that a true effect was not found in this study due to Type II-error.

All measures in the RCTs were self-reported. Self-reported data are at risk of recall bias and social desirability bias. Social desirability was assessed in the RCTs using the Marlowe Crowne Social Desirability Scale (MCSDS, [23]) and it was accounted for by adding the MCSDS score as a covariate in the main analyses. Alcohol use and tobacco use were assessed through the Timeline Follow-Back approach, which asks participants about their alcohol/tobacco use in the 7 days prior to the assessment, and should diminish recall bias as much as possible [24].

Methodological considerations

Self-reports might also have impacted variables on the cancer diagnosis, the reported healthcare costs and reported costs due to productivity loss. In The Netherlands, a possible alternative for assessing these costs is the use of so-called micro-data from Statistics Netherlands (CBS, [25]). Statistics Netherlands provide the opportunity, given explicit informed consent by the participants, to link a study dataset to data from centralized datasets, for example to complete the dataset with data on income and data on health insurance use. The Netherlands Cancer Registry (NKR, [26]) provides a similar opportunity to extract and link data on cancer diagnosis and treatment from cancer registries with a study dataset. For future research, the use of centralized datasets could provide more reliable data than self-reports and might decrease the assessment load for participants. Due to the significant amounts of time needed to link different datasets together, this was not done in the current study.

Participants were not explicitly informed about their allocation, but it is plausible that participants in the control group knew they were not allocated to the experimental condition, because the recruitment material described an interactive intervention. As the control condition received a static, although digital, information brochure, it is plausible that some participants have realized that they were allocated to the control group. Thus, participants could not be considered blinded. Which might have led them to search for additional support, as was clear in the smoking cessation trial (increased use of nicotine replacement therapy). As blinding is difficult in a pragmatic RCT comparing a digital intervention to a non-interactive intervention, a future RCT could consist of three arms, in which the third arm receives an interactive digital webpage, without any of the active ingredients of the experimental condition, in order to assess any bias from not being blinded. The webpage could instead show interactive questions, videos and exercises unrelated to alcohol moderation or smoking cessation, for example memory games.

This is related to the next limitation; the assessment load in the RCTs was high relative to the intensity of the interventions and might have had an additional intervention effect. Participants filled out online questionnaires at baseline, 3, 6 and 12 months, with each questionnaire taking

about 30 minutes to complete. Non-responders in our study received up to three reminder emails and, in case of continued non-response, were reminded by telephone. These repeated calls might have had an additional intervention effect, as participants might have felt supported by them. An assessment effect was also one of the hypothesized explanations for not finding a difference between a control group and several alcohol treatments in the landmark study Project MATCH [27]. Since, more evidence has mounted for the impact of assessments on drinking outcomes, although more high quality studies are needed to confirm and elucidate the effect [28–30]. In future studies on low-intensity alcohol and smoking interventions, attempts could be made to minimize the assessment load, for example by making use of previously collected data from registries, as mentioned previously, or routinely collected outcome data.

Lastly, only cancer survivors who already had the intention to moderate their alcohol use or quit smoking were included in the RCTs. The interventions might not be suitable for those who are more ambivalent or have no wish to moderate or quit. It is important for clinical practice to also understand how those who are more ambivalent could be supported. MI could inform these efforts, as demonstrated in a study on hardcore smokers [31].

Methodological considerations beyond the RCTs

In discussing the limitations of the present thesis, we mentioned several limitations that are related to challenges in conducting randomized controlled trials, in particular for the evaluation of digital health interventions. These challenges included the blinding of participants, the required sample sizes, the representativity of samples, and the study burden for participants. Even when an RCT is able to overcome these difficulties, by the time the RCT is completed, the evaluated digital intervention is likely to be outdated because of its generally long processing period that is outpaced by the current quickly evolving technological landscape. Furthermore, many RCTs are carried out in highly controlled settings and the effects they find are often small. RCTs are the gold standard in assessing intervention effectiveness, as internal validity is maximised and none of the alternatives below will be able to answer the same research questions as an RCT. However, there are several alternative methods that might be more suitable to evaluate other aspects of digital health interventions.

Single case experimental designs

Single case experimental designs (SCED) focus on intra-individual change instead of changes on the group-level. In a SCED, two or more experimental phases are compared within one individual, and the individual is frequently assessed over time allowing for the assessment of outcome trajectories within each individual. Hence, the individual acts as its own control. A SCED includes more than one participant, despite its name. Usually it includes around 6, but SCEDs with up to 40 participants or more are also described [32–34]. By comparing several trajectories of different individuals and replicating treatment effects, internal validity can be

increased. SCEDs come in a range of options, including variations on ABAB designs, changing criterion designs, and multiple baseline designs [35].

For brevity we will only elaborate on one example. For digital alcohol moderation and smoking cessation interventions, a multiple baseline across participants design could be suitable. In a randomised multiple baseline across participants design the individual starts with a baseline phase (the duration of which is randomised across participants), in which the individual has no access to the intervention. After the baseline phase, the intervention is presented. Alcohol or tobacco use are measured repeatedly (multiple times a week or daily) throughout both phases. The resulting individual trajectories are analysed visually and statistically. It would be expected that after introducing the intervention, the alcohol and tobacco use patterns change.

One of the main advantageous characteristics of SCEDs for the evaluation of digital health interventions is the rapid assessment possibility, making sure that any gained knowledge is not outdated by the end of the study and making it more suitable to assess optimizations to an intervention. Next, it eases assessment of the intervention's effects in individuals of underserved populations, as smaller sample sizes are required. By carefully selecting participants, the conditions under which an intervention is effective can even be determined [36]. Lastly, digital interventions provide a good opportunity for (digital) frequent, real-time, and thus more precise assessments. Many challenges in applying SCED center around the lack of widely adopted guidelines and the requirement of in-depth knowledge, e.g.: how to handle missing data, how to calculate power or adequate sample size, how to determine the optimal allocation sequence [37]. The methodological quality of meta-analyses of SCED studies needs to be improved and validated tools to support this are as of yet unavailable, but there are several guides for the analyses [38, 39]. Although the SCED has many advantages, few studies on digital health interventions incorporating SCED have been published as of yet. The unfamiliarity of many researchers, reviewers and funding organisations with this design and the interpretation of its results possibly contribute to its limited use [40].

Multiphase Optimization Strategy

The Multiphase Optimization Strategy (MOST) is an evaluation framework in which an intervention is not only evaluated as a whole (as in a traditional RCT), but by its distinct components. MOST consists of three phases: the preparation-, optimization-, and the evaluation phase [41]. In the preparation phase, potential components for the intervention are identified, informed by previous research, clinical experience or pilot testing. Examples of optimization criteria might be: the most effective intervention at a specified maximum cost per participant, a certain effect size or that each component in the intervention should be effective [41]. The next optimization phase is characteristic of MOST. In this phase, all the potential intervention components are experimentally studied and it is determined which intervention components are included according to the optimization criterium. The experimental studies in this phase are

fully powered [41]. In the last phase of MOST, the optimized intervention is still evaluated in an RCT to confirm effectiveness compared to a control or alternative group, but only when the intervention components seem sufficiently promising.

For the optimization phase different experimental designs can be used, depending on available resources and the type of intervention. Instead of a series of RCTs, which would be inefficient, other experimental designs are available. In the case of the MyCourse interventions, a factorial experiment or fractional factorial experiment could be considered. In a factorial experiment each component corresponds to a factor with different levels, and each combination of those levels to a condition in the experiment [42]. Examples of components in MyCourse would be: the peer support platform (yes or no), the setting of a quit plan (yes or no), guidance (minimal or intensive), ACT-based exercises (yes or no), CBT-based exercises (yes or no). Each participant is randomly assigned to one of these conditions. The number of different conditions is greater than in an RCT, but the required sample size is not necessarily greater. In fractional factorial experiments, only a subset of conditions is tested [42]. Other alternatives in this phase are the Sequential Multiple Assignment Randomized Trial (SMART) [43] or a micro randomized trial [44].

