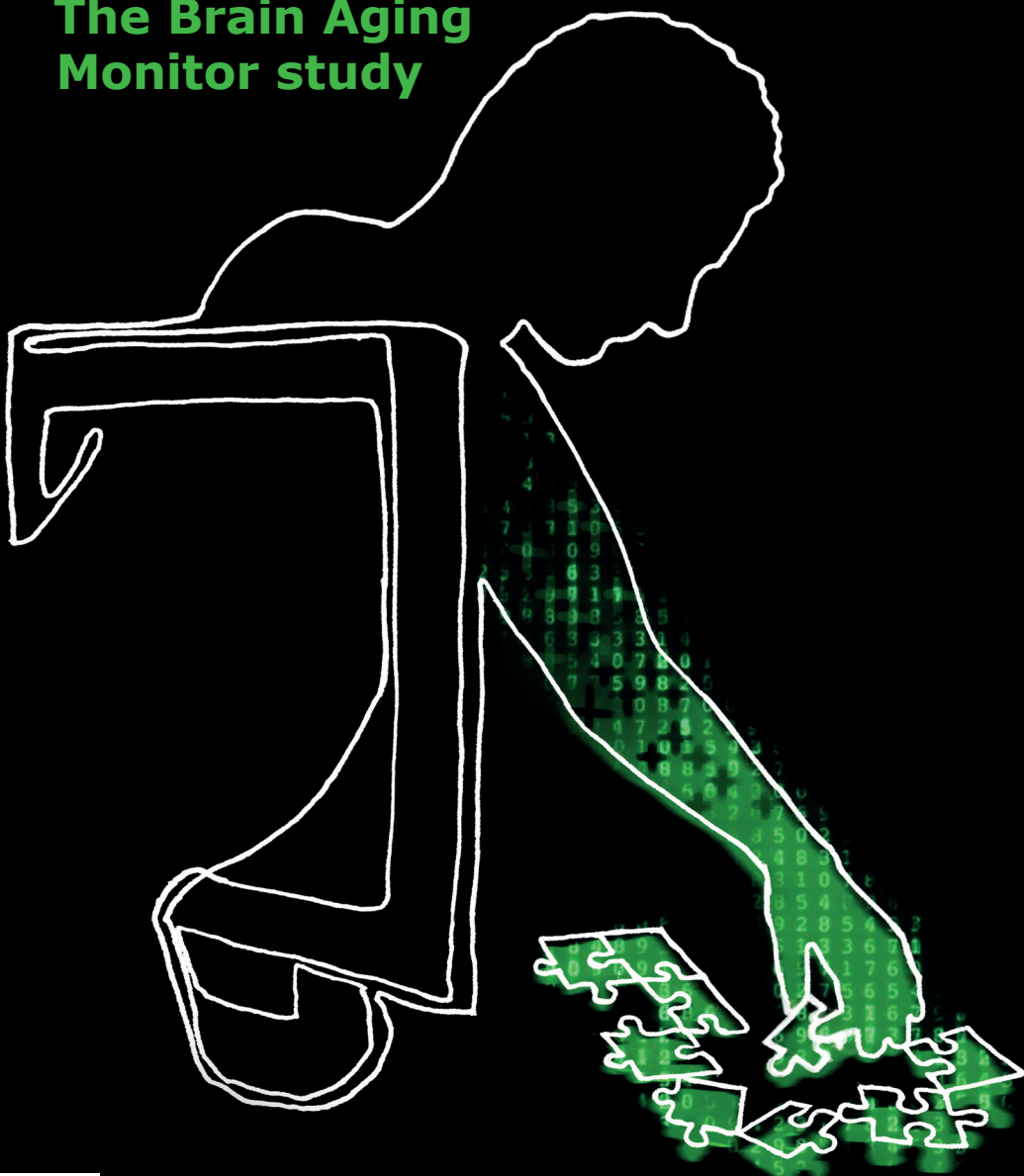


eHEALTH IN THE PRIMARY PREVENTION OF COGNITIVE DECLINE:

**The Brain Aging
Monitor study**



DONDERS
S E R I E S

Teun Aalbers

eHEALTH IN THE PRIMARY PREVENTION OF COGNITIVE DECLINE:

The Brain Aging Monitor study

Teun Aalbers

eHealth in the primary prevention of cognitive decline; The Brain Aging Monitor study

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eHEALTH IN THE PRIMARY PREVENTION OF COGNITIVE DECLINE: The Brain Aging Monitor study

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according to the decision of the Council of Deans
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1

GENERAL INTRODUCTION



Case

A 47 year old male is slouched in his chair, he just accidentally knocked his bag of potato chips to the floor and in the attempt to rescue it, spilled his drink all over the keyboard of his gaming pc. To his horror he witnesses the screen going dark just before completing his World of Warcraft mission. His progress of the last two hours of game time is lost. Sighing he gets himself on his feet to get some paper towel from the kitchen. He will have to start all over again, which means playing well into the night, losing valuable sleep over it. Strangely enough he feels this is kind of exciting. World of Warcraft is a great game after all. Even after all the countless hours he spend on this game it still gives him the fulfillment and excitement that it gave him the first time he opened the box. Quite contrary to the diet and exercise program he gave up on this week after only completing a total of seven workouts in three weeks time.

This is not just an incidental story about a particular gamer. It is a story about millions of people, a story that is told every day, all around the world, in people of all walks of life. People spent thousands of hours in bars, behind books, in virtual realities, or behind their screens at work. Yet, when it comes to their health, people do not seem so eager to allocate their valuable time to a healthy lifestyle.

This thesis addresses this problem and specifically focuses on the power of eHealth in preventing early cognitive decline. Conceptualizing, developing, implementing and evaluating eHealth is an activity that is new and exciting, may offer opportunities in realizing such an ambitious goal, but also challenges researchers and the prevailing scientific methodology. Led by Simon Sinek, entrepreneurs are told to start the story of their business with the *why* of their business (Sinek, 2009). It is useful to introduce *why* healthy living is beneficial for aging individuals, and to establish why and how eHealth can play a role in obtaining and maintain such a healthy lifestyle. Next to addressing these questions I will give a short description of what is considered to be eHealth, which is a buzz-word nowadays, and how it has transformed and will continue to shape the health care landscape. Finally, this chapter ends with a concise overview of the content of this thesis.

Why healthy living at midlife is beneficial at old age

A number of modifiable lifestyle risk factors have been identified over the last years that all have an impact on both physical and cognitive health. A recent systematic review listed the most common and therefore most promising preventable risk factors, all increasing the relative risk of getting Alzheimer's disease. Diabetes mellitus (RR 1.46), Midlife hypertension (RR 1.61), Midlife obesity (RR 1.60), Physical inactivity (RR 1.82), Depression (RR 1.65), Smoking (RR 1.59), and Low educational attainment (RR 1.59), all result in increased relative risk profiles (Norton et al, 2014). Together with the

notion of the frequent co-occurrence of unhealthy behavior within the general population, it becomes clear that individuals who live their lives in an unhealthy manner have a lot of room for improvement (Hofstetter et al, 2014).

To learn if people were actually motivated to change their lifestyle behavior and if there was any room for improvement, we send out an internal survey amongst nearly half the Radboudumc employees at the outset of my PhD. With this survey we collected data on willingness to change, showing that 36.5% of middle aged employees would appreciate help from their employer while working on their lifestyle. In our Dutch society where a substantial percentage of the population is overweight or obese (ranging between 48.9-56.3% for age cohorts between 40-65 years old (CBS)), approximately 35-40% of the adult population does not adhere to the Dutch healthy exercise norm (NNGB), 25% of the adult population still smokes, one third of the adults suffers from sleeping problems, and 13% of the workforce suffered the consequences of a burn-out. In sum, there definitely is room for improvement for healthy brain aging. The current state of affairs in the Netherlands and relative risk for cognitive decline due to unhealthy habits led to the research questions this thesis aims to answer. The type of intervention suitable for potential population wide implementation was found in eHealth.

Why would we stimulate the use of eHealth?

A quote by Dave deBronkart, cancer survivor and health care reformist, beautifully explicates the *why* of the need for change and innovation in health care, and why we need information technology to be successful in these changes;

"The stakes are obviously very high in healthcare; you are potentially 'playing' with people's lives when utilizing new technologies. By trying to reform and change healthcare by doing exactly what we are already doing, and trying to jam this reform into existing and broken models of delivering care, and expecting better health outcomes and more efficiencies is the epitome of insanity. We have to accept that the prevailing Western model of delivering healthcare is broken and free up the regulatory framework (while protecting physician/patient safety) to unleash new opportunities for innovation." (Mesko, 2014)

deBronkart's plea for large scale innovation in health care, for effective and efficient, new information technologies, which fit the contemporary request for individualized care. He summarizes a number of health care challenges, the answer to which could lie in eHealth. Our current Western health care systems are too expensive to maintain into the near future which will be dominated by longer life expectancy (Salomon et al, 2012), a chronic disease pandemic (Nair et al, 2012; Terzic & Waldman, 2011) and age-related neurodegenerative diseases (Prince et al, 2013; Prince et al, 2015), which contributes to the ever increasing health care costs in the Netherlands, already

doubling over the period 1999-2011 and expected to rise only further (CBS Statline, 2013; <http://www.webcitation.org/6fvnyqrhr>). In order to be able to manage and control these oncoming challenges, deliver sustainable health care, and be able to customize health services delivery to the increasing heterogeneity of the aging populations, we urgently need new cost-effective alternatives, which are likely disruptive innovations.

Just as in the mission statement of the Radboudumc, DeBronkart and many other patients call for innovations that make *the patient partner in health care delivery*, and allows patients to exert more control about their own treatment, improve self-management and shared decision making (Bravo et al, 2015; Radboudumc, 2014). These topics also found their way into the scientific literature (Bravo et al, 2015; Sacchi et al, 2015). eHealth is, can and most likely will play a major role in the patient's process of self-management, both in self-monitoring, self-diagnosis and self-treatment. This does not necessarily mean that everyone will and should take a similar high level of involvement in one's own health care, but that ample opportunity should be provided for those people that want to be in control. This *new patient* therefore requires new tools, will be greatly helped with eHealth facilities, and will be in favor of a new *type of professional*, that is more technology minded (Barakat et al, 2013).

What is eHealth?

Following the World Health Organizations definition of eHealth it is "*the transfer of health resources and health care by electronic means. It encompasses three main areas: 1) the delivery of health information, for health professionals and health consumers, through the Internet and telecommunications; 2) using the power of IT and e-commerce to improve public health services, and; 3) the use of e-commerce and e-business practices in health systems management.*" (<http://www.webcitation.org/6dnm3vH2m>). In addition, the Dutch Council for Public Health and Health Care (Meurs et al, 2015), in their definition, emphasize the use of internet technology to *support* and *enhance* health and health care (Meurs et al, 2015). This thesis mostly focuses on the *delivery of health information* and the *support* of health care.

There still is great lack of information on how digital health information is best delivered to the end user. Evidence acquired on face-to-face or paper-and-pencil approaches, in preventive medicine on age-related health problems, does not necessarily apply to eHealth services. This thesis is aimed at providing another piece of the puzzle. Moreover, finding an appropriate evaluation framework, to study and monitor efficacy and cost-effectiveness of the quickly changing eHealth interventions also needs further research and is a very important research goal on itself (Webb et al, 2010) for the coming decade. Classical research methods in medicine often are too slow, and

cannot keep up with technological advances made possible by Moore's law of exponential IT innovation. Therefore, we will also pay attention to methodological aspects of eHealth evaluation in this thesis.

What are the eHealth priorities in our aging societies?

The need for more prevention research, and the emergence of this pillar of research was recently acknowledged by the Dutch Council for Public Health and Health Care. Specifically the increasing problem of cognitive decline in aging populations ask for urgent and large scale preventive measures, as these have been proven to be effective (Larson et al, 2013; Norton et al, 2014). Consumer directed eHealth will probably (have to) play a major role in preventing or delaying dementia and other chronic and neuro-degenerative diseases, or guiding patients and caregivers throughout the process (Nijhof, 2013). Increasing efforts are noticeable in primary, secondary and tertiary prevention trials and application development. A perfect illustration of this trend is the release of the Dutch Dementia App in 2015; through which, informal caregivers and their loved ones can browse through pictures, listen to their favorite music, plan their upcoming day, share agendas, video call, and even play games.

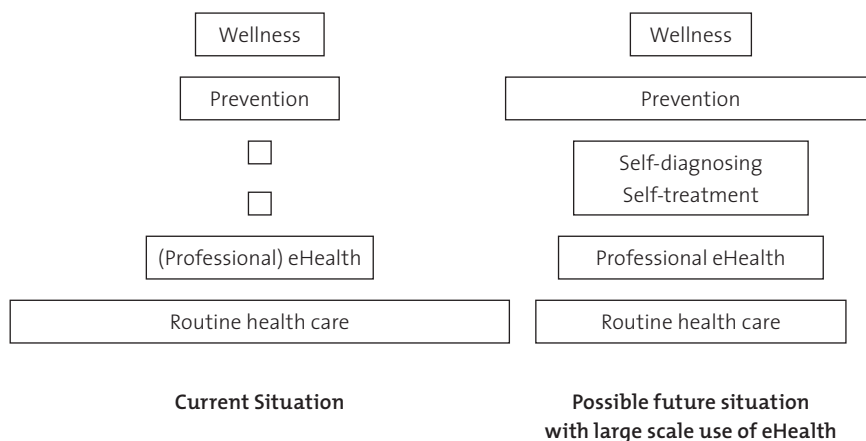
At a next stage, enhanced self-diagnosing tools will help many people through more refined sensors that are widespread through mobile technology, and enhanced self-treatment for standard protocols, through real-time digital consults (eg. in diabetes and hypertension care this is rapidly becoming standard practice). This may also contribute to increased efficiency of our current health care system.

Such a type of health care system, which would be patient-centered and have numerous eHealth applications guiding patient and doctor, is completely in line with Dave deBronkart's ideas about health care reform, and the RVZs prediction of how future health care systems will turn out. Figure 1.1 further details this expectation of the RVZ that focuses on health care shifting away from the traditional cure paradigm, towards prevention and self-management. The most notable benefits of eHealth and mHealth (where 'm' stands for mobile) are the increased ease of self-management and self-monitoring, faster communication and data transfer, decreased number of physical visits to clinical sites, and greater overall engagement throughout the entire process (Steinhubl et al, 2013). This is badly needed in a health care system that has held on to centralized, institutionally based, physically localized and professionally controlled procedures (Berwick et al, 2015).