The main advantage of MOST is that it leads to better informed intervention optimizations [45], whereas changes to an intervention following an RCT are biased. With MOST, we can determine which intervention components are effective, what antagonistic or synergistic interactions between components are happening, and which components can be removed. By considering constraints in the optimization criterium (eg, maximum cost) during intervention development, MOST can enhance translational impact. Another advantage is the much needed flexibility in the optimization phase, allowing researchers to choose the experimental design best suited to broadly differing digital interventions and resources (e.g., time, financial resources, number of potential participants). The iterative character of MOST ensures that any changes to an intervention can be evaluated more quickly. However, the larger number of conditions in factorial experiments may require additional strategies to avoid contamination of the conditions [46]. In unguided digital interventions this is probably less of a problem than in guided digital or traditional face-to-face interventions, which may require more instructing of health care providers. Other disadvantages of MOST include that it is not less time-consuming than a parallel-group RCT, it still needs a substantial number of participants, and funding organisations need to be convinced of its benefits [47].

SCED or MOST for the evaluation of MyCourse

For the evaluation of the MyCourse interventions, a SCED could more rapidly answer whether the digital intervention helps reduce alcohol and tobacco use in cancer survivors and whether it also reduces alcohol and tobacco use in underserved groups of cancer survivors. Because of the rapid assessment approach, there would be time for a series of SCEDs to evaluate different optimizations of the interventions and assess the effect of our control condition. SCEDs could thus help to faster

implement the demonstrated lacking alcohol moderation and smoking cessation support for cancer survivors. While an RCT is still required to definitively determine superior effectiveness of an intervention over a control condition, both SCEDs and the early phases of MOST (including factorial experiments) can provide unique additional information, improving the quality of digital interventions and the pace at which they can be optimized. A remaining barrier is convincing stakeholders of the benefits of employing SCED and MOST over an RCT for digital interventions.

Clinical implications

This thesis provides several interesting insights for the clinical practice of providing digital alcohol and tobacco support for cancer survivors. They concern both the content of interventions as well as their implementation.

This thesis (in particular Chapter 4 and 8) suggests that digital interventions to support cancer survivors in alcohol moderation or smoking cessation should not be presented as disease-specific interventions, even though their content is tailored to cancer survivors. Many do not identify as cancer survivors as time since diagnosis passes, but would benefit from tailoring (e.g., extra information on benefits for cancer survivors) of these interventions. Additionally, a non-specific intervention would avoid feelings of stigmatization. Therefore, instead the intended target group can be reached through targeted implementation methods (targeted advertisements, referral by healthcare professionals). The recruitment material for MyCourse could for instance be less focused on cancer survivors, while retaining its tailored content. Next, the importance of a non-judgemental, non-patronizing, positive and pro-active tone-of-voice for such health behaviour interventions was stressed. It is important that any such intervention avoids to elicit any feelings of guilt in cancer survivors. Cancer survivors are open to discussing alcohol and tobacco use with their healthcare providers, as long as their autonomy is respected. This thesis provides several other specific recommendations for the content and delivery method of alcohol and tobacco digital interventions for cancer survivors (see Chapter 4).

As for when to address alcohol moderation and smoking cessation, previous studies showed that the number of tobacco quit attempts per year decreased as time since diagnosis increased [48] and that during treatment it was easier for cancer survivors to quit smoking or drinking, because of the shift in focus on their own health [49]. However, after treatment the risk of relapse became larger, as their well-being improved and stressful situations arose [49]. The current study showed that healthcare professionals who might address alcohol and tobacco use, will usually only see patients once around the time of diagnosis or a few times during the treatment period. Healthcare providers' advice was highly valued by cancer survivors. Thus, addressing AM and SC around the time of diagnosis is valued and practical, but the need for support will likely be greater after treatment. A combination of an initial brief intervention (advice by the healthcare provider) and later a (guided) digital intervention, might prove useful.

We also found that healthcare providers struggle with addressing alcohol and tobacco use in cancer survivors. They are not sure who should address these themes and in what way, since maintaining a good relationship with the patient is crucial. For alcohol use there is the added barrier of problem recognition; it is difficult to identify those who drink more than the guidelines, especially without routine assessment of alcohol use. Because of their highly valued advice, efforts should be made to increase healthcare providers' knowledge on the benefits of alcohol moderation and smoking cessation in cancer survivors, and increase their capabilities in addressing these health behaviours.

The MyCourse digital interventions were not convincingly more effective than the control conditions. However, both interventions showed significant reductions in alcohol and tobacco use and these reductions were sustained over a 12-month period. It is plausible that the newly developed recruitment materials and control condition – which contained a positive, non-judgemental tone-of-voice and explained the benefits of alcohol moderation and smoking cessation after a cancer diagnosis – have influenced the moderation and cessation rates in the control groups, which were higher than in previous comparable studies [6, 9]. So perhaps, our control condition can be seen as a meaningful intervention in itself. Thus, it may at least be advisable to inform cancer survivors of the short-term benefits of alcohol moderation and smoking cessation.

When funds to maintain and optimize the interventions are secured, it might be preferred to additionally implement the (optimized) digital MyCourse interventions. The main reason being that the satisfaction scores were higher for the MyCourse interventions than the control conditions and because healthcare providers found it useful to be able to refer patients easily to support when addressing alcohol or tobacco use.

In order to significantly increase the cessation and moderation rates of the interventions several modifications to the interventions are warranted, some of which are discussed in Chapter 8 (e.g., increased guidance and increased flexibility in goals). Cincirpini (2019) [50] showed that tobacco cessation rates as high as 43.7% after 9 months could be achieved when cancer survivors are intensively counselled and provided with proactive pharmacological therapy. The program also included automated referrals on the basis of electronic health records. Thus, to truly enhance smoking cessation rates in Dutch cancer survivors, the MyCourse interventions should be part of a comprehensive tobacco treatment program at each oncology department, by example of Cinciripini (2019) [50].

Reflections on the findings in a societal context

Funding for the current thesis was granted in 2014 and inclusion for the first studies started in 2016. Since then, several societal developments have had significant impact on the context in which the findings of this thesis should be interpreted. In order to help translate the current findings to society and support their contribution to public health improvement, what follows is

a reflection on several relevant aspects of our societal context in relation to digital support for alcohol moderation and smoking cessation among cancer survivors.

National policy developments

New guidelines on alcohol use In this thesis, we have shown differences between the views on alcohol (including alcohol moderation) and tobacco use (including smoking cessation). Alcohol use was seen as more socially acceptable and few alcohol users considered moderation or cessation, whereas smoking cessation was considered (at some point) by most tobacco users (Chapter 4). However, since the new Dutch guidelines on alcohol use were established in 2015 [51], attention for alcohol moderation has increased. This was fuelled by the publication of several large scale meta-analyses on the adverse health effects of (even low amounts of) alcohol use, particularly increase of cancer risk [52–57].

The National Prevention Agreement In this period, an important policy development in The Netherlands was the adoption of the National Prevention Agreement [58] in 2019. This agreement states the joint ambitions and action plans of a broad group of stakeholders on the prevention of problematic alcohol use, tobacco use, and overweight. These three themes were selected because they contribute the most to the disease burden in the Netherlands [58]. Parties involved were not only national and local government, but also included civil-society organisations, patient organisations, healthcare providers, health insurance companies, the business community, and more. Financially, the national government allocated €27 million in 2019 to reach objectives in the National Prevention Agreement.

Low-threshold and low-burden digital smoking cessation interventions can help in achieving the objective of fewer smokers, and more patients referred to and making use of appropriate care and guidance [58], because we found that MyCourse – Quit Smoking had a low threshold for cancer survivors and was helpful to healthcare providers. It is also one of the few dedicated smoking cessation support interventions for the oncology setting. However, the interventions should be optimized to enhance effectiveness over a digital information brochure. The objectives from the National Prevention Agreement are also in line with our conclusions: attention is needed to instruct and empower healthcare providers in addressing tobacco use, and systematic healthcare changes may be needed to ensure that all cancer survivors receive smoking cessation support and substantially improve quit rates. In the meantime, smoking has been banned in public transportation (waiting stations), and many hospitals, sports organisations and schools have also banned smoking from their premises [59].

Enhancing of knowledge on alcohol's effects, more awareness of one's own alcohol use, and enhanced early detection of problematic alcohol use are some of the agreement's objectives on alcohol use [58], and they are fully in line with this thesis. Increased awareness is needed to encourage more people to (consider to) moderate their alcohol use. Currently, a yearly

recurring survey on the general population's knowledge of alcohol use is in place and will enable monitoring of progress. The first edition showed that 55.6% of the adult Dutch population knows the Dutch guideline on alcohol use, 38.5% still believes 2 glasses of red wine are beneficial for health, and only 15.3% is aware that alcohol use can increase risk of breast cancer in women [60]. The focus on enhancing early detection is also in line with this thesis' findings, as we found that one of the barriers for healthcare providers to address alcohol use lies in difficulties with problem recognition. Our findings also showed that it is important to instruct healthcare providers on addressing alcohol use in a positive, non-judgemental tone-of-voice and emphasize the autonomy of the patient. So while increasing the overall knowledge on alcohol's adverse health effects is important, patients will appreciate more emphasis on short-term positive effects of alcohol moderation.

Selection of national initiatives In 2020, the Alcohol Policy Netherlands Alliance (Alliantie Alcoholbeleid Nederland) was founded [61]. This alliance is formed by several health and patient organizations. Its main objectives are for the Dutch policy on alcohol to be primarily informed by recommendations from the World Health Organization and to normalize the non-use of alcohol. 2018 saw the foundation of the Alcohol Prevention Alliance (Alliantie Alcoholpreventie) as part of the Healthy Generation Initiative, in which several health funds, including the Dutch Cancer Society (KWF Kankerbestrijding), are united to change societal alcohol norms by preventing alcohol use in youth [62].

Trimbos Institute, the Dutch national institute on mental health and addiction, founded the Expert Centre on Alcohol (Expertisecentrum Alcohol) in 2016 [63]. This centre collects and disseminates the latest scientific evidence on a broad array of alcohol-related topics, as well as policy developments, on a dedicated website. A complete subsection of the website focuses on the relation between alcohol and cancer [64].

International policy developments

Europe's Beating Cancer Plan In addition to these national agreements, the growing awareness of the association between alcohol use and cancer has also led to alcohol being a key part in the European Union's 'Europe's Beating Cancer Plan' [65]. This plan contains actions to support and coordinate efforts in member states to reduce the cancer burden throughout Europe, and prevention of tobacco use and reducing alcohol consumption are key elements. For example, efforts will be supported in reducing availability and affordability of tobacco and alcohol, as well as the implementation of brief interventions for alcohol use in health settings. As in the National Prevention Agreement, a key objective in this plan is to raise awareness on the risk of cancer development and alcohol use. A specific objective is to improve the quality of life of cancer survivors, focusing on unmet psychosocial needs, cancer recurrence, and late effects of treatment, amongst others. Financially, € 4 billion has been earmarked by the European Commission towards efforts in Europe's Beating Cancer Plan [65].

Policy developments summarized

We can thus conclude that since 2015 – the start of this project – there has been broader support for the discussion of adverse health effects of alcohol use and that smokers are increasingly being encouraged to quit smoking by more bans on tobacco use. In addition, the quality of life of the growing population of cancer survivors receives more systematic attention. This is the ideal time to implement support for alcohol moderation and smoking cessation among cancer survivors, with support from national and European initiatives, and use the lessons learned in the present thesis.

Financing and scaling digital health interventions

As one of the main features of the MyCourse interventions is that they present a low burden to healthcare providers and pose a low threshold to participants, to financially maintain these interventions, a construction in which the patient does not have to pay for the interventions would be recommended. For instance, a health insurance company or governmental institutions might reimburse the (relatively low) costs of hosting and updating the digital interventions. A recent promising development was the reinstatement of complete reimbursement of smoking cessation support in 2020 [59].

Financially maintaining digital health interventions has been an important, but as of yet unresolved question for many years. In the meantime, regulations for digital products have become more sophisticated in recent years. An important example is the introduction of the European General Data Protection Regulation Act in 2018 [66]. In this act, the protection of personal data in digital spaces is ensured in the European Union. There is a record amount of health promotion applications available, but each have their own limitations and they complicate finding the appropriate app. Several parties have attempted to order these apps in different overviews (in The Netherlands e.g., GGD Appstore, Loket GezondLeven [67, 68]) or incorporate them into broader programs (OncoKompas [69]), but they are limited by being used in specific settings only, thus a general, national overview is lacking. Due to the high paced development of new technology, many regulations, the fragmentation of digital healthcare, and the unresolved financial maintenance question, offering digital interventions on a small-scale is not feasible anymore. To tackle these issues and implement high quality digital interventions for the long-term, what is needed is clear ownership of a digital intervention and strong alliances between research institutions, healthcare providers, insurance companies and technological companies. These parties should work together in developing and later implementing a digital intervention, while determining clear responsibilities for each stakeholder, e.g. in the area of maintenance, security, dissemination, and financing.

Health inequalities

A major global concern in the public health field is the widening health gap [70]: systematic, potentially avoidable differences in health between social groups [71]. This is an increasing

concern in The Netherlands as well, as the gap in life expectancy between different education levels (a proxy for socio-economic status) has widened in the last decade [72]. While digital health interventions held the promise to deliver evidence-based care to more (traditionally underserved) people, in practice, they have been found to likely widen this gap, not close it. Those who are most in need of support are the least engaged with digital health interventions, while the high income, highly educated population has most access to these interventions [73–75]. Among cancer survivors specifically, it is those who are higher educated, married, employed, younger and have a higher income, who are most likely to use digital self-management interventions [20]. The demographic characteristics of participants in this thesis confirm this finding (Chapter 5 and 6). For the MyCourse interventions to not add to the exacerbation of health inequalities, they need to be easily accessible to all cancer survivors, not only by not charging participants for using them, but also by making sure that the content is suitable and appealing to those of lower socio-economic status and other groups who are currently underserved by digital interventions. What is more, as digital health interventions might not be suitable for all people, the MyCourse interventions should be part of a comprehensive strategy to provide support based on the patient's needs and preferences, in order to encourage alcohol moderation and smoking cessation equally among all cancer survivors. To inform this comprehensive strategy, we might look at descriptions of the implementation of comprehensive tobacco programs in oncology settings [76, 77]. Furthermore, specialists on underserved groups would have to be involved as well as the different underserved groups themselves.

Health messages in the 2020s

Throughout this thesis, the need for increased awareness on alcohol's adverse health effects has been emphasized. At the same time, our studies showed that people tend to be tired of health messages. For cancer survivors specifically, the amount of guidelines on diet, activity, and other health behaviours can be overwhelming. Further confusing the public is the problem posed by the abundance of (unverified) information on the Internet, which is presented without differentiation in sources, sometimes contradicting public health messages by healthcare organizations [78]. In the case of alcohol and tobacco use, misinformation or deliberate questioning of scientific evidence by the industry is an issue [79, 80]. Further complicating this problem are algorithms on search engine machines and social media, which as a consequence cause the received (mis)information to differ on an individual level. This can make it more difficult to dismantle misinformation. More generally a concerning development is that in recent years, scientific information seems to have lost some of its natural authority [78]. This has been attributed to a number of societal changes, including the aforementioned abundance of readily available misinformation, but also governmental leadership's response to scientific information [81]. Related to the health inequalities discussed before, it was found that people with limited health literacy were less likely to trust information from healthcare providers and less likely to search for health-related information on medical websites, but were more likely to trust social media, blogs, friends and television [82]. Several strategies have been proposed

to counter the increasing mistrust in science, including fostering of a symbiotic relationship between journalism and science [81, 83].