As mentioned earlier on, one of the main reasons why our health care system is rapidly becoming too expensive, is the increase in our life expectancy, and the associated accumulation in absolute number of individuals who get diagnosed with a form of dementia. The primary prevention of this type of neurodegenerative diseases is

becoming more pressing and has found its way to the international research agenda. One of the most promising and feasible prevention paths lies in improving modifiable lifestyle risk factors during mid- and late life (Di Marco et al, 2014; Norton et al, 2014). At the outset of this research project, eHealth had shown the potential to be beneficial in a wide range of health issues, amongst others the primary prevention of risk factors for chronic diseases, but also to alleviate stress and depressive symptoms (Bennett & Glasgow, 2009). However, the full scope of this promise and the effectiveness to go along with it were still unknown (Bennett & Glasgow, 2009). The link to the primary prevention of dementia had so far been neglected. This generated our perspective of large potential improvement of public health and lower dementia incidence by developing eHealth applications filling this gap.

Figure 1.1. The type and size of health care in current and future situation (Meurs et al, 2015)



How is this innovation and intervention possible through eHealth?

When this research project began in 2010, approximately 68% of all European households had internet access. Last year, in 2014 this figure increased to 78%, adding up an additional 51.5 million households with stable internet access across the European Union (<http://www.webcitation.org/6dnmP2OxB>). This staggering number alone signifies the growth, importance and impact that the Internet, and digital identities have, and underlines the potential power eHealth has for modern Western societies. The mere fact that Internet penetration in the Netherlands, with an astonishing 94% across all households and all ages, is nearly complete, means that a

society without Internet has become inconceivable and impossible. What is more, approximately 80% of all Internet users, search for health related information online (Van de Belt et al, 2013). This makes eHealth a tool with great potential, even in cultural minorities, and in large demographic groups such as older persons, whom are traditionally considered to have a larger distance to using internet and its applications, but in reality might not be (Verhoef et al, 2014). Elderly can profit from its use as well; increasing self efficacy, health knowledge, the ability to independently remain at home and to increase quality of life are all positive outcomes of eHealth trials in older populations (Verhoef et al, 2014). Importantly, the acceptance and perceived ease of use of eHealth are on the rise in populations aged 57-77 (de Veer et al, 2015). We only have to look at the Dutch regional health care providers and their screen-calling procedure, where for example diabetic elderly self administer their insulin under professional supervision using a tablet, to see that with the proper adaptation to protocol, a lot is possible, and compliance to complex regimens can be increased on a large scale.

In addition to the conventional Internet access from a desktop computer, the mobile device market has emerged, if not exploded, over the last five years. Market research by Google shows that in the period from 2011 to 2013 smart phone penetration in the Netherlands went up from 33% to 52%. This creates a new state of connectivity, by which the general population or patients can be in touch with their digital health websites, applications or games, 24 hours per day, making telecommunications and tele-monitoring powerful tools for disease management and primary prevention.

This Internet of Things, the connection between all electronics surrounding us, is happening and not slowing down (Wortmann & Flüchter, 2015). In itself it is a big challenge to fully exploit, appreciate, and harness the power and possibilities the Internet gives the authorities, academia, health care institutions and educational organizations alike. Paradoxically, at the same time, safeguarding privacy and preventing cybercrime has rapidly become one of the biggest societal challenges of the 21st century (Rainie et al, 2013; Kraemer-Mbula et al, 2013). Combined, the ever growing theoretical framework, the practical prerequisites necessary for the successful implementation of eHealth innovation, and the call for evidence for interventions on the primary prevention of neurocognitive decline, the *why*, *how*, and *what* for this thesis aligned.

Therefore, we decided to develop an online, self-motivated eHealth program called the Brain Aging Monitor. The Brain Aging Monitor aimed at stimulating its participants in making healthy lifestyle decisions focusing on modifiable risk factors for cognitive decline; physical inactivity, unhealthy nutrition, smoking, alcohol consumption, sleep, and stress. My research focused on delivering the evidence for efficacy, effectiveness, and implementation of this new type of preventive health care.

Outline of this thesis

The central research question of this thesis is threefold:

1. Can development and implementation of a website with the aim of stimulating and helping participants to adopt healthy 'brain aging' behavior successfully change health behavior of Dutch adults?
2. Is testing cognitive functioning in adults, through the use of specifically for this purpose developed applied games, valid and feasible?
3. Does active use of the combination of an e-health lifestyle website that promotes healthy brain aging, and applied games to assess cognition, lead to improved cognitive functioning over time?

This thesis thereby aspires to deliver part of the puzzle towards more (cost-)effective (digital) health care.

To answer these three questions, a systematic approach was used. In **chapter 2** we delivered a solid theoretical base for our scientific quest by performing a systematic review in which we wanted to answer the question if prior research gave any indication that triggering health behavior change through eHealth interventions was at all possible in populations aged 50 and older at that time. Connected to the review and our intervention (i.e. the Brain Aging Monitor) development, we critiqued a publication in the American Journal of Clinical Nutrition, contributing to the scientific literature and questioning the statement by Kesse-Guyot and colleagues that the Mediterranean Diet, as a corner stone of healthy living, does not mediate cognitive aging (Kesse-Guyot et al, 2013). Next, **chapter 3** describes the development and validation of the gamified self-monitor for cognitive functioning, the Brain Aging Monitor Cognitive Assessment Battery (or BAM-COG). The BAM-COG was specifically designed to be used in our intervention study (**chapter 5 and 6**), because at the outset of this trajectory there were no freely available online self-monitors for cognitive functioning. Since we did need such an application for our research purposes, we developed our own monitor application. **Chapter 4** describes the protocol for the intervention study with the Brain Aging Monitor. The results of which are presented in **chapter 5 and 6**. These two studies separately analyze the BAMs capacity to: 1) change behavioral risk factors for cognitive aging, and 2) assess and monitor the resulting effect of these behavioral changes on cognitive outcome measures. **Chapter 7** summarizes the previous chapters and discusses the implications for the field of cognitive aging when preventive eHealth interventions are used, and the state of eHealth and its methodology in general. Because in the end, we would like to see our gamer from the beginning of this chapter, to see his (brain) health as his next quest, and to see any other group of people to express the same type of enthusiasm for healthy living, as for their favorite other pastimes.



2a

CHARACTERISTICS OF EFFECTIVE INTERNET-MEDIATED INTERVENTIONS TO CHANGE LIFESTYLE IN PEOPLE AGED 50 AND OLDER; A SYSTEMATIC REVIEW

T. Aalbers, M.A.E. Baars & M.G.M. Olde Rikkert
Ageing Research Reviews (2011) 10:487-497

Abstract

Worldwide, the number of people aged 60 years and older steadily grows to a predicted 2 billion in 2050. Online interventions increasingly target lifestyle risk factors to promote healthy aging. The objective of this systematic review is to evaluate whether Internet mediated lifestyle interventions can successfully change lifestyle in people aged 50 and older. A PubMed search was conducted resulting in twelve articles, based on ten studies. The studies focused on physical activity, weight loss, nutrition, and diabetes. Nine studies used feasible interventions, with an average small to moderate effect size. The most important result is that there are multiple studies reporting positive lifestyle changes in an older population. On average, complex interventions, whether they present tailored or generic information, and online or offline comparison, are more effective than interventions with only one component. Internet mediated interventions hold great potential in implementing effective lifestyle programs, capable of reaching large populations of older persons at very low costs.

Introduction

Worldwide, the number of people aged 60 and older steadily grows to a predicted 2 billion in 2050. Due to this phenomenon, decline of cognitive functioning and cognitive disorders like dementia become an increasingly prevalent health issue (Bishop et al, 2010). Therefore, it is highly urgent to learn whether Internet can be used to implement evidence based lifestyle changes. In this paper we will summarize the results of a systematic review to learn whether Internet mediated lifestyle interventions can be effective in the older population, and to analyze what may be prerequisites for future web-based interventions to be as effective as possible.

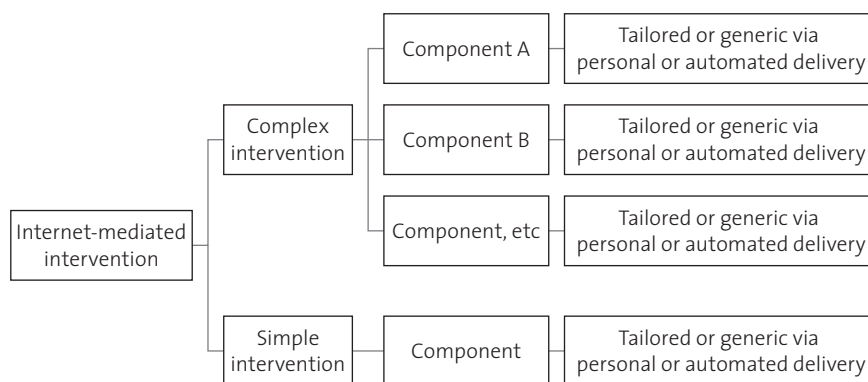
Increasing research efforts are aimed at prevention and delay of cognitive decline and dementia, as dementia is still an incurable syndrome. Current risk factor research aims at finding the risk factors that show the highest likelihood to contribute to these prevention aims. For example, increase in physical activity, healthier nutrition, learning to cope with stress, proper chronic disease management, and healthy drinking and smoking habits are factors stated to have a positive influence on brain aging (Karp et al, 2006; Peters et al, 2008; Ritchie et al, 2010).

Internet-mediated health interventions are a new and developing area of research. In 2006, researchers who directly delivered their health interventions via the internet were still described as ‘pioneer researchers’ (Griffiths et al, 2006). However, in 2009, already 64.2% of the European households had access to the internet in their homes (<http://www.webcitation.org/6g39FOLIW>), and logically more and more researchers use this medium for prevention aims. Main reasons for the increasing interest in intervention research via Internet are: (1) the unique worldwide coverage and quick spread of the technology, (2) increasing convenience and interaction opportunities of the technology, (3) reducing health care costs, (4) the ability to reach isolated or stigmatized groups, and (5) the ability for the supplier and user to tailor the intervention to personal needs (Griffiths et al, 2006).

Interventions, both online and offline, vary in level of complexity. In this review interventions will be categorized as being simple or complex, with tailored or generic information, being delivered personally or automatically (see Figure 2.1). The Medical Research Council described complex interventions as interventions consisting of more than one component that seem relevant to the functioning of the intervention, but where the ‘active ingredient’ of the intervention is hard to specify (Craig et al, 2008; Perera et al, 2007). In contrast, simple interventions exist of only one component. The different components in preventive interventions, often are the different behavior change techniques used. Next, interventions can provide either generic or tailored

information. Tailored information is defined as ‘any combination of information or change strategies intended to reach one specific person, based on characteristics that are unique to that person, related to the outcome of interest, and have been derived from an individual assessment’ (Kreuter et al, 1999). Finally, Internet interventions may or may not include personal contact, which in the current review does not include peer-to-peer contact in intervention groups, personal contact in control groups (e.g. usual care), or personal contact during pre- and post testing. For example, many internet interventions to maintain weight loss are complex, having several components, amongst which self-monitoring tools to keep track of body weight. These self-monitoring tools may be used with the aid of a general practitioner providing personalized advice, specifically tailored to the lifestyle and environment of the participant.

Figure 2.1. Schematic presentation of complex and simple interventions, with tailored or generic information, and personal or automated information delivery



This review focuses on the evidence base of Internet-mediated lifestyle interventions in older populations. That online lifestyle interventions in general can be effective is already described in other reviews (Bennett & Glasgow, 2009; Murray et al, 2005). However, it should be noted that a lot of the reported randomized controlled trials (RCT) were small, underpowered, had a high attrition rate and mostly reported changes in secondary instead of primary outcomes (Bennett & Glasgow, 2009). It is likely that most problems were encountered in applying Internet interventions in older populations, since this group is least familiar with the Internet. However, as information and communication technology (ICT) competencies are quickly growing, it is a serious option to stimulate healthy cognitive aging by means of an Internet-me-

diated lifestyle intervention. Therefore, it is crucial to learn what internet component may be effective in promoting healthier lifestyle in people aged 50 and older, which is the main objective of this systematic review.

Methods

To ensure high quality reporting in this systematic review we used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for reporting systematic reviews (Moher et al, 2009).

Data sources and Searches

We performed a search in PubMed, from January 1, 1995 to September 15, 2010, including articles in English and Dutch. The starting date was selected because prior to this date Internet-mediated interventions and public Internet access were uncommon. A comprehensive search strategy was developed and is provided in Appendix 1. To identify the appropriate search terms we conducted an exploratory literature search. Keywords identified by this search were extended and tailored to increase sensitivity of the search strategy.

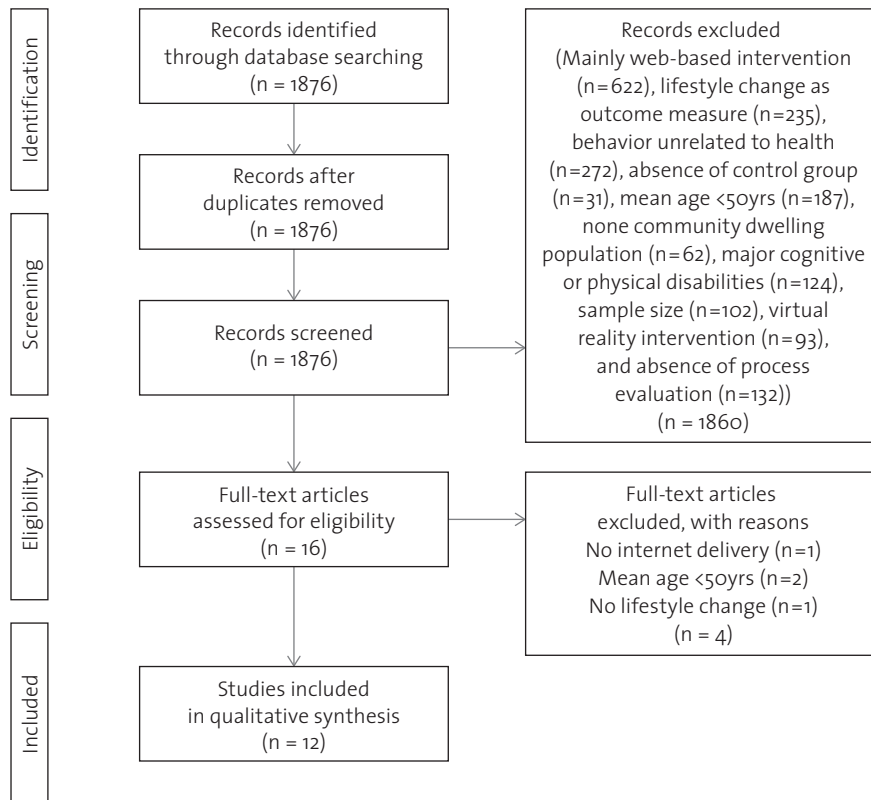
Study selection

We included randomized and non-randomized pre-post controlled trials. Studies were eligible for inclusion if (1) the intervention had at least one study arm that was mainly web-based. An intervention was defined as being web-based when the user had direct access and could interact with the intervention instruction program on the worldwide web, without the need of installing any software. (2) The intervention goal had to be lifestyle change in the experimental population (3) on a specific behavior possibly related to healthy aging (e.g. physical activity, nutrition, diabetes management, etc). The intervention (4) needed to include a control group of some kind (both online and offline are possible). The population (5) had to have a mean age of 50 years or older, (6) be community dwelling, and (7) not suffer from major physical or cognitive disabilities (e.g. paralysis, dementia or schizophrenia). (8) Studies based on virtual reality were beyond the scope of this review. At last (9) some form of process and outcome evaluation was needed so that the study included would provide information on feasibility and effectiveness of the intervention and the techniques used.