This is not a problem that only affects cancer survivors or the raising of awareness on the benefits of alcohol moderation and tobacco cessation. It will take national and global effort, across many disciplines, from policy makers to media companies and researchers, to ensure the trust of the general population, including cancer survivors, in scientific evidence. To bring across the message of the benefits of alcohol moderation and smoking cessation in cancer survivors, healthcare organizations can contribute by being as transparent as possible, actively disseminating their knowledge, focusing on underserved populations who might take more effort to reach (e.g., by efforts towards improving health literacy), and examining which factors increase trust in a health message. Any online marketing strategy for digital alcohol moderation and smoking cessation interventions should also take these developments into account.

General conclusion

There is a lack of dedicated, evidence-based support for alcohol moderation and smoking cessation in cancer survivors, especially for alcohol moderation. First, awareness needs to be raised on the benefits of both alcohol moderation and smoking cessation after a cancer diagnosis, both among the general population and among healthcare providers. Because of the significant influence of healthcare providers, they should be involved in any strategies to encourage alcohol moderation and smoking cessation in cancer survivors. Addressing alcohol and tobacco use in cancer survivors in a positive, non-judgemental, but proactive manner with emphasis on autonomy is important. Although the MyCourse interventions did not show increased effectiveness over control conditions, they did result in higher satisfaction rates and showed indications of beneficial cost-effectiveness. Digital interventions are low-cost and are valued by participants and healthcare providers, but the MyCourse interventions need to be optimized to increase their effectiveness over a digital information brochure. Alternative designs might be better suited than an RCT to evaluate individual components of digital interventions efficiently, or to evaluate individual differences in the effectiveness. A comprehensive strategy, incorporating other types of support in addition to digital interventions, will be needed to support all cancer survivors equally and not widen the health gap. Online health marketing can be a viable part of this strategy. To implement a comprehensive strategy for alcohol moderation and smoking cessation support including high quality digital interventions in any setting, including in the oncological setting, many stakeholders will have to collaborate.

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CHAPTER 10

Nederlandse samenvatting
(Dutch summary)

Ajla Mujčić

NEDERLANDSE SAMENVATTING

Verminderen van alcoholgebruik en stoppen met roken kan voor iedereen gezondheidsvoordelen opleveren, maar voor mensen die kanker hebben (gehad) kunnen deze gedragsveranderingen bovendien bijdragen aan gunstigere behandelresultaten en algeheel welzijn [1, 2]. Echter, gerichte ondersteuning bij het veranderen van alcohol- en tabaksgebruik onder mensen die kanker hebben (gehad) ontbreekt vaak [3, 4]. Mogelijk kunnen digitale interventies deze lacune opvullen. Dit proefschrift beschrijft de ontwikkeling en evaluatie van twee digitale interventies voor het verminderen van alcoholgebruik en stoppen met roken voor mensen die kanker hebben (gehad), en werpt licht op de rol die digitale interventies kunnen spelen bij het ondersteunen van mensen die kanker hebben (gehad) bij hun inspanningen om minder (of geen) alcohol te drinken en te stoppen met roken.

Samenvatting van de belangrijkste bevindingen

Hoofdstuk 2 presenteerde een systematische review en meta-analyses van op afstand geleverde (d.w.z. digitale, telefonische en gedrukte) alcohol- en tabaksinterventies voor mensen die kanker hebben (gehad). We hebben 17 onderzoeken (12 gerandomiseerde gecontroleerde onderzoeken (RCT's) en 4 niet-gerandomiseerde onderzoeken) in de kwalitatieve synthese opgenomen, waarvan 15 in de meta-analyse met in totaal 3.796 deelnemers. De meta-analyse van stoppen-met-roken-interventies resulteerde in hogere stoppercentages voor op afstand geleverde interventies bij mensen die kanker hebben (gehad) met een odds ratio (OR) van 1,56 (95% BI 1,13-2,15), gebaseerd op 10 onderzoeken die een op afstand geleverde interventie vergeleken met een controleconditie na 6 maanden (of de follow-up die het dichtst bij die periode ligt). De controlecondities varieerden van een wachtlijst tot gedrukte informatiebrochures of actieve begeleiding. De resultaten veranderden niet wanneer alleen de RCT's werden opgenomen of wanneer de missende waarden als rokers werden beschouwd. Er waren geen aanwijzingen voor publicatiebias. De heterogeniteit was echter hoog en voor alle onderzoeken waren er op zijn minst enige zorgen over vertekening van de resultaten.

Voor het verminderen van alcoholgebruik was er onvoldoende bewijs beschikbaar dat op afstand geleverde interventies tot meer vermindering van alcoholgebruik leidden dan controlecondities bij mensen die kanker hebben (gehad). Belangrijk om op te merken is dat er geen enkelvoudige gedragsinterventies werden gevonden die enkel gericht waren op het verminderen van alcoholgebruik. We vonden slechts drie onderzoeken naar interventies die een alcoholmodule bevatten, maar zij waren verder gericht op meerdere leefstijlgedragingen tegelijk.

Subgroepanalyses gaven aanwijzingen dat interventies gericht op één gedraging effectiever zouden kunnen zijn dan interventies gericht op meerdere gedragspatronen, bij het aanmoedigen van stoppen met roken. Dit werd geconcludeerd op basis van meta-analyses die de rookpercentages voor en na de behandeling vergelijken (in plaats van tussen een behandeling en een controlegroep).

Deze aanwijzingen werden niet gevonden in de meta-analyse waarin experimentele groepen werden vergeleken met controlegroepen, die een lager risico op bias hebben. Verder hebben we in hoofdstuk 2 laten zien dat maar weinig alcohol- en tabaksinterventies voor mensen die kanker hebben (gehad) digitaal waren, de meerderheid van de interventies was telefonisch.

In **Hoofdstuk 3** hebben we ingezoomd op het gebruik van een specifieke digitale alcoholinterventie voor de algemene bevolking in het Verenigd Koninkrijk: Down Your Drink. Deze onbegeleide, zelfhulpinterventie waaraan deelnemers in hun eigen tempo konden deelnemen en konden kiezen welke onderdelen ze gebruikten, was gebaseerd op technieken van motiverende gespreksvoering (MG) en cognitieve gedragstherapie (CGT). De interventie bevatte veel interactieve elementen en veel open tekstvelden bij vragen, waardoor een analyse mogelijk was van de aanwezigheid van verandertaal (*change talk)* en behoudtaal (*sustain talk*), evenals een analyse van het gebruik van andere belangrijke MG- en CGT-elementen.

Twee onafhankelijke codeurs beoordeelden de aanwezigheid van verandertaal en op basis van de antwoorden van de deelnemer tijdens de interventie met behulp van het Client Language EASy Rating (CLEAR)-coderingssysteem, evenals het gebruik van verschillende belangrijke MG- en CGT-componenten. Het bleek dat Down Your Drink verandertaal kon uitlokken. De meeste deelnemers toonden meer gevallen van verandertaal dan van behoudtaal. Een derde van de gebruikers (34,4% van degenen die minstens één keer hebben ingelogd) maakte gebruik van elementen die als actieve ingrediënten worden beschouwd bij korte alcoholinterventies: het monitoren van hun eigen alcoholgebruik en het opstellen van een terugvalplan.

In een verkennende secundaire data-analyse werd gevonden dat het aantal benoemde moeilijke situaties sterk geassocieerd was met een lager alcoholgebruik na 3 maanden follow-up (B_{adj} −2,15, 95% BI −3,92 tot −0,38, *P* =.02), zelfs na controle voor het aantal ingevoerde woorden als proxy voor de totale activiteit binnen de interventie. De bevindingen over de associaties tussen alcoholgebruik en de aanwezigheid van verandertaal, behoudtaal en het aantal genoemde strategieën om met moeilijke situaties om te gaan, waren inconsistent. Deze componenten kunnen mogelijk bijdragen aan een effectieve digitale alcoholinterventie, maar studies met een vooraf geregistreerd analyseplan zullen dit moeten bevestigen.

Voor de ontwikkeling van digitale interventies voor het minderen met alcohol en stoppen met roken, onderzochten we in **Hoofdstuk 4** hoe Nederlandse mensen die kanker hebben (gehad) kijken naar digitale ondersteuning. We maakten daarvoor gebruik van meerdere methoden. We voerden een online-enquête uit (n=240), vier focusgroepen (n=15) en semi-gestructureerde interviews met mensen die kanker hebben (gehad) (n=8). Ook werden een expertmeeting (n=7) en interviews (n=6) georganiseerd met experts op het gebied van eHealth voor mensen die kanker hebben (gehad) en experts op het gebied van ondersteuning bij minderen met alcohol of stoppen met roken. Eén van de belangrijkste bevindingen was dat er grote verschillen zijn

binnen de populatie van mensen die kanker hebben (gehad). Bij de meesten heeft de diagnose kanker hun dagelijks leven beïnvloed, zij het in verschillende mate. Velen zouden zich echter niet noodzakelijkerwijs identificeren als mensen die kanker hebben (gehad). Autonomie was een belangrijk thema, dat zich vertaalde in verschillende voorkeuren voor de toon en inhoud van de interventies. Dit was in lijn met eerder onderzoek naar ondersteuning bij het stoppen met roken voor mensen die kanker hebben (gehad). Digitale interventies voor minderen met alcohol en stoppen met roken voor mensen die kanker hebben (gehad) werden gezien als een waardevolle oplossing, op voorwaarde dat ze een positieve, niet-veroordelende en niet-betuttelende toon hadden en specifieke problemen die relevant zijn voor mensen die kanker hebben (gehad) bespreken (bijvoorbeeld grote vermoeidheid of bijwerkingen van behandelingen). Ook is het belangrijk dat stigmatisering wordt vermeden in deze interventies. Sommigen geven de voorkeur aan persoonlijk contact boven digitale interventies. We ontdekten ook dat om minder alcohol drinken bij mensen die kanker hebben (gehad) aan te moedigen, de herkenning van problematisch alcoholgebruik en kennis over de voordelen van minderen met alcohol moeten worden verbeterd. Het advies van zorgprofessionals werd over het algemeen zeer gewaardeerd door mensen met kanker. Oncologische zorgprofessionals zouden aangemoedigd kunnen worden om alcohol- en tabaksgebruik bij mensen die kanker hebben (gehad) meer routinematig aan te kaarten.

In **Hoofdstuk 5** wordt beschreven hoe de bevindingen uit de vorige hoofdstukken de ontwikkeling van de digitale interventies MijnKoers – Minderen met drinken en MijnKoers – Stoppen met roken vorm hebben gegeven. In dit hoofdstuk geven we een uitgebreide beschrijving van de twee interventies en het onderzoeksprotocol van de twee afzonderlijke – maar sterk vergelijkbare – pragmatische RCT's die zijn uitgevoerd om de interventies te evalueren. MG, CGT en *acceptance and commitment*-therapie (ACT) vormden de theoretische basis voor beide interventies. De interventies waren volledig digitaal, minimaal begeleid (alleen technische assistentie) en bevatten interactieve componenten. Deelnemers werden begeleid bij het opstellen van een moderatie- of stopplan, waarna ze verschillende oefeningen konden doen, een dagboek konden invullen om hun alcohol- of tabaksgebruik te monitoren, informatieve teksten konden lezen over minderen met alcohol of stoppen met roken, en gebruik konden maken van een peer-supportplatform.

De RCT's zijn prospectief geregistreerd in het Nederlands Trial Register (alcohol RCT: NTR6010; tabak RCT: NTR6011). Beide RCT's werden volledig online uitgevoerd met nametingen na 3, 6 en 12 maanden. De primaire uitkomstmaat in de alcohol RCT was alcoholgebruik in de afgelopen 7 dagen, voor de tabak RCT was het stoppen met roken geoperationaliseerd als niet roken in de afgelopen 7 dagen, beide uitkomstmaten werden beoordeeld bij de nameting na 6 maanden. Deelnemers werden gerandomiseerd naar ofwel de nieuw ontwikkelde MijnKoers-interventie of naar een controlegroep die een statische, online informatiebrochure ontving zonder interactieve elementen. Voor de analyse van de gegevens hebben we de *intention-to-*

treat-benadering gevolgd en eventuele ontbrekende gegevens zijn geïmputeerd met behulp van een meervoudige imputatiemethode.

In dit hoofdstuk presenteren we naast de RCT's ook het protocol voor de gezondheidseconomische evaluaties. We berekenden incrementele kosteneffectiviteitsratio's (ICER) om de kosteneffectiviteit en kostenutiliteit van beide interventies te evalueren. We hebben interventiekosten, kosten voor gezondheidszorg en kosten als gevolg van productiviteitsverliezen geschat over de volledige studieduur van 12 maanden. De Trimbos/iMTA-vragenlijst voor kosten geassocieerd met psychiatrische aandoeningen (TiC-P) werd gebruikt om zelfgerapporteerde zorgkosten en kosten als gevolg van productiviteitsverlies te beoordelen, terwijl kwaliteit van leven (QALY's) werd beoordeeld met behulp van de instrumenten EQ-5D en SF-36.

In **Hoofdstuk 6 en 7** presenteren we de effectiviteit, kosteneffectiviteit en kostenutiliteit van de MijnKoers-interventies voor mensen die kanker hebben (gehad), zoals geëvalueerd in twee pragmatische RCT's in een praktijksituatie. In de alcohol RCT werden 103 deelnemers geïncludeerd en geanalyseerd. In de tabak RCT hebben we 271 deelnemers geïncludeerd.

MijnKoers – Minderen met drinken en MijnKoers – Stoppen met roken verminderden respectievelijk het alcoholgebruik en bevorderden het stoppen met roken op de lange termijn, maar waren niet effectiever dan de controlegroepen, behalve dat MijnKoers – Stoppen met roken na 12 maanden leidde tot een grotere vermindering van sigaretten in vergelijking met de controlegroep.

Uit de gezondheidseconomische evaluatie bleek dat de kosten van het aanbieden van de MijnKoers-interventies laag zijn; per deelnemer waren de kosten US$ 193 voor MijnKoers – Stoppen met roken en US$ 279 voor MijnKoers – Minderen met drinken. MijnKoers – Minderen met drinken leidde tot een grotere vermindering van alcoholgebruik tegen lagere maatschappelijke kosten in vergelijking met de controlegroep; gemiddelde incrementele maatschappelijke kosten per deelnemer per verminderd drankje waren US$ −1.158 (95% BI −1.609 tot −781) voor de MijnKoers-interventie.

MijnKoers – Stoppen met roken leidde tot een grotere reductie van pakjaren (*pack-years*), maar tegen hogere maatschappelijke kosten, waardoor de controleconditie (bestaande uit een online niet-interactieve informatiebrochure) mogelijk economisch duurzamer is. De gemiddelde incrementele maatschappelijke kosten per deelnemer per voorkomen pakjaar waren US$ 52.067 (95%CI US$ 32.515 tot US$ 81.346) voor de MijnKoers-interventie.