All studies identified by the search were assessed for relevance based on title and abstract by two independent researchers (TA and MB). The selected articles were retrieved full-text and reassessed by both authors (TA and MB) for final inclusion based on consensus. When full-text articles were unavailable the authors were

contacted requesting the article. Using the snowball method additional relevant articles were selected by hand search using the reference lists of the included articles. A flowchart of the study selection is presented in Figure 2.2.

Figure 2.2. Flowchart depicting the study selection procedure



Data extraction & Assessment of risk of bias

Data extraction was performed independently by two researchers (TA and MB) collecting data on intervention characteristics, components used, and process and outcome evaluation. Data collection was conducted using a standardized form, which was piloted on the first four articles and refined accordingly. We extracted data from the last follow-up possible, used results from the intention-to-treat analysis when provided, and when more than two groups were measured in the intervention we compared the control group to the group with the most intensive intervention, to be

able to report the largest possible effect size. Risk of bias assessment was performed using the 2009 Cochrane EPOC (Evidence Practice and Organization of Care Group) (Higgins & Altman, 2008) form. Additionally, the use of (financial or non-financial) incentives was registered as potential source of bias, as this is a frequently used form to increase intervention adherence, which thereby not necessarily reflects the retentiveness of the intervention itself.

Data synthesis & Analysis

Qualitative and descriptive summaries are presented in the results section on intervention exposure, intervention components and characteristics, and effect sizes. We could not perform a meta-analysis because of the heterogeneity in intervention types, area of focus and outcome measures reported. Cohen's d effect sizes were calculated when possible, and were computed as: $d = M_1 - M_2 / \sigma_{\text{pooled}}$, where $\sigma_{\text{pooled}} = [(\sigma_1^2 + \sigma_2^2) / 2]$. Using Cohen's classification the calculated effect sizes were divided into five groups: very small (Cohen's $d \leq .2$), small ($> .2$), moderate ($> .5$), large ($> .8$), and very large (> 1.3) effects. A positive effect size indicates a larger health benefit for the intervention group, whereas a negative effect size indicates a larger health benefit for the control group. We tested for baseline differences (if not reported in original article) by using an independent t-test to make sure that effect sizes calculated were not based on differences at baseline. According to the RE-AIM principles (Crutzen, 2010; Glasgow et al, 1999) an intervention with a small effect size that can reach a large population still may have a large public health impact (Crutzen, 2010; Murray et al, 2005; Webb et al, 2010). Therefore, even Internet-mediated interventions resulting in small effects will be considered as potentially effective.

Results

A total of 1876 citations were identified by the initial search. Finally, twelve articles based on ten studies were eligible for study inclusion. See flowchart in Figure 2.2. No other references were identified by hand searching the reference lists. A total of 4,984 participants were recruited for these studies with an average age of 54.9 years (± 8.3). Overall 62.2% were female participants. When the two studies that only recruited women were excluded 55.8% of the participants were female. Seven articles described a randomized controlled trial (Barrera et al, 2002; Bennett et al, 2010; Ferney et al, 2009; Glasgow et al, 2007; Stevens et al, 2008; Svetkey et al, 2008; Verheijden et al, 2004) and five a pre- posttest pilot study design (Bosak et al, 2009; Bosak et al, 2010; Hageman et al, 2005; Pullen et al, 2008; Riley et al, 2007). Eight studies (Barrera et al, 2002; Bennett et al, 2010; Bosak et al, 2010; Ferney et al, 2009; Glasgow et al, 2007; Pullen et al, 2008; Svetkey et al, 2008; Verheijden et al, 2004) used complex and

two simple interventions (Hageman et al, 2005; Riley et al, 2007). Nine studies found their intervention feasible (Barrera et al, 2002; Bennett et al, 2010; Bosak et al, 2009; Ferney et al, 2009; Glasgow et al, 2007; Hageman et al, 2005; Pullen et al, 2008; Riley et al, 2007; Stevens et al, 2008; Svetkey et al, 2008), one study clearly stated that their program failed to work (Verheijden et al, 2004). Average length of follow up time was 7 months, with a range of 1.5 to (Bosak et al, 2009; Bosak et al, 2010) 30 months (Svetkey et al, 2008). On average the interventions had an attrition rate of 18.3%. The focus of the articles was on weight loss (Bennett et al, 2010; Glasgow et al, 2007; Pullen et al, 2008; Stevens et al, 2008; Svetkey et al, 2008), physical activity (Bosak et al, 2009; Bosak et al, 2010; Ferney et al, 2009; Hageman et al, 2005), nutrition (Riley et al, 2007; Verheijden et al, 2004), and diabetes (Barrera et al, 2002). Five different types of recruitment strategies were used. Recruitment through the general practitioner or other health care services, and newspapers both occurred five times, followed by four times mass mailings, flyers and posters. Once people were screened by telephone. A complete overview of relevant study characteristics is provided in Table 2.1.

Quality assessment results are presented in Table 2.2. No studies scored positive on all quality criteria. The majority of studies lacked a concise description on the sequence generation in randomization (6), allocation concealment (7), and protection against contamination (6). So results have to be viewed with caution, because of potential bias in randomization and blinding. Baseline characteristics were similar in eight out of ten studies, the other two didn't report these characteristics clearly.

Out of the six studies reporting on dropout characteristics two noted higher attrition in men than women: 13 men versus 3 women ($p = 0.01$) (Bennett et al, 2010) and OR (CI) 1.50 (1.12-2.01) $p = .006$, respectively. (Glasgow et al, 2007) Two studies reported equal dropout rates (Barrera et al, 2002; Verheijden et al, 2004), and the last studies only recruited women so no difference in gender dropout could be reported (Hageman et al, 2005; Pullen et al, 2008). Two studies reported dropout and compliance differences by age: in one study younger participants dropped out more frequently OR (CI) 1.02 (1.01-1.03) $p < .001$ (Glasgow et al, 2007) and in the other study subjects using the site were significantly younger than non-users (58 ± 8 versus 64 ± 11 yrs, respectively), $p = .03$ (Verheijden et al, 2004). Only one type of selection bias existed in the current review. Three studies reported highly educated study populations (Bennett et al, 2010; Hageman et al, 2005; Svetkey et al, 2008) compared to the general US population (www.census.gov) and none reported lower educated populations. Finally, financial incentives were used three times as an extra stimulus for participants to sign up or adhere to the intervention.

Effect size and intervention exposure

In Table 2.3 the effect sizes and outcome measures for the interventions are presented. Effect size calculation was possible in seven studies, the other three did not report the necessary data. Six studies present eight effect sizes that are considered effective. It is important to notify that there are two types of effect sizes; comparing offline controls with online intervention groups (Bennett et al, 2010; Svetkey et al, 2008; Verheijden et al, 2004), and comparing online controls with online intervention groups (Barrera et al, 2002; Ferney et al, 2009; Hageman et al, 2005; Pullen et al, 2008). The average effect size for the online interventions in comparison to the offline and online control groups is 0.19 (± 0.21) and 0.39 (± 0.37), respectively. On average the effect sizes are small to moderate-small. The negative effect size in Hageman's study deserves special attention. These effect sizes do not imply that their Internet intervention did not work, but rather that their online generic newsletter had more effect than their online tailored newsletter. The small effect sizes in Ferney's study represent the difference between a tailored and generic website, which is small, even though both groups increased their neighborhood walking and total physical activity significantly compared to baseline ($p = 0.001$ and $p = 0.04$, respectively; Ferney et al, 2009). The simple interventions, both online versus online comparison, have an average effect size of 0.15 (± 0.20) (Hageman et al, 2005), in the complex offline versus online interventions the average effect size is 0.19 (± 0.21) (Bennett et al, 2010; Svetkey et al, 2008; Verheijden et al, 2004), and the average effect size for complex online versus online interventions is 0.51 (± 0.33) (Barrera et al, 2002; Ferney et al, 2009; Pullen et al, 2008).

Out of the ten unique studies only two provided information on dose/response relationships. The first study reported that meeting the log-in goal for over ten weeks significantly increased weight loss in comparison to using it less than ten weeks (-4.50 ± 3.29 kg versus -0.60 ± 1.87 kg respectively, $p < 0.05$; Bennett et al, 2010). Furthermore, participants in the highest exposure quartile lost significantly ($p = 0.0007$) more weight than people in the two lowest exposure quartiles (Bennett et al, 2010). The second study found a significant interaction effect in maintaining increased total physical activity values between control and intervention group ($p = 0.04$) (Ferney et al, 2009). The intervention group had significantly more exposure ($p < 0.01$; 8.2 versus 2.8 total logins) to their website than the control group. Within the intervention group, users maintained their increased use of the community walking path significantly better than the non-users (59.2 versus 25.0 min/week respectively, $p = 0.05$; Ferney et al, 2009).

Table 2.1. Overview of study characteristics

Study	Population ^a	Intervention
Barrera (2002)	160 participants 53.1% women 59.3 years (9.4) I/C: 40/40	Effects of a Social Support Program in Diabetes Mellitus Type2 Comparing the control group with the social support only group 3 months follow-up Generic intervention
Bennett (2010)	101 obese hypertensive participants 47.5% women 54.4 years (8.1) I/C: 51/50	Effects of Weight Loss Program 3 months follow-up Tailored intervention
Bosak (2009) Same study as Bosak (2010)	22 metabolic syndrome participants 37.5% women 50.9 years I/C: 12/10	Feasibility of Physical Activity Program 1.5 months follow-up Generic intervention
Bosak (2010)	22 metabolic syndrome participants 37.5% women 50.9 years I/C: 12/10	Effects of Physical Activity Program 1.5 months follow-up Generic intervention
Ferney (2009)	106 underactive participants 72% women 52 years (4.6) I/C: 52/54	Effects of Physical Activity Program 6.5 months follow-up Tailored intervention
Glasgow (2007)	2311 (909 with diabetes or heart disease) 53.3% women 46.5% >60years I/C: n/a	Effects of Weight Management Program 12 months follow-up Tailored intervention
Hageman (2005)	31 underactive participants 100% women 56.1 years (4.9) I/C: 15/16	Effects of Physical Activity Program 3 months follow-up Tailored intervention

Recruitment ^b		Techniques / Components	% Attrition ^c	% Attrition ^d
GP		<ul style="list-style-type: none"> - Social network forum - Social network forum in real time - Online article access / specialized information 	23%	7.7%
1. EMD 2. Mail		<ul style="list-style-type: none"> - In-person goal setting - In-person motivational coaching - Telephone motivational coaching - Online messaging of health coach - Social network forum - Online biweekly information update - Online self-monitoring - Online health recipes 	16%	5.3%
EMD		<ul style="list-style-type: none"> - Social network forum - Online email advice - Online self-monitoring - Online goal-setting - Online daily self-efficacy strategy - Emailed knowledge quizzes 	14%	9.3%
EMD		<ul style="list-style-type: none"> - Social network forum - Online email advice - Online self-monitoring - Online goal-setting - Online daily self-efficacy strategy - Emailed knowledge quizzes 	14%	9.3%
1. Mail & Newspaper 2. Telephone		<ul style="list-style-type: none"> - Social network forum - Online tailored email advice - Online biweekly information update - Online self-monitoring - Online goal-setting - Online database of local physical activities - Emailed knowledge quizzes 	18%	2.8%
HMO Mail Flyer & Poster		<ul style="list-style-type: none"> - Online email notification system - Online tailored newsletters - Online goal-setting 	52%	4.3%
Newspaper		<ul style="list-style-type: none"> - Online tailored newsletters 	3%	1.0%

Table 2.1. Continued

Study	Population ^a	Intervention
Pullen (2008)	21 participants 100% women 55.5 years (4.9) I/C: 11/10	Effects of Weight Loss Program 3 months follow-up Generic intervention
Riley (2007)	76 participants 75% women 51 years (15) I/C: 42/34	Effects of Food Portion Estimation Program 0 months follow-up Tailored intervention
Stevens (2008) Same study as Svetkey (2008)	1032 participants 63% women 55.6 years (8.7) I/C: 348/342	Effects of Weight Loss Maintenance Program 12 months follow-up Tailored intervention
Svetkey (2008)	1032 participants 63% women 55.6 years (8.7) I/C: 348/342	Effects of Weight Loss Maintenance Program 30 months follow-up Tailored intervention
Verheijden (2004)	146 participants 45% women 63 years (10.5) I/C: 73/73	Effects of Nutrition Counseling and Social Support Program 8 months follow-up Generic intervention

^a I/C = n in Intervention group / n in control group

^b GP = General Practitioner; HMO = Health Management Organization; EMD = Electronic Medical Database

^c % Attrition of total subjects included

^d % Attrition per month of follow-up

Intervention components

A total of 18 different intervention components were identified. On average 4.4 techniques were used per study with a range of 1-8 (see Table 2.1). No large differences between the different focus areas were found. Social network forums (n=7), online self-monitoring (n=6), online goal setting (n=5), and use of email (n=5) had the highest frequency. While social networking forums were used in seven of the studies only four discussed the use or impact of this component. In one study 36% of the participants used the forum consistently (Pullen et al, 2008). Two studies reported the actual use of the forum, reporting a total of 15 posts in 6 weeks and 1 post in 26 weeks (Bosak et al, 2010; Ferney et al, 2009). A self-monitoring tool was used in six studies, amongst others with the purpose to decrease attrition. The median attrition in these

Recruitment ^b	Techniques / Components	% Attrition ^c	% Attrition ^d
Newspaper Flyer & Poster	- Social network forum with nurse - Online newsletters - Online self-monitoring - Online goal-setting	23.8%	8.0%
Newspaper Flyer & Poster	- Online learning protocol	0%	0%
Mail Newspaper Flyer & Poster	- Online prompting to use website - Social network forum - Online email notification system - Online self-monitoring - Online goal-setting - Online tailored feedback	20%	1.7%
Mail Newspaper Flyer & Poster	- Online prompting to use website - Social network forum - Online email notification system - Online self-monitoring - Online goal-setting - Online tailored feedback	7%	0.2%
GP	- Social network forum - Online email advice - Online article access / specialized information - Online self-monitoring - Online health recipes	11%	1.4%

six studies was below the median attrition for the other components. Goal setting is a component that lets participants set behavior change goals to accomplish within a set timeframe. Five studies reported the use of online goal setting of which two reported sustained usage at the last follow-up measurement (Bosak et al, 2010; Ferney et al, 2009; Glasgow et al, 2007; Pullen et al, 2008; Svetkey et al, 2008). Three studies reported a large decline in use of online goal-setting over time (Bosak et al, 2010; Ferney et al, 2009; Glasgow et al, 2007). Explanations given for this result were: not clarifying its use and importance properly, lack of prompts, and overall attrition rates. The five studies using email delivery made different use of this option. Two studies used emails solely as an generic notification system (Glasgow et al, 2007; Svetkey et al, 2008), another two studies used emails to give generic behavior feedback (Bosak et al,

2010; Verheijden et al, 2004), and one study used emails to deliver tailored behavior feedback to the participants (Ferney et al, 2009). Only the last study presented significant changes on their behavioral outcome measures compared to the generic control condition, and the participants positively reported on the usefulness of this tool.