De maatschappelijke kosten waren US$ 5.404 (SD = 42.859) lager in de MijnKoers – Minderen met drinken-groep in vergelijking met de controlegroep, en waren US$ 3.493 (SD = 38.913) hoger in de MijnKoers – Stoppen met roken-groep in vergelijking met de controlegroep. De belangrijkste oorzaak van de kostenverschillen tussen de MijnKoers-groepen en de controlegroepen waren

zorgkosten en kosten als gevolg van productiviteitsverlies, maar de variatie in deze kosten binnen de groepen was ook hoog, mogelijk als gevolg van de hoge heterogeniteit in zorggebruik onder mensen die kanker hebben (gehad). Om de bron van de kostenverschillen te bepalen is meer onderzoek nodig.

Beide MijnKoers-interventies leidden tot marginaal lagere winsten in QALY's in de economische evaluatie, er is geen significant effect gevonden op QALY's in de effectevaluaties. Bij de MijnKoers – Minderen met drinken-interventie werden minder QALY's gewonnen tegen lagere kosten, voor de MijnKoers – Stoppen met roken-interventie werden minder QALY's gewonnen tegen hogere kosten.

Beide MijnKoers-interventies leidden tot hogere tevredenheidsscores dan de controlegroepen. Het is mogelijk dat de relatief hoge belasting met vragenlijsten een effect op de primaire uitkomstmaten maskeerde. Bovendien was de duur van de laatste nameting (12 maanden) mogelijk te kort om een effect op de kwaliteit van leven op te merken bij de populatie van mensen die kanker hebben (gehad).

Ten slotte evalueerden we de MijnKoers-interventies vanuit een breder perspectief ten behoeve van mogelijke toekomstige implementatie. **Hoofdstuk 8** beschrijft het gebruik van een *mixed method*-benadering voor de evaluatie van de interventies volgens de RE-AIM-benadering, wat een evaluatie inhoudt op vijf dimensies: bereik (*reach*), effectiviteit (*effectiveness*), adoptie (*adoption*), implementatie (*implementation*) en onderhoud (*maintenance*). We gebruikten zowel offline als online wervingsstrategieën voor de interventies. Online wervingsstrategieën, met name via sociale media, slaagden erin om mensen die kanker hebben (gehad) te bereiken, maar de zeer specifieke online *targeting*-mogelijkheden kunnen voor onbehagen zorgen en daarom moet bij online advertenties extra aandacht worden besteed aan het respecteren van de privacy en aan het vermijden van stigmatisering. De deelnamepercentages waren redelijk met 32-35%, maar zouden buiten een studiesetting hoger kunnen zijn vanwege de studiebelasting. We beschreven kort een observationeel onderzoek waarin degenen die niet in aanmerking kwamen voor de RCT's, voornamelijk omdat ze geen kankerdiagnose hebben gehad, direct toegang hadden tot de interventies, nadat ze een korte vragenlijst hadden ingevuld. We vonden adoptiepercentages vergelijkbaar met die bij mensen die kanker hebben (gehad), wat suggereert dat de MijnKoers-interventies kunnen worden aangepast en vervolgens ook aan de algemene bevolking kunnen worden aangeboden. De interventies werden door mensen die kanker hebben (gehad) en professionals in de gezondheidszorg als laagdrempelig en niet-belastend ervaren. Mensen die kanker hebben (gehad) waardeerden de focus op voordelen op de korte termijn. Om blijvend gebruik van de interventie te bevorderen, stelden mensen die kanker hebben (gehad) voor om de interventies aan te passen (bijv. meer begeleiding en flexibiliteit, technische verbeteringen), terwijl voor professionals in de gezondheidszorg het voortzetten van het gebruik zou afhangen van de effectiviteit van de interventies. We vonden

opnieuw, zoals eerder in **Hoofdstuk 4**, dat het aanpakken van alcohol- en tabaksgebruik door professionals in de gezondheidszorg zou moeten worden aangemoedigd. Daarnaast constateerden we dat op veel oncologieafdelingen niet duidelijk was wie verantwoordelijk was voor leefstijladviezen aan patiënten en dat dit verder werd bemoeilijkt door de variatie in organisatiestructuren tussen afdelingen en ziekenhuizen.

Reflecties op de belangrijkste bevindingen in de context van eerdere literatuur

We vonden geen verschil in verminderen van alcoholgebruik of stoppen met roken tussen de MijnKoers-groepen en controlegroepen. Studies naar vergelijkbare digitale interventies gericht op de algemene bevolking vonden wel een effect op het alcoholgebruik in de afgelopen 7 dagen [5]. We vonden een afname van ongeveer 90 g ethanol (SD = 15,0) in de MijnKoers-groep en 60 g (SD = 16,4) in de controlegroep na 6 maanden, die na 12 maanden toenam tot respectievelijk ongeveer 120 g en 70 g. Er werd echter geen significant verschil gevonden tussen de groepen. Een meta-analyse van digitale interventies onder de algemene bevolking toonde aan dat digitale interventies (begeleid én onbegeleid) het alcoholgebruik met 50 g meer verminderden dan controlegroepen [5]. Deze meta-analyse omvatte begeleide interventies, maar ook wanneer alleen werd gekeken naar onbegeleide interventies werd een significant interventie-effect gevonden van ongeveer 30 g meer alcoholvermindering. Wanneer alleen werd gekeken naar het effect van begeleide digitale interventies, was de vermindering 100 g groter dan in controlegroepen. Uitkomsten verschilden afhankelijk van het type controlegroep; in vergelijking met controlegroepen op de wachtlijst waren de effecten van een digitale interventie hoger dan in vergelijking met controlegroepen die uit een vragenlijst bestonden of controlegroepen die een minimale interventie bevatten. De periode van de nametingen varieerde in de meta-analyse van 1 tot 6 maanden en had geen invloed op de uitkomsten [5]. Voor zover wij weten, is er geen meta-analyse of onderzoek naar een digitale interventie enkel gericht op minderen met drinken bij mensen die kanker hebben (gehad). Het effect op het verminderen van alcoholgebruik in de MijnKoers-interventiegroep is kleiner dan in eerdere onderzoeken naar digitale alcoholinterventies.

We ontdekten dat het percentage gestopte rokers na 6 maanden 27,7% was in de MijnKoers-groep en 25,6% in de controlegroep, zonder significant verschil tussen de twee groepen. Onder de algemene bevolking toonde een meta-analyse van digitale interventies voor stoppen met roken significant hogere stoppercentages van 14,8% in digitale interventiegroepen vergeleken met 12,9% in niet-actieve controlegroepen (bijv. gebruikelijke zorg of zelfhulpgidsen) (Relatief risico [RR] = 1,15, 95% betrouwbaarheidsinterval [BI] 1,01 tot 1,30) [6]. Echter, wanneer digitale interventies werden vergeleken met een actieve controlegroep (bijv. telefonische counseling), verschilden de stoppercentages niet significant tussen groepen (RR = 0,92, 95% BI 0,78 tot 1,09). Onder mensen die kanker hebben (gehad) vonden we hogere stoppercentages voor op afstand geleverde stoppen-met-roken-interventies in vergelijking met controlegroepen

in **Hoofdstuk 2** (OR = 1,56; 95% BI, 1,13-2,15) [7]; deze meta-analyse omvatte zowel actieve als inactieve controlegroepen. Vergeleken met onze RCT vonden de onderzoeken waarnaar in de power-analyse wordt verwezen, vergelijkbare (23% [8]) of hogere (30% [9]) stoppercentages in de experimentele groep, maar veel lagere stoppercentages in de controlegroepen met 15% [9] en 10% [8], versus 25,6% in ons onderzoek. De controlegroepen in die eerdere onderzoeken bestonden uit gebruikelijke zorg, waaronder een verwijzing voor meer ondersteuning [9] of een landelijke website voor stoppen met roken [8]. Een recentere pilotstudie naar een mobiele applicatie om te stoppen met roken voor mensen die kanker hebben (gehad) vond voorlopige stoppercentages van 20% in de experimentele groep en 7% in de controlegroep (missende waarden werden buiten beschouwing gelaten). De controlegroep in die pilotstudie ontving ook een smartphone-applicatie voor stoppen met roken, maar die applicatie was niet afgestemd op mensen die kanker hebben (gehad) [10].