Table 2.2. Quality assessment of reviewed studies using an adapted version of the Cochrane EPOC 2009 form^a

	Adequate sequence generation	Allocation concealment	Similar baseline outcome measures	Similar baseline characteristics	Incomplete outcome data addressed	Blinding	Adequate protection against contamination	Free of selective reporting	Free of incentives	Selection bias
Barrera (2002)	+	?	+	+	?	?	?	+	+	+
Bennett (2010)	?	?	+	+	?	?	?	+	-	-
Bosak (2010)	?	?	?	+	+	+	+	+	+	-
Ferney (2009)	+	+	+	-	+	+	?	?	+	+
Glasgow (2007)	?	?	?	?	+	+	+	-	-	?
Hageman (2005)	?	?	+	?	?	?	?	+	+	-
Pullen (2008)	?	?	+	+	?	+	+	+	+	-
Riley (2007)	?	?	+	+	+	+	+	+	-	+
Svetkey (2008)	+	+	+	+	+	+	?	+	+	-
Verheijden (2004)	+	+	+	+	?	+	?	?	+	+

^a For additional information on the Cochrane EPOC 2009 form:
<http://epoc.cochrane.org/epoc-resources-review-authors>

Table 2.3: Group differences, p-value, and effect sizes for primary intervention outcomes.

Study	Measurement	Intervention Group ^a	Control Group ^a	p	Cohen's d
Barrera (2002)	ISEL ^b	0.19	-0.08	p < 0.01	0.82
	DSS ^b	1.20	0.10	p < 0.01	0.76
Bennett (2010)	Body weight (kg)	-2.28	0.28	p < 0.05	0.41
Ferney (2009)	Neighborhood walking (min/wk)	17.4	15.7	p = 0.44	0.05
	Total physical activity (min/wk)	57.8	12.7	p = 0.32	0.06
	Community walking path users/non-users (min/wk)	22.6	-16.2	p = 0.04	0.54
Hageman (2005)	Moderate or great physical activity per week (min)	-265	-322	p > 0.05 ^c	0.33
	% Body fat				
	VO ₂ max (ml/kg/min)	-0.76	-3.29	p < 0.05 ^c	-0.30
Pullen (2008)	Body weight (kg)	0.83	-2.00	p < 0.05 ^c	0.42
Svetkey (2008)	Body weight regain (kg)	-5.0	-2.4	p ≤ 0.05	0.82
Verheijden (2004)	Body weight regain (kg)	5.2	5.5	p = 0.51	0.38
	BMI (kg/m ²)	-0.02	-0.01	p = 0.12	0.06
	Perceived social support	-0.17	-0.07	p = 0.31	-0.08

^a All scores reported are group differences between pre- and posttest^b ISEL = Interpersonal Support Evaluation List, DSS = Diabetes Support Scale^c In comparison to baseline

Tailored versus Generic intervention design

Comparison between interventions that provide tailored information versus interventions with generic information showed that the tailored studies have a 2.7% attrition rate per month of follow-up (Bennett et al, 2010; Ferney et al, 2009; Glasgow et al, 2007; Hageman et al, 2005; Svetkey et al, 2008), whereas the generic interventions have a 6.6% attrition rate per month of follow-up (Barrera et al, 2002; Bosak et al, 2010; Pullen et al, 2008; Verheijden et al, 2004). Additionally, tailored interventions were rated as more interesting (80% positive comments versus 38% in the generic group, $p = 0.01$), and helped subjects to become more active (44% versus 24% in the generic group, $p = 0.001$) (Ferney et al, 2009). However, the most interactive features were still used the least (Ferney et al, 2009). Hageman et al. concluded that tailoring is only as good as the information on which the tailoring is based, emphasizing the importance of using reliable screening instruments (Hageman et al, 2005).

Discussion

The objective of this systematic review was to identify characteristics of effective internet mediated interventions that focus on promoting healthier lifestyle in people aged 50 and older. The most important result is that there are multiple studies reporting positive lifestyle changes in an older population, e.g. in stimulating physical activity, facilitating weight loss, and improving social support. So, even though the Internet is still developing and finding its way to all age cohorts of society, there is sufficient evidence that even an older population can be positively influenced to change lifestyle via the Internet. On average, complex interventions, whether they present tailored or generic information, and online or offline comparison, are more effective than interventions with only one component.

To describe online intervention tools remains difficult because different authors report their findings differently or not at all. Especially in a setting where complex interventions are used it is vital to document and evaluate how components work, are used, and influence the outcome. Process data about how frequent the tool is used, for what period of time, by which subgroups, and for what reason should standard be provided. Furthermore, a qualitative participant-oriented approach should be used, questioning participants which components they felt were effective in changing their lifestyle. To increase the knowledge in the field and develop effective lifestyle interventions on the Internet this is an absolute necessity. Until these reports become widespread it will remain very difficult to link specific intervention components used in complex interventions to intervention effect sizes. In order to standardize the documentation and give insight into which components need evaluation we

recommend to use the design proposed by Perera et al. (Perera et al, 2007) and the revised Medical Research Council development stages (Craig et al, 2008).

Social network forums were used in more than half of the studies reported by this review. All reports on the usage of these forums pointed towards low uptake and activity rates. Eysenbach et al. reported no robust evidence on the effectiveness of consumer led social communities (Eysenbach et al, 2004). The inclusion of social support tools frequently means the inclusion of personal contact or requires the attention of a professional. This excludes the option of developing a fully automated online lifestyle intervention, decreasing the interventions reach. Which, considering the RE-AIM principles will make it less likely for an intervention to have a positive public health impact (Crutzen, 2010; Glasgow et al, 1999). On the contrary social media like Twitter, Facebook, and Myspace are described as possible means to change social support and lifestyle (Bennett & Glasgow, 2009). The use of these social media and an automated tailored information system could make the involvement of professionals redundant.

Goal setting is an effective way to facilitate lifestyle behavior change in people above 50 years of age (Nothwehr & Yang, 2007), and self-monitoring is a core behavioral intervention component in weight loss (Khaylis et al, 2010) and physical activity (Michie et al, 2009) interventions. Both self monitoring and goal setting are shown to have positive effects on physical activity levels during cardiac rehabilitation (Ferrier et al, 2010). These two interactive intervention components are intertwined. By means of self-monitoring the goals set are tracked on their progress. However, even though self-monitoring is, amongst others implemented to increase retention, goal setting activity decreased over time in all studies. So if these components are used it is advisable to clearly state the goal of both components and the added value that they can have on achieving lifestyle change. Using email notification systems and generic or tailored feedback via email could provide the opportunity to engage people in the intervention and remind participants of their behavior change goals and progress.

Alongside the content, we need more data on the dose-effect relation, i.e. the effect of intervention exposure on intervention effectiveness. Keeping track of participants' number of logins, login frequency over time, length of logins, and number of pages visited can be linked to demographic variables and primary outcomes to calculate which intervention exposure maximizes results. This enables authors to report in more detail on the characteristics of the dropout population.

In all studies identified in this review participants were recruited offline. Bennett already stated that little is known about the reach and effectiveness of purely

Internet-based recruitment (Bennett & Glasgow, 2009). Although offline recruitment may have benefits in some situations, online recruitment strategies should be developed additionally. Exploiting recruitment features of the Internet has huge potential. Possibilities lie in Internet advertisement, optimizing a website to gain a large amount of hits on search engines, web links on other health related, national health associations and governmental agencies-websites or sending recruitment emails to all employees of large corporations. This gives researchers the means to reach a larger population not restricted by any other feature than the reach of the worldwide web. Based on the current review researchers of Internet-mediated interventions should take precautions to recruit an equal number of lower educated people and men into their intervention to avoid selection bias.

This systematic review was conducted using standardized PRISMA and Cochrane protocols for documentation. We used an elaborate search strategy, tailored on Internet-mediated interventions specifically aimed at older populations. Study selection and data extraction was performed independently by two researchers and decisions were made based on consensus. However, some limitations need to be considered on this review. Most importantly, the small amount of articles in this area makes it hard to draw generalized conclusions. The spread on focus areas and the fact that some studies compare online groups with online control groups, while other studies compare online groups with offline control groups, makes comparison difficult and meta-analysis impossible. Third, all study populations, in the current review, except for Riley et al. (Riley et al, 2007), are specific populations unrepresentative of the general population. While this provides evidence that some isolated or stigmatized groups can be reached by internet interventions (Griffiths et al, 2006), it does not provide external validity of this evidence for the general population. Last, the decision to limit the literature search to articles published in English and Dutch may have lead to selection bias, though English is by far the leading language in this field of research. Nevertheless, despite of these limitations, the overall findings are positive, underlining for the first time the huge potential of the Internet to stimulate and to reach healthier lifestyles in our aging societies.

Recommendations and conclusions

Most important for future research in this field is to notice the need for more standardized ways of reporting on the process evaluation of Internet interventions. In order to develop low-cost, highly effective lifestyle interventions detailed accounts on the use and efficacy of different Internet components are needed.

Therefore, we conclude that it remains questionable which specific modes of delivery can be considered most effective for an Internet intervention in people aged 50 or older. What we can say is that social networking forums are frequently used as a tool but rarely used by the participants, and thus are ineffective. Time may have come to incorporate modern features (i.e. web 2.0) into online lifestyle interventions. This review clearly showed that Internet mediated interventions hold great potential in implementing effective lifestyle programs, capable of reaching large populations of older persons at very low costs.



2b

THE MEDITERRANEAN DIET AS PREVENTION STRATEGY FOR DEMENTIA AS A MULTICAUSAL GERIATRIC SYNDROME

T. Aalbers, M.A.E. Baars & M.G.M. Olde Rikkert

Letter to the Editor in the American Journal of Clinical Nutrition (2013) 97:1411-7.

In response to "Mediterranean diet and cognitive function: a French study"

by Kesse-Guyot and colleagues.



Dear Sir:

With great interest we read the article by Kesse-Guyot et al which is presented as evidence against the beneficial long term effects of the Mediterranean Diet on cognitive aging (Kesse-Guyot et al, 2013). Our own research focuses on an internet-mediated intervention on lifestyle changes, including improving dietary habits (Aalbers et al, 2011). We acknowledge the great value of a long term follow-up study on the Mediterranean diet. This long term follow-up on cognition, linking it to the enormous global threat of dementia in our aging societies, is the strongest point of the study. However, the long-term gap in data collection is by far the weakest point of the study, which makes the data very hard to interpret and severely jeopardizes external validity for primary prevention in daily practice.

As previously indicated, the 13-y follow-up period of the large trial is impressive. However, we argue that the use of Mediterranean diet adherence measures from the initial 1994-1996 period combined with cognitive results from a 2007-2009 period is unreliable. At best, there is an 11-y gap between both measurements. Within these 11-y, dietary habits of the entire population could have undergone drastic changes. Given the fact that the unknown period is, at a minimum, 5 times longer than the period of measurement, the effects this probably has on cognitive aging patterns far outweigh the effects of the 2-y intervention period described in the article.

A very recent randomized trial on the Mediterranean diet in middle-aged persons with high cardiovascular risk in Spain showed a 0.70 (unadjusted hazard ratio with 95% CI: 0.53-0.94) improvement in the incidence of cardiovascular endpoints over 5 y of follow-up with a Mediterranean diet enriched with olive oil or nuts (Estruch et al, 2013). This is in line with several positive health outcomes that previously have been related to adhering to the Mediterranean diet. Kesse-Guyot et al do not specifically take these cardio- and cerebrovascular endpoints into account in their study. We are curious on the positive effects the study's Mediterranean diet may have had on onset of type 2 diabetes, high blood pressure, and cardiovascular diseases (Domínguez et al, 2011; Esposito et al, 2010). All of these factors have been firmly associated with the way our brain ages (Exalto et al, 2012; Sörös et al, 2012; de la Torre, 2012). Therefore, adherence to the Mediterranean diet mechanistically is expected to have at least an indirect positive effect on cognitive aging patterns. This is in contrast to this article's conclusion that the "study does not support the hypothesis of a significant neuro-protective effect of a MedDiet on cognitive function.". By failing to discuss this indirect effect of healthy nutrition on cognitive aging Kesse-Guyot et al oversimplify the complex problem at hand.

In conclusion, we find the long term effects of the Mediterranean diet raised by Kesse-Guyot et al very relevant but cannot share their opinion that their results provide compelling evidence that the Mediterranean diet does not provide a neuro-protective effect on cognitive function. Methodologic flaws in monitoring the intervention and the outcomes seriously weaken their lack of evidence for effect, which should not be confused with evidence for the absence of effect. On the contrary, there are still strong arguments for long-lasting beneficial effects of the Mediterranean diet. First, there is increasing evidence that dementia among the elderly is not a monocausal neurological disease but a geriatric syndrome based on several component causes, including neurodegenerative cortical loss, disorders of cerebral circulation, nutritional deficiencies, and potentially many others (Strandberg & O'Neill, 2013). This, together with the strong recent findings on the beneficial effects of the Mediterranean diet on cardio- and cerebrovascular endpoints, strongly supports the hypothesis that great beneficial effects may be expected in populations that change their current Western diet to a nutritional lifestyle that seriously adopts the Mediterranean diet.



3

PUZZLING WITH ONLINE GAMES (BAM-COG): RELIABILITY, VALIDITY AND FEASIBILITY OF AN ONLINE SELF-MONITOR FOR COGNITIVE PERFORMANCE IN AGING ADULTS

T. Aalbers, M.A.E. Baars, M.G.M. Olde Rikkert & R.P.C. Kessels
Journal of Medical Internet Research (2013); 15(12):e270.

Abstract

Background: Online interventions are aiming increasingly at cognitive outcome measures but so far no easy and fast self-monitors for cognition have been validated or proven reliable and feasible.

Objective: This study examines a new instrument called the Brain Aging Monitor – Cognitive Assessment Battery (BAM-COG) for its alternate forms reliability, face and content validity, and convergent and divergent validity. Also, reference values are provided.

Methods: The BAM-COG consists of four easily accessible, short, yet challenging puzzle games that have been developed to measure working memory (“Conveyer Belt”), visuo-spatial short-term memory (“Sunshine”), episodic recognition memory (“Viewpoint”), and planning (“Papyrinth”). A total of 641 participants were recruited for this study. Of these, 397 adults, 40 years and older (mean 54.9, SD 9.6), were eligible for analysis. Study participants played all games three times with 14 days in between sets. Face and content validity were based on expert opinion. Alternate forms reliability (AFR) was measured by comparing scores on different versions of the BAM-COG and expressed with and intraclass correlation (ICC: two-way mixed; consistency at 95%). Convergent validity (CV) was provided by comparing BAM-COG scores to gold-standard paper-and-pencil and computer-assisted cognitive assessment. Divergent validity (DV) was measured by comparing BAM-COG scores to the National Adult Reading Test IQ (NART-IQ) estimate. Both CV and DV are expressed as Spearman rho correlation coefficients.

Results: Three out of four games showed adequate results on AFR, CV, and DV measures. The games Conveyer Belt, Sunshine, and Papyrinth have AFR ICCs of .420, .426, and .645 respectively. Also, these games had good to very good CV correlations: $\rho = .577$ ($P = .001$), $\rho = .669$ ($P < .001$), and $\rho = .400$ ($P = .04$), respectively. Last, as expected, DV correlations were low: $\rho = -.029$ ($P = .44$), $\rho = -.029$ ($P = .45$), and $\rho = -.134$ ($P = .28$) respectively. The game Viewpoint provided less desirable results with an AFR ICC of .167, CV $\rho = .202$ ($P = .15$), and DV $\rho = -.162$ ($P = .21$).

Conclusions: This study provides evidence for the use of the BAM-COG test battery as a feasible, reliable, and valid tool to monitor cognitive performance in healthy adults in an online setting. Three out of four games have good psychometric characteristics to measure working memory, visuospatial short-term memory, and planning capacity.

Introduction

With the rise of the Internet and the introduction of eHealth, the new research area of online health care has evolved rapidly over the last decade (Ritterband & Tate, 2009). The field of research focusing on public health promotion is no exception (Portnoy et al, 2008). Also, and already for a slightly longer period of time, the gaming industry has established itself as a major global industry (MiniWatts Marketing Group, 2013). Nowadays, eHealth and “serious gaming” are increasingly intertwined and more researchers are venturing into the realm of (online) game research. In turn, game developers show heightened interest in supporting and helping solve scientific research and societal issues (Baranowski et al, 2008). For example, games are used to assist in stroke rehabilitation (Bower et al, 2013), in programs aimed at the prevention of youth obesity (Miller et al, 2013), and in enhancing gait balance in nursing home residents (Janssen et al, 2013).

From a health-behavior change perspective, both eHealth and gaming are of high interest. Widespread Internet access provides the behavior-change researcher with the platform necessary to reach large populations. In Europe and North America, Internet penetration ranges between 63.2-78.6% of the total population (<http://www.webcitation.org/6g39FOLIW>). With its massive reach, online gaming has long since shifted from being a typical pastime for younger generations to serving millions of gamers of every age, race, sex, and cultural background (Haagsma et al, 2012).

An important drawback of the Internet is that its content has to be fast and entertaining (Jadad & Enkin, 2006; Vasilyeva et al 2005). When researchers consider using the Internet as their medium and want to profit from its enormous reach, their interventions and evaluation methods should comply with these characteristics. Therefore, there is a need for quick, easily accessible, and attractive applications and instruments that provide the user with direct feedback (Kreps & Neuhauser, 2010). If an intervention fails to do so, it will be difficult to recruit a sufficient number of participants. Also, dropout rates may be high, which will subsequently heavily affect the power of a study (Cugelman et al, 2011) and its external validity.

The effects of aging on cognitive functions have been studied increasingly (Eve & de Jager, 2013; Sternberg et al, 2013). Typically, this has been done by both paper-and-pencil and offline computer-assisted neuropsychological testing (Deary et al, 2009). One of the domains within the area of eHealth involves online assessment and monitoring of cognitive (dys)function (Mather, 2010). Quantifying cognitive performance in tangible measures that are readily interpretable for neuropsychologists and patients alike has gained increasing interest and cognitive training programs like Lumosity

have experienced a steep rise in popularity (Lezak et al, 2012). Now that intervention studies are scaling up in the number of recruited participants, a demand exists for short and easy-to-use validated neuropsychological tests (Houx et al, 2002). Traditional person-to-person neuropsychological testing may in this respect often be inefficient from a time and cost perspective (Haworth et al, 2007; Naglieri et al, 2004) and certainly does not meet the criteria for successful use in an online environment.

Online cognitive testing has already been proven valid and reliable in children aged 10-12 years (Haworth et al, 2007), as well as adult and older populations ranging from 18-80 years of age (Mather, 2010; Murre et al, 2013). We set out to develop an online self-monitor for cognitive functioning in people aged 40 years and older—the BAM-COG (Brain Aging Monitor–Cognitive Assessment Battery). The BAM-COG consists of four easily accessible, short yet challenging puzzle games that can be completed online, aimed to assess key aspects of cognitive function that are susceptible to aging-related changes, that is, working memory, executive function, and episodic memory. This empirical validation study consisted of two parts. First, we examined the alternate forms reliability and, second, we studied convergent and divergent validity of the BAM-COG. Also, reference values are presented from a sample of 397 adults aged 40-85 years.

To our knowledge, this is the first study to describe, validate, and examine an online self-monitor for cognitive functioning that makes use of visually attractive, easy-to-instruct puzzle games. The BAM-COG was not developed as a diagnostic tool (eg, for the assessment of pathological cognitive aging such as dementia), nor was it designed to predict cognitive decline over time. The aim of the BAM-COG was to enable users to establish their cognitive performance and to monitor their personal cognitive development over time. This is of major importance because it greatly increases the possibilities of online research on cognitive functioning, it increases reach, and it decreases costs both monetary and in time.

The hypotheses for this study are that the BAM-COG games have good alternate forms reliability and that the face and content validity of the four newly developed puzzle games of the BAM-COG transfer into good convergent and divergent validity, compared with standard paper-and-pencil and computer-assisted cognitive assessment.

Methods

Population

We set out to validate the BAM-COG in a cohort of community-dwelling individuals aged 40 years and older. Rationale for the 40-year cut-off point is that from approximately this age onwards normal cognitive aging is firmly evidenced (Singh-Manoux et al, 2012). The only inclusion criterion, apart from age, was that participants had adequate Internet access. Within the given age restrictions, the target population was unrestricted since we searched for a study population representative of the general population. No regional, ethnic background, sex, or language restrictions were applied, although the website description was only available in Dutch. Participants for Part 1 of the study were recruited online through several websites, social media, and blogs. A convenience sample was recruited for Part 2 of the study using flyers in community centers, shopping areas, mid-sized regional organizations, and senior centers. Furthermore, the study received national radio and newspaper attention, which resulted in the recruitment of participants as well.

Study Design

The research website was available to participants for four months (www.spellenonderzoek.nl). Upon enrollment, we registered sex, age, and education level—the latter ranging from 1–8, where 1 is the lowest value (elementary school) and 8 is the highest value (university level education; see (Murre et al, 2013) for the Dutch system which is similar to the ISCED [International Standard Classification of Education] standards from the United Nations (UNESCO, 1997)). The online games could be completed in the uncontrolled setting of the participants' day-to-day lives (Naglieri et al, 2004). Once participants were logged in, they played the BAM-COG games for the first time. An automated reminder system prompted the participant to visit the website again after 14 and 28 days to perform the second and third round of BAM-COG games.

On their first two visits, participants performed the same BAM-COG games (see Table 3.1 for more information on the BAM-COG games). In the third round, they performed a different batch of BAM-COG games, thus playing different trials with approximately the same difficulty. To check whether the different batches did not differ with respect to difficulty, we performed alternate forms reliability (AFR) analyses (see Statistical Analyses). In total, there were three different batches of trials. A participant was randomly assigned to any of the six possible sequence groups (1-1-2, 1-1-3, 2-2-1, 2-2-3, 3-3-1, or 3-3-2) by an online random placement script. After completing all three rounds, a participant was awarded a promotional code with a value of 4.99 (US\$6.75) that could be used for a one-month subscription to a puzzle website.

There were two parts in this study. Part 1 involved the data collection for AFR analyses and reference values, which was done exclusively via the Internet. Participants in Part 1 were estimated to need approximately 45 minutes per session to complete the BAM-COG. In total, after three rounds of BAM-COG puzzles within 28 days, participants were estimated to have spent approximately 135 minutes on the BAM-COG. This group will be abbreviated as “Online group” from this point on. Part 2 involved the data collection necessary to calculate the BAM-COG’s convergent (CV) and divergent validity (DV). For this procedure, in addition to playing the BAM-COG games online, participants visited the Radboud University Medical Centre (RUMC) once (this group will be abbreviated as the “RUMC group”). This group of participants performed both computerized cognitive tests (subtests from the Cambridge Automated Neuropsychological Test Battery or CANTAB) and paper-and-pencil neuropsychological tests (PnP) (see Table 3.2 for an overview of the tests and Appendix 2 for a more detailed description of the BAM-COG). Specific subtests were related to the individual BAM-COG’s cognitive constructs by consultation with experienced neuropsychologists (MAEB, RPKK; see Table 3.2 for overview of used measures of comparison). Order of the offline testing (CANTAB first vs PnP tasks first) was randomized by flipping a coin. BAM-COG results from participants in Part 2 are also included in the results of Part 1. Duration of the test session was approximately 90 minutes per participant. In addition to the 135 minutes spent on the BAM-COG measurements, participants in Part 2 were estimated to have spent about 225 minutes on the BAM-COG validation study.

For the group of participants visiting the RUMC, two additional inclusion and exclusion criteria were applied. Potential participants were excluded if they had a score ≤ 24 on the Mini-Mental State Examination (MMSE (Folstein et al, 1975)) to make sure none of the participants had any symptoms of neurodegenerative disease (Deary et al, 2009). To ensure that participants were capable of working with the CANTAB touch screen and test environment, the session started with performing the CANTAB Motor Screening Task where participants need to touch a flashing “x” stimulus on the screen as quickly and accurately as possible. If participants failed to either comprehend or execute this task, they were excluded from further participation. Since this study design was, in part, focused on gathering reference values, current participants did not receive feedback on their individual scores in comparison to their peers. After completing the three measurements, participants did not have continued access to the games, because the BAM-COG was not designed to be a training instrument, but an assessment instrument. This resembles the manner in which it primarily should be used in further practice.

Table 3.1. BAM-COG (Brain Aging Monitor–Cognitive Assessment Battery) game details.

BAM-COG game	Cognitive domain	Total levels ^a	Range of scores	Short description
Conveyer Belt	Working memory	7	4-10	This game shows a participant a grocery list on screen. After 1 second, the conveyor belt turns on. Groceries run down the belt and participants need to select only those products that are on their list.
Sunshine	Visuospatial short-term memory	8	3-10	In this game, a sun creates visual patterns in a 5x5 cloud matrix. This visual pattern dissolves and, after it has completely disappeared, participants are asked to reproduce this pattern in the exact same order as it initially appeared on screen.
Viewpoint	Episodic recognition memory	8	1-8	This game presents a 5x5 matrix filled with stimuli (asterisks) to the participant. The participant gets 3 seconds to memorize this presented pattern before it disappears from the screen. After 3 seconds, 3 answer possibilities appear on screen from which the participant is to pick the answer that is an exact match to the previously shown matrix.
Papyrinth	Executive function - planning	5	3-7	This game starts with presenting the participant with a scrambled path. The participants task is to unscramble the path so their pawn can move from start to finish unobstructed. Clearing the route is done by sliding columns and rows in the correct order so that all pieces of road end up connected to each other.

^aExcluding the practice level.

Sample Size Calculation

According to our sample size calculations for CV and DV, we needed 37 participants for Part 2 (alpha error probability <.05, power (1-beta error probability =.8) of our study. Sample size calculation was performed using GPower 3.1 (Faul et al, 2009).

Instruments

The BAM-COG consists of four puzzle games developed to measure working memory, visuospatial short-term memory, episodic recognition memory, and executive function-planning (see Table 3.1 for game details). Every game started with brief and clear instructions as to what the participant should expect. In an attempt to maximize

Table 3.2. BAM-COG^a domains and proposed matching computerized and paper-and-pencil cognitive tests.

BAM-COG game (domain)	CANTAB ^b	Paper and pencil
Conveyer Belt (working memory)	Spatial Working Memory (Robbins et al, 1994)	Letter-Number Sequencing Task from WAIS-III ^c (Wechsler, 1997a)
Sunshine (visuospatial short-term memory)	Spatial Span (Robbins et al, 1994)	Spatial Span subtest from WMS-III ^d (Wechsler, 1997b)
Viewpoint (episodic recognition memory)	Pattern Recognition (Robbins et al, 1994)	Continuous Visual Memory Task (Deary et al, 2009; Larrabee et al, 1992; Trahan & Larrabee, 1988; Trahan et al, 1990)
Papyrus (planning)	Stockings of Cambridge (Robbins et al, 1994)	Zoo Map Task, part of the BADS ^e (Deary et al, 2009; Norris & Tate, 2000)

^aBAM-COG: Brain Aging Monitor–Cognitive Assessment Battery. For a short description of the BAM-COG games, see Appendix 2; ^bCANTAB: Cambridge Automated Neuropsychological Test Battery; ^cWAIS-III: Wechsler Adult Intelligence Scale, third edition; ^dWMS-III: Wechsler Memory Scale, third edition; ^eBADS: Behavioral Assessment of the Dysexecutive Syndrome.

comprehension of the instructions, the written instructions were accompanied by actual game screenshots. After the mandatory instructions, participants performed one practice trial to further familiarize themselves with the game. Following this first practice trial, the actual test commenced. Each level of each game consisted of three trials. To advance to the next level, at least two out of three trials had to be completed successfully. If a participant failed to successfully complete two or three trials, a “game over” screen appeared and the participant was linked back to the main screen where the next game could be selected. For an overview of the games and their instructions, see Appendix 2. Appendix 3 include short videos of the BAM-COG gameplay. Scores for the Conveyer Belt, Sunshine, and Papyrus games were the total number of stimuli or moves that needed to be processed. For the Viewpoint game, the score was the number of levels successfully completed.

Measures of Comparison

Subjects in the RUMC group also participated in tasks from the CANTAB and PnP tasks matched for the BAM-COGs cognitive domains (see Table 3.2). All these games were carefully selected to mimic the cognitive domains primarily relied on in the BAM-COG games as closely as possible.

Instrument Development

Based on expert opinion from two neuropsychologists, a geriatrician, a public health researcher, and a professional game-design team, the four puzzle games were considered to cover the chosen cognitive constructs of working memory, visuospatial short-term memory, episodic recognition memory, and planning. After this initial assessment, the instrument outline was discussed with a broader group of health care professionals consisting of neuropsychologists, epidemiologists, public health care researchers, and general psychologists. It was agreed that from a content point of view, it would be impossible to cover every cognitive domain that decreases in functionality across the lifespan, when fast and easy access are key criteria. It was decided that choosing three executive functions and one specific memory function, all of which have been established to decline in normal aging and neurodegenerative syndromes (Baddeley et al, 1986; Kumar & Priyadarshi, 2013; Salthouse & Babcock, 1991; Samson & Barnes, 2013; Singh-Manoux et al, 2012), would provide good insight into overall aging patterns.