Samenvattend zijn de effecten op het verminderen van alcoholgebruik en stoppen met roken in de MijnKoers-interventiegroepen kleiner dan in eerdere onderzoeken naar digitale alcoholinterventies en ze zijn enigszins vergelijkbaar met andere digitale tabaksinterventies. Tegelijkertijd zijn de effecten die we in de huidige controlegroepen vonden groter dan in de literatuur.

We stellen verschillende verklaringen voor, voor de kleine verschillen tussen de MijnKoers-groepen en controlegroepen. Aangezien de studiebelasting aanzienlijk was (12 maanden inclusief meerdere nametingen) en de deelnemers zichzelf aanmeldden voor het onderzoek, is het mogelijk dat de deelnemers aan het onderzoek een selectie waren van zeer gemotiveerde individuen, waardoor het effect in de controlegroepen toenam. Het is ook mogelijk dat deelnemende mensen die kanker hebben (gehad) nog gemotiveerder zijn dan de algemene bevolking, aangezien weinig studies zich specifiek op deze doelgroep hebben gericht. De vele nametingen en meerdere herinneringen hebben mogelijk als interventie-elementen in de controlegroep gefunctioneerd, omdat ze de deelnemers aanspoorden om regelmatig na te denken over hun alcohol- of tabaksgebruik. Deelnemers in de controlegroep van de roken-RCT gebruikten vaker nicotinevervangende middelen, wat mogelijk de relatief hoge stoppercentages verklaart. Beide groepen in de alcohol-RCT maakten zelden gebruik van aanvullende ondersteuning. Buiten de context van een onderzoek, wanneer er geen vragenlijsten en herinneringen meer van toepassing zijn, kan de controleconditie nog steeds een effect hebben op minderen met alcohol en stoppen met roken. In onderzoek naar psychotherapie trad bij sommige mensen direct na het maken van een eerste afspraak al verbetering op, nog voor aanvang van de daadwerkelijke behandeling [11]. Positieve verwachtingen over de behandeling verklaren dit effect deels [12, 13]. In ons onderzoek was het wervingsmateriaal voor de interventies en de informatiebrochure in de controleconditie duidelijk gericht op het positief aankaarten van alcohol- en tabaksgebruik, wat in **Hoofdstuk 4** een belangrijke voorwaarde bleek te zijn voor acceptatie bij mensen die kanker hebben (gehad). Verder was het Trimbos-instituut, een gerenommeerd instituut, de afzender van deze berichten. Het is daarom aannemelijk dat de

controleconditie een interventie-effect had op basis van positieve verwachtingen. Dit 'placebo-effect' is momenteel onderbelicht in psychologische behandelingen, maar als het eenmaal wordt begrepen, kan het de evaluatie van psychologische interventies verbeteren [13].

De interventies waren gebaseerd op ACT, CGT en MG. Interventies en componenten op basis van deze theorieën zijn in eerdere studies effectief gebleken [14-16]. Toch leidt het gebrek aan gevonden effect in dit proefschrift tot de conclusie dat de componenten op basis van deze theorieën op zichzelf niet krachtig genoeg waren om een grotere effectiviteit te bereiken dan een informatiebrochure. Betrokkenheid bij en gebruik van de interventie moet mogelijk meer worden aangemoedigd om het effect van deze componenten te merken. Bevindingen uit andere disciplines kunnen deze optimalisaties informeren [17].

Op basis van de reflecties op onze belangrijkste bevindingen en onze RE-AIM-analyse in **hoofdstuk 8**, stellen we de volgende aanpassingen aan de interventie voor om de betrokkenheid bij en de effectiviteit van de MijnKoers-interventies te vergroten: toevoeging van begeleiding door een zorgverlener, bij voorkeur *on-demand* begeleiding op moeilijke momenten, meer flexibiliteit bij het opstellen en wijzigen van doelen, meer aanmoediging van het gebruik van nicotinevervangende middelen en verdere verbeteringen aan het gebruikersgemak van de interventies. Ten slotte hadden we door een andere onderzoeksopzet te kiezen wellicht beter kunnen begrijpen welke componenten behouden, toegevoegd of verwijderd moeten worden om de effectiviteit te optimaliseren.

Algemene conclusie

Er is een gebrek aan gerichte, empirisch onderbouwde ondersteuning voor het minderen met alcohol en het stoppen met roken bij mensen die kanker hebben (gehad), en dan met name voor het minderen met alcohol. Ten eerste moet het bewustzijn worden vergroot over de voordelen van minderen met alcohol en stoppen met roken na een diagnose van kanker, zowel bij de algemene bevolking als bij zorgverleners. Vanwege de aanzienlijke invloed van zorgverleners, moeten zij worden betrokken bij alle strategieën om minderen met alcohol en stoppen met roken bij mensen die kanker hebben (gehad) aan te moedigen. Het is belangrijk om alcohol- en tabaksgebruik bij mensen die kanker hebben (gehad) op een positieve, niet-veroordelende, maar proactieve manier aan te kaarten met de nadruk op de autonomie van de cliënt. Hoewel de MijnKoers-interventies geen verhoogde effectiviteit lieten zien ten opzichte van controlecondities, resulteerden ze wel in hogere tevredenheidspercentages en indicaties van gunstige kosteneffectiviteit. Digitale interventies hebben lage kosten per deelnemer en worden gewaardeerd door deelnemers en zorgverleners, maar de MijnKoers-interventies moeten worden geoptimaliseerd om hun effectiviteit te vergroten ten opzichte van een digitale informatiebrochure. Alternatieve ontwerpen zijn wellicht beter geschikt dan een RCT om individuele componenten van digitale interventies efficiënt te evalueren, of om individuele verschillen in effectiviteit te evalueren. Er zal een veelomvattende strategie nodig zijn, die naast

digitale interventies ook andere soorten ondersteuning omvat, om alle mensen die kanker hebben (gehad) in gelijke mate te ondersteunen en de gezondheidskloof in de samenleving niet verder te vergroten. Online gezondheidsmarketing kan onderdeel zijn van deze strategie. Om een alomvattende strategie voor de ondersteuning bij minderen met alcohol en stoppen met roken te implementeren, inclusief digitale interventies van hoge kwaliteit, zullen in iedere setting en zo ook in de oncologische setting, veel belanghebbenden moeten samenwerken.

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APPENDICES

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Portfolio

Curriculum Vitae of author

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Enis, mijn alles, die als geen ander het belangrijke onderscheidt. Al het mooie in deze wereld komt samen in jou. En ons lieve, kleine wonder.

Ajla Kahrimanović-Mujčić

PORTFOLIO

List of publications

Mujcic, A., Blankers, M., Boon, B., Berman, A.H., Riper, H., Van Laar, M., Engels, R. Effectiveness, cost-effectiveness and cost-utility of a digital alcohol moderation intervention for cancer survivors: health economic evaluation and outcomes of a pragmatic randomised controlled trial. 2022. doi:10.2196/30095.