Statistical Analysis

Alternate forms reliability (AFR) was determined to compare the three batches of BAM-COG games, administered at different time points. Every batch resembles a parallel version of the BAM-COG containing an equal number of levels and trials. Theoretically, these batches do not differ from one another in difficulty. The AFR was determined with an intraclass correlation (ICC: two-way mixed; consistency at 95%) on the results of the second and third round performances of the participants. With respect to interpretation of the ICCs, we needed to take into consideration that the study was executed outside of a clinical laboratory setting where people could be easily distracted, which may affect the test's reliability. Therefore, ICC values between .4 and .6 were considered sufficient to support AFR for the BAM-COG. This is in line with another online validation study (Mather, 2010). Also, note that no specific cut-off scores for ICCs exist (Weir, 2005).

To further analyze possible systematic differences between measurements, Bland-Altman plots were calculated. In these plots, the differences between two sessions were plotted against their mean. Furthermore, the scores' means and limits of agreement were calculated as the mean of the difference between the two measurements ± 2 SD of these differences. The standard error of measurement and the 95% confidence intervals for the mean difference between the two measurements were also calculated. If the 95% confidence interval does not include zero, this indicates a systematic and undesirable change in the mean (Altman & Bland, 1983).

The CV determines whether the cognitive domain supposedly measured by the BAM-COG game is actually assessed, using validated cognitive tasks as gold standards. In contrast, the DV examines to what extent the BAM-COG correlates with cognitive domains it should not correlate with. By comparing the BAM-COG game scores to a non-related cognitive construct (in this study, IQ scores derived from the Dutch version of the National Adult Reading Test, NART), the distinctive capacities of the BAM-COG are established. Due to non-normal data distribution on BAM-COG outcome measures and small samples, both CV and DV of the BAM-COG are calculated using a one-tailed Spearman's rho correlation coefficient.

For interpretation purposes, the data from the three batches were aggregated into one measure for the calculation of CV and DV. This enables us to judge the task as one entity instead of three separate batches. Single test statistics were generated based on participants' average game scores (for more information on scoring, see Instruments). Reference values are provided for the games to provide some insight into the expected distribution of scores in a normal aging population of people aged 40 years and older. For every analysis, participants with a raw test score of 0 were excluded. This was done as these participants had either viewed the instructions but not started playing or played only one or two trials out of the necessary three to advance to the next level.

This study was deemed exempt from formal ethical evaluation by the local medical ethics committee (region Arnhem-Nijmegen, registration number: 2011/490). All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0. The Bland-Altman plots were performed with GraphPad Prism version 5.03 for Windows.

Feasibility

BAM-COG's feasibility was assessed based on the total number of registrations and dropouts, the percentage of participants who played and completed the first, second, and third rounds, and examination of the score distributions for floor and ceiling effects.

Results

Participants

Through our research website, 641 participants were enrolled in this study of whom 124 (19.3%) were excluded as they did not fulfill the age criterion. Immediately after registering, each participant was asked to perform the BAM-COG test battery for the first time. A total of 76.8% (397/571) participants in this group played at least one game and were therefore eligible for analyses; 78.6% (312/397) of these were women. The mean age was 54.9 (SD 9.6) years and the modus of education level was 6 (range 1-8).

We recruited 56 participants to participate in Part 2 of the study. Of these 56 participants, 41 were willing to register online, with a mean age of 60.8 (SD 8.2) years, of whom 58.5% (24/41) were female with a modus of educational level of 7 (range 1-8). All participants were native Dutch speakers. All were able to successfully complete the CANTAB Motor Screening Task. In total, 21 (51.2%) of the 41 participants completed the CANTAB tasks first as compared to 20 (48.8%) of the 41 participants completing the PnP tasks first.

In Table 3.3, scores for the MMSE, NART-IQ, and mean BAM-COG scores are presented. Data from the three batches were pooled to get an overall average score on all four games. The RUMC group was significantly older ($t_{395}=3.78$, $P<.001$) and had a higher education level ($\chi^2_7=33.8$, $P<.001$). This resulted in higher overall test scores (except for Viewpoint) even though these differences only reached statistical significance in Sunshine. Since there was such a large inequality in gender distribution in our sample, we controlled for systematic differences between men and women on the raw BAM-COG scores. Using a Fisher Exact test, we found no significant differences (ranging from $F_{13}=18.68$, $P=.07$ to $F_{19}=21.82$, $P=.19$).

Alternate Forms Reliability

Table 3.4 shows the AFR with their respective 95% confidence intervals for all four BAM-COG games. With the exception of Viewpoint, all games have good (>.4) to very good (>.6) AFR. To further clarify this relationship, Appendix 4 shows the generated Bland-Altman plots. These also show that, with the exception of the Viewpoint game, the error bias does not deviate far from zero. This ascertains the absence of systematic error between the second and third round measurements.

Table 3.3. Mean (SD) for age, MMSE^a, NART-IQ^b, and BAM-COG^c scores and mode (range) for education for RUMC^d and online group.

	Online group	RUMC group
Age, years, mean (SD)	54.9 (9.6)	60.8 (8.2)
Education, mode (range)	6 (1-8)	7 (1-8)
MMSE, mean (SD)	--	29.4 (1.07)
NART-IQ, mean (SD)	--	123.2 (12.83)
Conveyer Belt score	5.95 (n=217)	6.33 (n=26)
Sunshine score	4.60 (n=236)	5.10 (n=24)
Viewpoint score	3.97 (n=306)	3.90 (n=28)
Papyrinth score	4.64 (n=152)	5.30 (n=21)

^aMMSE: Mini Mental State Examination; ^bNART-IQ: National Adult Reading Test–Intelligence Quotient;

^cBAM-COG: Brain Aging Monitor–Cognitive Assessment Battery; ^dRUMC: Radboud University Medical Centre.

Table 3.4. Alternate forms reliability (AFR) of BAM-COG^a games in intraclass correlations (ICC^b).

BAM-COG game	AFR	95% CI
Conveyer Belt (n=55)	.420	0.17–0.62
Sunshine (n=78)	.426	0.23–0.59
Viewpoint (n=101)	.167	–0.04 to 0.36
Papyrinth (n=37)	.645	0.41–0.80

^aBAM-COG: Brain Aging Monitor–Cognitive Assessment Battery; ^bAll ICC values >.4 are considered to support sufficient AFR.

Convergent and Divergent Validity

With the exception of Viewpoint, the BAM-COG games have good (>.4) to very good (>.6) CV in comparison to both the CANTAB and PnP tasks (see Table 3.5). Conversely, as hypothesized, all games also show good (<.2) DV with an unrelated overall measure of IQ. Please note that a poor AFR for Viewpoint also translates into poor CV and DV values.

To control whether the individual games did not heavily load on the same cognitive domain, we performed Spearman correlation analysis using aggregated game scores. As was expected with a large sample, most correlations are significant. However, the

size of the correlations range from very small ($\rho=.143$, $P=.056$), between Conveyor Belt and Viewpoint, up to medium small ($\rho=.406$, $P<.001$), between Sunshine and Papyrinth.

Table 3.5. Convergent and divergent validity of BAM-COG^a (Spearman rho's correlation coefficient).

BAM-COG game	Convergent validity ^b		Divergent validity ^c	
	Cognitive test	rho (P value)	Cognitive test	rho (P value)
Conveyor Belt (n=26)	WAIS-III ^d Letter Number Sequencing	.577 (.001)	National Adult Reading Test	-.029 (.44)
	Spatial Working Memory	-.577 (.001)	National Adult Reading Test	
Sunshine (n=24)	WMS-III ^e Spatial Span Task	.669 (<.001)	National Adult Reading Test	-.029 (.45)
	Spatial Span	.620 (.001)		
Viewpoint (n=28)	Continuous Visual Memory Test	.202 (.152)	National Adult Reading Test	-.162 (.21)
	Pattern Recognition	-.157 (.212)		
Papyrinth (n=21)	BADS ^f Zoo Map	.400 (.036)	National Adult Reading Test	-.134 (.28)
	Stockings of Cambridge	.424 (.028)		

^aBAM-COG: Brain Aging Monitor–Cognitive Assessment Battery; ^bAll convergent validity values of $\rho \geq .4$ are considered to support good CV; values of $\rho \geq .6$ are considered very good; ^cAll divergent validity values of $\rho < .2$ are considered to support good DV; ^dWAIS-III: Wechsler Adult Intelligence Scale, third edition; ^eWMS-III: Wechsler Memory Scale, third edition; ^fBADS: Behavioral Assessment of the Dysexecutive Syndrome.

Reference Values

We present reference values for all games (Table 3.6) displaying the total number of times any given score was reached in all three batches.

Table 3.6. BAM-COG^a reference values.

Score	Conveyer Belt (n=217)		Sunshine (n=236)		Viewpoint (n=306)		Papyrinth (n=152)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
1	NA ^b	NA	NA	NA	145	27.5	NA	NA
2	NA	NA	NA	NA	57	10.8	NA	NA
3	NA	NA	75	19.7	32	6.1	57	25.3
4	78	24.4	148	38.9	90	17.1	82	36.4
5	100	31.3	79	20.8	70	13.3	27	12.0
6	26	8.1	55	14.5	41	7.8	15	6.7
7	43	13.5	15	3.9	13	2.4	44	19.6
8	58	18.2	6	1.7	79	15	NA	NA
9	12	3.8	2	0.5	NA	NA	NA	NA
10	2	0.7	0	0	NA	NA	NA	NA

^aBAM-COG: Brain Aging Monitor–Cognitive Assessment Battery.

^bNA: Not Applicable, as this score is not a possible outcome for this game.

Feasibility

The number of registrations totaled 641 participants. The BAM-COG received nationwide attention on two national radio shows and in several regional and national newspapers and magazines. Of the 517 eligible participants, only 397 participants played at least one game out of any of the three batches (76.8%).

The Conveyer Belt game was played most at all three assessments (314, 143, and 107 times respectively) and Papyrinth was played the least frequently (189, 123, and 87 times respectively). On average, 75.7% of participants played all four games and, from the participants that finished the last game on a previous round, on average 80.7% returned to play the next round.

Only 8 participants quit while in the middle of playing a game. All the other participants continued until the “game over” message appeared and either continued with the next game or decided to quit playing after this message. The 8 participants who dropped out all stopped while playing Papyrinth, which is the only game that does not have an integrated time limit.

No real floor or ceiling effects were present in the data. The only possible exception to this may be a slight ceiling effect on Papyrus and Viewpoint (with 19.6%, 44/225 and 15.0%, 79/527 respectively, completing the highest level). Otherwise, the percentages of participants completing the tasks were very low (0.5%, 2/380 and 0.7%, 2/319 respectively).

Discussion

Principal Findings

This article provides substantial support for the use of the BAM-COG game battery as an online self-monitor for cognitive performance. Three out of four games appear to be adequate measures of the related cognitive concepts (working memory, visuospatial short-term memory, and planning). Conveyor Belt, Sunshine, and Papyrus all have good alternate forms reliability and turned out to be feasible for use in aging adults. Furthermore, they all have good to very good convergent and divergent validity and reference values for the games are now available. Since all games were designed to measure some form of cognitive domains, it stands to reason that their correlations are statistically significant. Their size, however, is either considerably smaller or equal to the task correlations with outside gold-standard measurement tools. The game Viewpoint, designed to assess episodic recognition memory, did not have an adequate validity and reliability and is not suitable for inclusion in an online assessment battery. In addition, a strength of our setup are the correlations of the BAM-COG scores with the gold-standard CANTAB and PnP tasks. The fact that the BAM-COG games proved to be solid measures of the intended cognitive domains provides good hope that replication of these results is possible in other samples and the BAM-COG can be put to use for its intended purpose.

Limitations

Even though the current findings are promising with respect to the BAM-COG's applicability, some adjustments can be recommended on the basis of these results. First, we occasionally received feedback of technical difficulties, in particular with the performance of the Conveyor Belt game. Small-sized stimuli (in this case, groceries such as apples and pears) appeared difficult to click resulting in unintentional missed responses. However, although we cannot fully rule out technical issues on some remote systems, this may have also been due to suboptimal mouse handling by individual participants. This explanation is likely since neither the software developers nor the researchers have been able to replicate this problem on different systems with different operating systems and Internet browsers. Moreover, the problem did not emerge so frequently ($n=19$ out of $n=314$) that it would have severely influenced the

outcomes of our analyses. Second, feedback was given that there is a need for additional practice levels. Apparently just one trial to get acquainted with the task was not always enough for all participants to fully comprehend what was requested of them. This may have resulted in a slight underachievement in average scores. In a future release of the BAM-COG battery, this can easily be taken into account. Third, regardless of our follow-up efforts (one additional phone call and one personal reminder email), 15 participants in the RUMC group failed to register online even after they had visited the memory clinic. Reasons for this dropout could have been a sole interest in the neuropsychological screening at the research center, time restrictions, loss of motivation, or the relative ease with which reminder emails and online interventions can be ignored and forgotten. Additionally, the limited amount of personal contact with the researchers and the ease of the registration process may increase attrition (Eysenbach, 2005; Khadjesari et al, 2011), as well as technical or computer-access problems, physical illness, burden of the program, the static structure, and low adaptation to user preferences (Kohl et al, 2013; Mouthaan et al, 2013). This again stresses that high dropout rates are an important issue to consider when setting up Internet-based studies. However, since the characteristics of the group of dropouts did not differ in any way from the other registered participants, we do not feel this has significantly affected the current results.

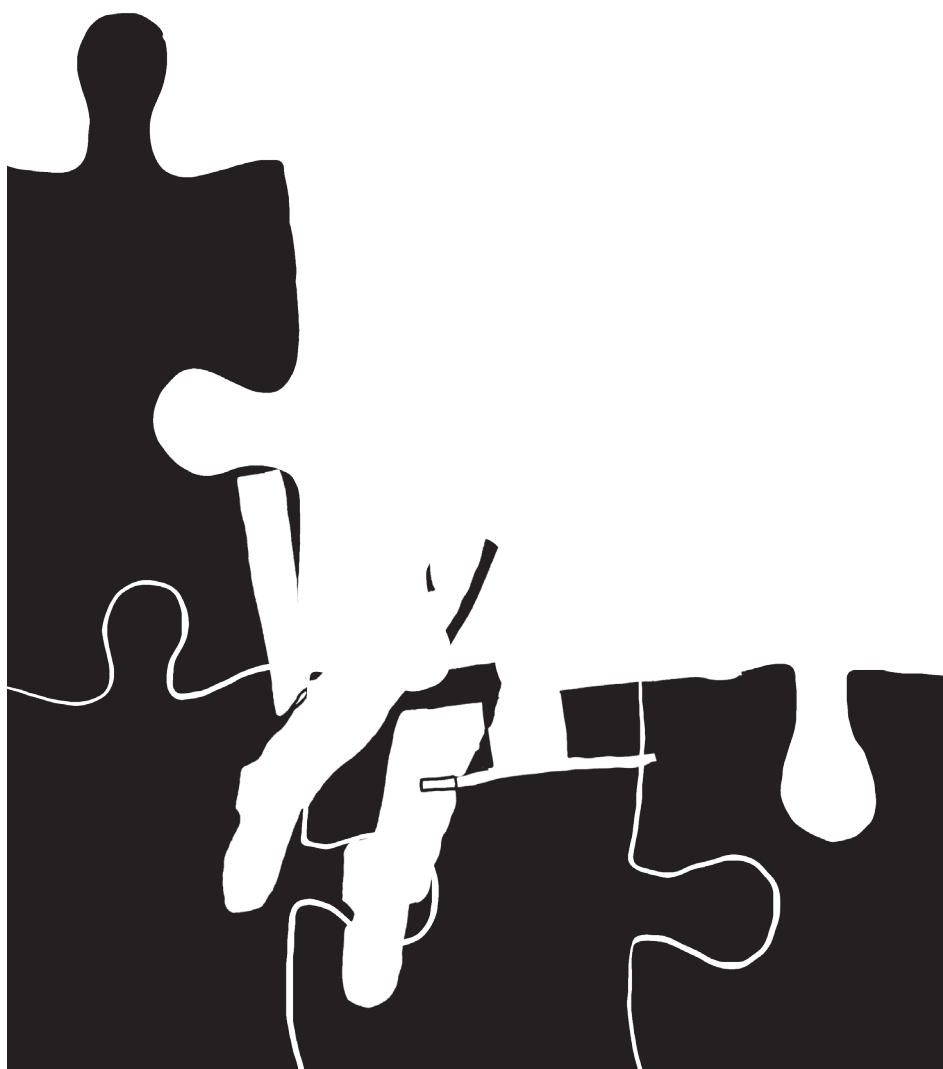
In the interpretation of these results, we need to take the naturalistic setting in which the games were performed into account. That is, laboratory studies in which results are produced under highly controlled conditions typically result in higher ICCs and correlations. The BAM-COG assessments in this study have all been performed in the participants' home environment without any supervision by the research team. Because the BAM-COG is not designed to be used in a laboratory setting, we feel the present design is a valid approach to examine its feasibility, validity, and reliability. If biased, the performance presented in this study may be an underestimation of the real reliability and validity of the BAM-COGs tasks (Weir, 2005). Therefore, we feel we can validly conclude that the BAM-COG is an adequate online self-monitor for cognitive performance.

The fact that our population consisted mainly of women (78.6%, 312/397 and 58.5%, 24/41 for Part 1 and Part 2 respectively) somewhat decreases the external validity of this study. However, this type of research and these types of puzzle games have previously been shown to attract more female participants than males (Haagsma et al, 2012; Mather, 2010; Murre et al, 2013). Also, the notion that not all participants finished (all) the games has consequences for the way ceiling and floor effect results should be interpreted. It remains possible that the participants not starting or dropping out in level 1 are, in fact, experiencing a floor effect. Finally, it should be

mentioned that the RUMC group differed from the online group, as the RUMC group was both older and better educated. This resulted in slightly higher average test scores. Further research in a more balanced sample could strengthen the conclusions drawn and external validity for the BAM-COG battery and validation studies with other cognitive measures should be performed to replicate the present results.

Conclusion

In sum, this study provides evidence for the use of the BAM-COG test battery as a feasible, reliable, and valid tool to monitor cognitive performance in healthy adults in an online setting. Three out of four games were found to have good to very good psychometric characteristics to measure working memory, visuospatial short-term memory, and planning capacity. It should be stressed that the results can by no means be used to either diagnose neurodegenerative disorders or predict cognitive performance. The BAM-COG is suitable for use in practice for online monitoring cognition and stimulating eHealth interventions for healthy brain aging.



4

USING AN EHEALTH INTERVENTION TO STIMULATE HEALTH BEHAVIOR FOR THE PREVENTION OF COGNITIVE DECLINE IN DUTCH ADULTS: A STUDY PROTOCOL FOR THE BRAIN AGING MONITOR

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Abstract

Background: Internet-delivered intervention programs are an effective way of changing health behavior in an aging population. The same population has an increasing number of people with cognitive decline or cognitive impairments. Modifiable lifestyle risk factors such as physical activity, nutrition, smoking, alcohol consumption, sleep, and stress all influence the probability of developing neurodegenerative diseases such as Alzheimer's disease.

Objective: This study aims to answer two questions: (1) Is the use of a self-motivated, complex eHealth intervention effective in changing multiple health behaviors related to cognitive aging in Dutch adults in the work force, especially those aged 40 and over? And (2) Does this health behavior change result in healthier cognitive aging patterns and contribute to preventing or delaying future onset of neurodegenerative syndromes?

Methods: The Brain Aging Monitor study uses a quasi-experimental 2-year pre-post test design. The Brain Aging Monitor is an online, self-motivated lifestyle intervention program. Recruitment is done both in medium to large organizations and in the Dutch general population over the age of 40. The main outcome measure is the relationship between lifestyle change and cognitive aging. The program uses different strategies and modalities such as Web content, email, online newsletters, and online games to aid its users in behavior change. To build self-regulatory skills, the Brain Aging Monitor offers its users goal-setting activities, skill-building activities, and self-monitoring.

Results: Study results are expected to be published in early 2016.

Conclusions: This study will add to the body of evidence on the effectiveness of eHealth intervention programs with the combined use of state-of-the-art applied games and established behavior change techniques. This will lead to new insights on how to use behavior change techniques and theory in multidimensional lifestyle eHealth research, and how these techniques and theories apply when they are used in a setting where no professional backend is available.

Introduction

Multiple systematic reviews and meta-analysis have shown that Internet-delivered intervention programs aimed at health behavior change can have a positive impact in their respective populations. These effects range from weight loss in obese men and women to moderating alcohol intake patterns, smoking cessation, and adjusting dietary patterns (Krebs et al, 2010; Lustria et al, 2013; Portnoy et al, 2008; Webb et al, 2010). Computer-tailored health programs are complex, long-term programs that are appropriate for targeting multiple behaviors requiring a change in behavioral habits (Portnoy et al, 2008; Lustria et al, 2009). In contrast with results reported by Portnoy et al who showed that increasing age was a negative predictor of program effectiveness, a systematic review by our group on the effectiveness of eHealth interventions in older populations provides evidence that older age cohorts can be reached with eHealth interventions (Aalbers et al, 2011). Within the next few years, the upcoming cohort of older adults will be adapted to a new electronic environment, in contrast to previous cohorts who often lacked computer experience and had limited Internet access. This would facilitate further use of eHealth tools, also for prevention targets in the elderly. With Internet penetration in the Netherlands reaching 94% of all households among the population aged 45-75, more widespread use of eHealth by the elderly is likely.

We use Bennett et al's definition for Internet interventions as "systematic treatment/prevention programs, usually addressing one or more determinants of health (frequent health behaviors), delivered largely via the Internet (although not necessarily exclusively Web-based), and interfacing with an end user" (Bennett & Glasgow, 2009). These eHealth interventions are characterized by being highly structured, mostly self-guided, interactive, visually rich, and they may provide tailored messaging based on end-user data (Lustria et al, 2013; Ritterband & Thorndike, 2006). Additional benefits of Internet programs are their 24-hour availability, uniformity in data dissemination and collection (Lustria et al, 2013; Budman et al, 2003), and their heightened reach (Lustria et al, 2009). An advantage of creating such a completely self-motivated eHealth program, in comparison to an expert-led intervention, is the fact that the reduction in needed external support exponentially increases the reach of Internet interventions. Thus, Internet interventions can reach as many participants as is technically allowed by the hosting servers (Ritterband et al, 2009). Moreover, since most of the cost of Web-delivered health programs are associated with the development stages rather than the implementation stage itself (in comparison to regular face-to-face treatment), even programs with relative low effectiveness but a very large reach, could significantly impact public health (Webb et al, 2010).

Lifestyle interventions through the Internet per se are not new. However, online lifestyle intervention programs with cognitive functioning as a primary outcome measure are not yet widespread. The next section presents a short overview of the relationship between six major modifiable lifestyle factors and cognitive functioning.

Physical activity is associated with a lower risk of Alzheimer's disease or any type of dementia, and older people with better cardiovascular function, who are more physically active, have decreased chances of cognitive decline (Abbott et al, 2004; Colcombe & Kramer, 2003). Already in 2007, a plea was made for physical activity trials as prevention for cognitive decline (Barnes et al, 2007). Furthermore, physical inactivity has been calculated to account for approximately 5.3 million premature preventable deaths in 2008, effectively decreasing global life expectancy by 0.7 years (Lee et al, 2012). The Internet has proven to be a valid way of changing participants' physical activity levels (Maon et al, 2012). Albeit in modest ways, average significant effect sizes of 0.14 (Davies et al, 2012), 0.16 (Krebs et al, 2010), and 0.17 (Webb et al, 2010) can mean great benefits on a societal level.

Good physical fitness (positively) and higher BMI (negatively) are related to academic performance as early as in third and fifth grade (Castelli et al, 2007). These effects seem to transfer to later life with high blood pressure and central obesity being negatively related to global cognitive functioning in general and more specifically executive functions, visuomotor skills, and memory (Gunstad et al, 2010; Wolf, 2009). Although the exact mechanisms and functions that are affected still need to be established by future research, being overweight appears to provide additional risk for cognitive impairment. A recent review summarizes the positive effects of antioxidants and balanced nutrition on the delay and avoidance of dementia onset (Polidori & Schulz, 2014).

Smoking is one of the most studied health behaviors, but only recently researchers have started to investigate whether smoking cessation has a positive effect on cognitive functioning. Even though results do not appear definitive yet, most research points towards current smoking as a risk factor for Alzheimer's and vascular dementia (Di Marco et al, 2014). However, smoking cessation seems to mitigate the effects of smoking in the past and relative risk of getting neurodegenerative diseases later in life decrease to normal levels (Di Marco et al, 2014; Tyas et al, 2003). Depending on the number of cigarettes a person smokes daily, the risk of various forms of dementia increases by 1.59 up to 2.72 times (Anstey et al, 2007; Peters et al, 2008; Rusanen et al, 2011). In addition to an increased risk of getting dementia, smokers generally have a lower level of cognitive functioning while smoking and experience faster decline as they age (Nooyens et al, 2008).

Alcohol consumption is not an unequivocal area in comparison with the behaviors discussed above. Low to moderate alcohol consumption may very well have positive effects on brain health, but too much alcohol is harmful to the brain. Cross-sectional studies show that moderate alcohol consumption (up to three units a day) may have beneficial effects on episodic memory, executive functioning, and processing speed of the brain (Anstey et al, 2009; Luchsinger et al, 2004; Ngandu et al, 2007; Ruitenberg et al, 2002). However, these results should be interpreted with care. There are no systematic or controlled-trial intervention studies available that examine the influence of alcohol consumption on cognitive functioning, but earlier research has shown that alcohol consumption higher than three units per day is harmful to the brain and can cause Korsakoff's syndrome (Letenneur, 2004). In addition, it is not clear whether the positive effects on cognition are the direct result of the alcohol consumption itself. It may also be that people who have a lifestyle that includes moderate alcohol consumption also moderate themselves in other lifestyle areas, making them better cognitive agers. Further, a recent meta-analysis of epidemiological studies claimed that a reduction of 17% in alcohol consumption causes a 10% reduction in risk of cardiovascular diseases (Holmes et al, 2014).

In a very elaborate review, Goel et al conclude that both acute and chronic sleep deprivation severely influence cognitive capabilities, starting with a measurable drop in performance on executive functioning tasks after being awake for 16 hours (Goel et al, 2009). Among others, sleep deprivation further negatively influences psychomotor speed, learning and memory, and working memory performance, and causes faster performance deterioration on longer tasks (Goel et al, 2009). Sleep deprivation by lifestyle choice, whether it is chronic or acute, affects executive functioning as the prefrontal and anterior cingulate cortices and posterior parietal systems are especially susceptible to sleep loss (Goel et al, 2009).

An increase in psychosocial stress can lead to burnout or depression, which negatively affects a person's cognitive functioning (Aggarwal et al, 2014). Among others attention, concentration, flexibility, and memory deteriorate with higher amounts of perceived stress (Jonsdottir et al, 2013; Wolf, 2009). Epidemiological research shows a connection between the tendency to experience stress and the risk of mild cognitive impairment and Alzheimer's disease (Wilson et al, 2003; Wilson et al, 2006; Wilson et al, 2007). Also, the speed at which older people experience cognitive decline is correlated with the tendency to experience stress (Wilson et al, 2006).

Managing these modifiable lifestyle factors could serve as a strong protective factor against neurodegenerative syndromes such as dementia. Stimulating health behavior change via the Internet appears feasible, and even the use itself of computers may

serve as a protective factor when it comes to dementia (Almeida et al, 2012). Therefore, we plan to design an online, complex eHealth intervention aiming at lifestyle improvement with cognition as primary outcome measurement. The research question for the current intervention with the Brain Aging Monitor (BAM) will be twofold: (1) Is the use of a self-motivated, complex eHealth intervention effective in changing multiple health behaviors, related to cognitive aging in Dutch adults in the work force, especially those aged 40 and over? and (2) Does this health behavior change result in healthier cognitive aging patterns, thereby possibly preventing or delaying future onset of neurodegenerative syndromes like Alzheimer's disease.

Methods

The methodology of this study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines that is specially developed to provide guidance for researchers to document their study protocol and make sure no relevant information is missing (Chan et al, 2013).

Study Design

For this study, we will use a quasi-experimental longitudinal pre-posttest design, with measurements at baseline and after 12 and 24 months. Only Dutch individuals within the Netherlands will be recruited. The intervention website is programmed in Dutch and as such will not be feasible for implementation outside the Netherlands. Since the Brain Aging Monitor is an eHealth intervention, and the Netherlands has an Internet penetration of 94% of all households (Eurostat, 2012), there is no limit to its potential reach within the Dutch-speaking community. There are no regional restrictions that keep uptake of the intervention pinned to the region of the research institute. Since the entire intervention is based on self-management, contact with the research team is strictly limited to technical support. Considering the fact that the protocol relates to a pragmatic field study that will recruit both at an individual and organizational level, we cannot give an accurate estimate of the number of sites needed to obtain the necessary number of participants. For a sample size calculation, we refer to the description of sample size (Nederlands Trial Register: NTR4144).

Eligibility Criteria

The intervention will be performed among the general Dutch population and is aimed at delaying and/or slowing down cognitive aging. A recent study by Singh-Manoux et al showed that cognitive decline can be measured as early as 45 years of age (Singh-Manoux et al, 2012). For this reason, participants are eligible for analysis of the primary outcome if they are at least 40 years or older. The upper age limit is a more

pragmatic one, since the intervention is aimed at the Dutch workforce and 67 is the official retirement age. Apart from this age restriction, a participant has to have sufficient comprehension of the Dutch language to understand the digital informed consent form (see Appendix 5) and should have regular access to an Internet connection. Because the entire intervention takes place outside of the research facility, no strict control or enforcement is possible over other ineligibility criteria such as neurodegenerative disorders, medicine use, or psychiatric symptoms. Therefore, we decided not to use these and other possible exclusion criteria, which also increases overall external validity.