Mujcic, A., Blankers, M., Boon, B., Verdonck-de Leeuw, I.M., Smit, F., Van Laar, M., Engels, R. Effectiveness, cost-effectiveness and cost-utility of a digital smoking cessation intervention for cancer survivors: health economic evaluation and outcomes of a pragmatic randomised controlled trial. 2022. doi: 10.2196/27588.

Mujcic, A., Blankers, M., Yildirim, D., Boon, B., Engels, R. Cancer survivors' views on digital support for smoking cessation and alcohol moderation: a survey and qualitative study. BMC Public Health. 2021;21:1763. doi:10.1186/s12889-021-11785-7.

Scheffers-van Schayck, T., Mujcic, A., Otten, R., Engels, R., & Kleinjan, M. The Effectiveness of Smoking Cessation Interventions Tailored to Smoking Parents of Children Aged 0–18 Years: A Meta-Analysis. European Addiction Research. 2021;27(4), 278-293. doi:10.1159/000511145.

Mujcic, A., Linke, S., Hamilton, F., Phillips, A., Khadjesari, Z. Engagement With Motivational Interviewing and Cognitive Behavioral Therapy Components of a Web-Based Alcohol Intervention, Elicitation of Change Talk and Sustain Talk, and Impact on Drinking Outcomes: Secondary Data Analysis. J Med Internet Res [Internet]. 2020 Sep 1;22(9):e17285. doi:10.2196/17285.

Mujcic, A., Blankers, M., Bommelé, J., Boon, B., Berman, A.H., Verdonck-de Leeuw, I.M., van Laar, M., & Engels, R. The effectiveness of distance-based interventions for smoking cessation and alcohol moderation among cancer survivors: A meta-analysis. Psycho-Oncology. 2019;18(October 2019), 49–60. doi:10.1002/pon.5261.

Mujcic, A., Blankers, M., Boon B., Engels, R., van Laar, M. Internet-based self-help smoking cessation and alcohol moderation interventions for cancer survivors: a study protocol of two RCTs. BMC Cancer. 2018;18:364. doi:10.1186/s12885-018-4206-z.

Blankers, M. & Mujcic, A. E-health and m-health: using new technologies to respond to drug problems. EMCDDA Drugs Library. 2017.

Submitted

Mujcic, A., Kesler, D., Blankers, M., Boon, B., Van Laar, M., Engels, R. Evaluation of two digital alcohol and tobacco interventions for cancer survivors using the RE-AIM framework. 2021. (*submitted*).

In Dutch

Van Laar, M., Beenakkers, E., Cruts, G., Ketelaars, T., Kuin, M., Meijer., R., Van Miltenburg, C., Mujcic, A., Strada, L. (2021). Jaarbericht Nationale Drug Monitor 2020. Trimbos-instituut, Utrecht & WODC, Den Haag.

Mujcic, A. Alcohol en kanker. Expertisecentrum Alcohol [Internet]. Trimbos.nl. [cited 2022 Feb 4]. Available from: https://expertisecentrumalcohol.trimbos.nl/dossiers/inzien/alcohol-en-kanker.

Presentations

14.10.2021: Webinar Alcohol and Cancer (in Dutch) Trimbos Institute – oral presentation – online

10.06.2021: Health by Technology Conference – poster presentation – online

18.09.2021: SRNT-E Society for Research on Nicotine and Tobacco Europe – oral presentation – online

26.09.2019: INEBRIA International Network on Brief Interventions for Alcohol & Other Drugs – oral presentation – Lübeck, D

06.06.2019: KBS Annual Alcohol Epidemiology Symposium of the Kettil Bruun Society – oral presentation – Utrecht, NL

30.06.2018: SPR Society for Psychotherapy Research – oral presentation – Amsterdam, NL

26.05.2018: EASAR European Association of Substance Abuse Research – oral presentation – Vienna, AU

14.10.2017: ISRII International Society for Research on Internet Interventions – poster presentation – Berlin, D

20.05.2017: EASAR European Association of Substance Abuse Research – oral presentation – Nunspeet, NL

10.02.2017: NNVT National Tobacco conference – oral presentation – Utrecht, NL

05.09.2016: Thematic meeting on Addiction – oral presentation – Marquette, MI, USA

17.05.2016: Dutch Cancer Society Psycho-oncology working group – oral presentation – Utrecht, NL

18.03.2016: NVPO-conference (National conference on psycho-oncology) – poster presentation – Utrecht, NL

Courses/training

16.09.2019: Project management (Phaos & Trimbos Institute)
17.05.2019: Large-scale register data for quantitative social research (CBS & Erasmus University Rotterdam)
14.05.2019: Data visualisation, web scraping, and text analysis in R (Erasmus University Rotterdam)
27.09.2018: EGSH Professionalism and integrity in research (Erasmus University Rotterdam)
19.03.2018: Modern methods in data-analysis (Utrecht University)
11.09.2017: Introduction to Epidemiology (Utrecht University)
14.08.2017: Applied Multivariate Analysis (Utrecht University)
12.01.2017: Qualitative Analysis: Theory and Practice (Utrecht University)
21.11.2016: Academic Writing in English (Babel)
14.03.2016: BROM Basis Regelgeving Onderzoeksmethoden (Trimbos Institute)

Workshops and masterclasses

26.10.2017: Workshop Logdata (Trimbos Institute & University of Twente)
06.04.2017: Masterclass on self-management by prof. dr. Kate Lorig (KWF Werkgemeenschap Psychosociale Oncologie)
15.03.2016: Workshop Health economic evaluation alongside randomized controlled trials (Trimbos Institute & Maastricht University)
23.02.2016: Workshop Intervention Mapping (Trimbos Institute & Maastricht University)

Regular intervision meetings

2017: Meta-analysis intervision meetings (Utrecht University)
2017: Intervention evaluation intervision meetings (Utrecht University)
2017: Studying development: Longitudinal analyses intervision meetings (Utrecht University)

Supervision

Supervision of 2 MSc students writing their Masters theses (University of Amsterdam), 2016 & 2018.

Visiting academic

University College London, Primary Care and Population Health, eHealth Unit, March - April 2019

Granted funding applications

2018: Erasmus Trust Fund Foundation (the Netherlands), Research visit UCL, € 700
2018: Foundation “De Drie Lichten” (the Netherlands), Research visit UCL, € 1000
2018: Foundation “Jo Kolk Studiefonds” (the Netherlands), Research Visit UCL, € 1000

CURRICULUM VITAE

Ajla Kahrimanović-Mujčić (*née*: Ajla Mujčić) was born on 9 September 1991 in Srebrenica, Bosnia and Herzegovina. After completing her secondary education at RSG 't Rijks in Bergen op Zoom, The Netherlands in 2009, she continued to study Psychology (track: Brain and Cognition) and Philosophy of Science at Erasmus University Rotterdam. She then continued to obtain her Master's degree in Clinical Neuropsychology from Leiden University in 2014. During her studies, she gained experience as a psychologist at GGZ Westelijk Noord-Brabant and subsequently gained her BAPD-certificate and LOGO-certification.

In October 2015 she started her PhD studies at the Trimbos Institute in Utrecht, The Netherlands. After being affiliated with Utrecht University until 2017, she finished her PhD studies at Erasmus University Rotterdam, following her supervisor. Ajla received competitive grants from the Erasmus Trust Fund Foundation, Foundation De Drie Lichten, and Foundation Jo Kolk Studiefonds, for a two-month research visit with the eHealth Unit at University College London.

Since 2020, she has worked as a scientific researcher at the Department of Drugs at the Trimbos Institute, focusing on the subjects of alcohol and cocaine as well as large population surveys. In 2021, she led the digital transition of the National Drug Monitor. She is part of the Expertise Center on Alcohol, where she holds the dossier on alcohol and cancer. In January 2022, she has been appointed head of the Centre of Innovation at the Trimbos Institute.