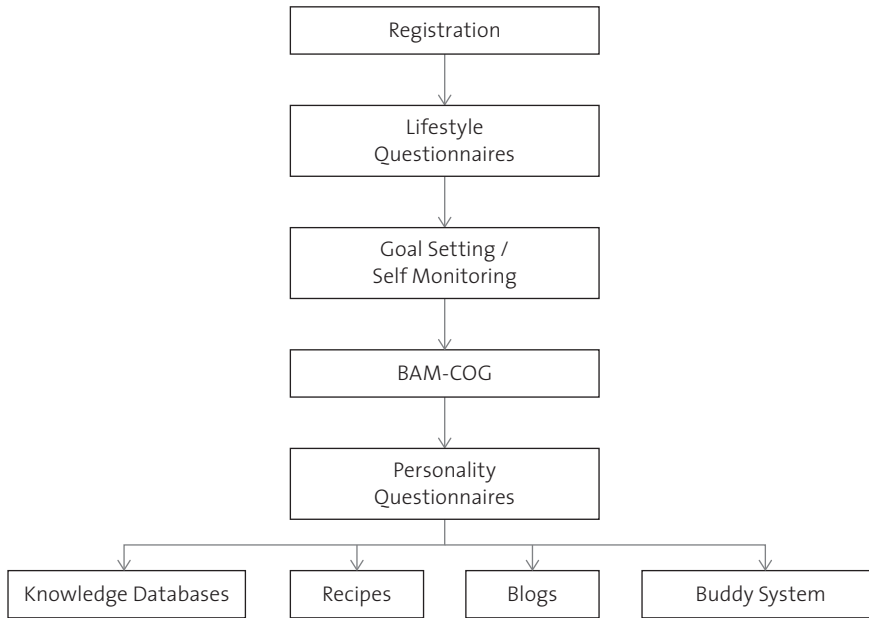
Health Behavior Change Theory

Using Lustria's organizing heuristic for strategies in computer-tailored online behavioral interventions, the BAM is an iterative, self-guided customized health program, with expert-led technical support (Lustria et al, 2009). The BAM uses different modalities such as Web content, email, online newsletters, and online games. To build self-regulatory skills, the BAM deploys goal-setting activities, skill-building activities, self-monitoring, and email reminders. According to a meta-analysis by Webb et al, applying a more extensive use of theory in online lifestyle tools increases overall effect size (Webb et al, 2010). Theory can aid intervention designers identify appropriate targets for intervention, select intervention techniques, and it can illuminate which mechanisms of change are effective (Michie & Prestwich, 2010). How theory is applied in the BAM will be described after the description of the intervention program itself.

Intervention

The BAM eHealth intervention website is open to anyone who is interested in the relationship between healthy living and brain aging. Figure 4.1 gives a short overview of the flow of a new participant within the intervention, and Figure 4.2 shows a screenshot of the BAM homepage. The BAM is a complex intervention (Craig et al, 2008), using multiple intervention components, aimed at multiple health behaviors. As mentioned, the BAM focuses on physical activity, nutrition, smoking, alcohol, sleep, and stress. The BAM has an assessment and feedback system. After registering, validating their email address, and signing a digital informed consent form, new participants fill out seven short questionnaires (ranging from 4-20 questions or statements): one questionnaire for every lifestyle factor and one additional questionnaire on individual characteristics. Full lifestyle questionnaires and their references can be found in Appendix 6. The answers to these questionnaires are used to create a personal lifestyle profile for the participant. The participant receives feedback per question using an easy-to-understand visual traffic light (green=conform to the norm, yellow=close to the norm, orange=much room for improvement,

Figure 4.1. Flowchart of process a new participant goes through upon registration

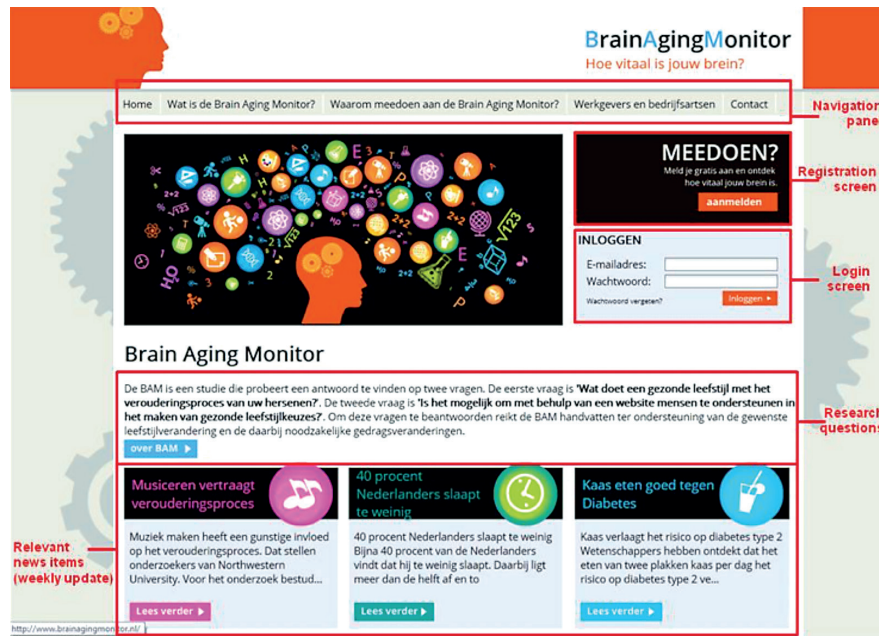


red=non norm compliant) based on the health authority recommendations, behavior specific feedback on health authority recommendations, and reference values on peer behavior (if possible and/or applicable divided for age and gender). Figure 4.3 shows a screenshot of the feedback on the nutrition questionnaire. This gives the participant a fast and detailed overview of their current lifestyle status. Also, the answers to the questionnaires tailor the intervention to the participant. For example, non-smokers will not be confronted with information about smoking or the option of setting goals that apply only to smokers.

The use of short self-reporting questionnaires on health behavior is a decision from a time-saving and retention perspective. Using more elaborate questionnaires would allow for better insight in a participant's behavior but will likely result in higher attrition (Edwards, 2010). Furthermore, more elaborate questionnaires are likely to pose questions that are difficult to answer for an individual. For example, obtaining a meaningful, valid answer on a participant's consumed dietary fiber (using the Dutch Healthy Diet index (van Lee et al, 2012)) is very difficult. This would require a 24-hour recall process during the initial registering procedure, risking immediate dropout.

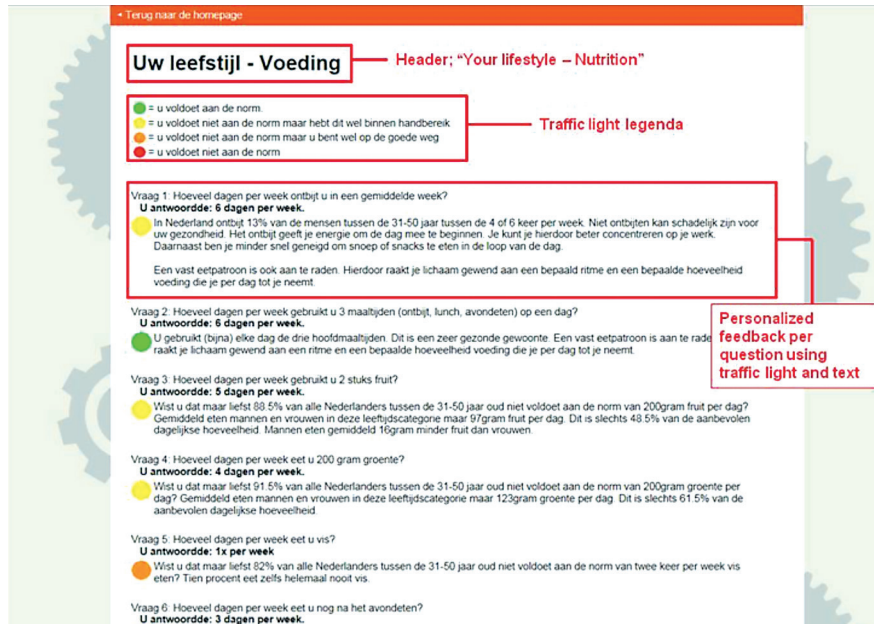
Therefore, we chose to use simple questionnaires for all lifestyle areas, where every question covers a behavioral trait that directly relates to a goal that can be set later on in the program.

Figure 4.2. Brain Aging Monitor homepage



After the questionnaires, the Brain Aging Monitor Cognitive Assessment Battery (BAM-COG) opens up on the game wall and the Goal Setting Module (GSM) is unlocked. The BAM-COG is an online cognitive assessment battery that has been specifically developed for use in the BAM and has been validated by our group (Aalbers et al, 2013). These games measure working memory, visuospatial short-term memory, episodic recognition memory, and planning. An instructional arrow will direct the participants' attention to the fact that the games are open for play. After receiving their personal lifestyle overview, participants can start setting monthly, personal-health behavior goals using the GSM. We based the GSM on the Goal Attainment Scaling (GAS) methodology by Kiresuk (Kiresuk & Sherman, 1968). Using the GAS triggers participants to be more conscious about their goals because it does not rely on a single digit. Instead, it requires the participant to fill out a complete scale from -2 to 2 (where -2 equals "I have made minimal progress", 0 equals "I have reached my original goal", and 2 equals "I have done a lot better than my original goal"). This not

Figure 4.3. Screenshot of feedback module on nutrition questionnaire



only requires more attention from the participant while setting the goal, but it also enables the BAM to give positive feedback on partially accomplished goals instead of a “yes” or “no” answer to the question “did you reach your goal?”.

Every potential goal is accompanied with a set of instructions guiding the participant towards personally relevant and realistic goal-setting. It starts with an example GAS scale, a case of a fictive participant, and a step-by-step instruction to complete the goal-setting process. The GAS system is programmed to return a number of restrictions or error messages to the user: (1) if values overlap, (2) if values are in the wrong direction or scrambled, (3) if values exceed the value of 7 days per week, or (4) if the given o-value is a step back from the value that was answered during the intake questionnaire. When the goal is set, the participant is given reinforcing feedback on making a good first step towards behavior change. After this message, a list of instructions and tips are given that are relevant for that specific goal. This list is open for the participant to choose their preferential working method and go from very basic instructions (eg, “buy fruit” in case of a goal “eat more fruit”) to signing social contracts or using implementation intentions (eg, “if there is no running group in the neighborhood, then I will start my own running group” in case of a goal “start to work out” (Adriaanse et al, 2011)).

After a participant has made the decision on which instructions and tips to use, the goal gets transferred to the short-term monitoring system (STMS). Here, participant can monitor their own behavior on a day-to-day basis. Inputting their behavior in the STMS, the system automatically graphs a quick overview of how well a participant is doing for that goal on a week-to-week basis. After a month, the STMS asks the participant to what extent the goal is accomplished on their own original GAS scale. For any score specific to that goal, the BAM gives tailored feedback. If a score of -2 or -1 is obtained, the goal is deleted from the participant's profile and encouragement to try again is given. However, if a score of 0, 1, or 2 is obtained, the goal gets transferred to the long-term monitoring system (LTMS). In the LTMS, a participant gets monthly follow-up questions to monitor if they still are maintaining their initial level of behavior change. With every monthly question that gets answered, the participant is given tailored feedback to acknowledge their success or motivate the participant to maintain their initial behavior change. Multiple goals can be graphed over time giving a personal overview of all acquired and maintained behavior change goals. If multiple goals are set on the same subject, new goals will overwrite old goals so that only the most up-to-date information is shown. Because the BAM does not dictate how many a goals a participant sets and in what order they do this, it implicitly provides the participant with a conceptual choice between simultaneous or sequential goal-setting, giving every participant the option to work at their own pace and preference (Hyman et al, 2007; Spring et al, 2004; Vandelandotte et al, 2008).

In order not to overload the participant with questionnaires immediately after registering, the personality questionnaires become available to the participant 7 days after registration. These are the Dutch General Self-Efficacy Scale (Schwarzer & Jerusalem, 1995), lifestyle factor specific self-efficacy questions (Kelly et al, 1991), the Positive Affect Negative Affect Scale (Watson et al, 1988), and the Self Control Scale (Tangney et al, 2004). These questionnaires are administered to perform secondary analyses to check if the BAM is more effective in certain personality types. No feedback on the personality questionnaires is provided for the participants.

After all baseline data are collected, the tailored knowledge databases, the buddy system, healthy recipes, and blogs on health behavior and cognitive aging become available. The buddy system is a built-in control mechanism the BAM uses to ensure goal safety. A subset of goals that are suitable for this purpose are anonymously sent to another BAM user to be judged by a BAM buddy on its feasibility and safety. A buddy can judge a goal to be "ambitious", "not ambitious enough", "just right", or in the case of losing weight, "this seems unhealthy". This gives the goal setter an opportunity to get instant feedback on the feasibility of their goal. Also, it gives the buddy a "look behind the scenes" that may provide feedback on their own goal-setting

behavior, as the exact same situation for somebody else may be perceived as harmful whereas this same goal would be deemed applicable to the participant themselves. At the same time the buddy system becomes available, participants also get access to the knowledge databases that contain up-to-date information on healthy living and the relationship between the different behaviors and brain health. Last, participants get access to weekly blogs on lifestyle, research and brain aging, and healthy recipes. After 365 and 730 days upon completion of the baseline measurement, they will be recruited for 1-year and 2-year follow-up measurements.

No reasons for discontinuation of the study of a participant by the research team have been specified. There is no disease load that can be exacerbated by participating in the BAM nor is there any medication prescribed that could have negative health consequences. Participants are provided with the option of unsubscribing to the study at any given time in their personal profile space. When a participant decides to leave the program, a short questionnaire is automatically presented to collect data on the reason for unsubscribing and to inquire if the participant may be approached to partake in the 1-year and 2-year measurement, regardless of subscription status. All of this is voluntary and participants can always choose to skip this questionnaire.

Keeping participants engaged with eHealth intervention programs has been a major problem since the field originated (Bennett & Glasgow, 2009; Ferney & Marshall, 2006; Leslie et al, 2005). Several adherence enhancing strategies are in place with the BAM. First, we upload weekly news updates on the homepage regarding health behavior and brain aging from the largest Dutch news websites. Second, on the dashboard of the participant we will upload weekly blogs and healthy recipes so that the content, apart from user input, changes on a weekly basis. Blogs will discuss current topics in research on anything BAM-related in an easy accessible form. Recipes will use fresh and healthy products and provide participants with ideas to prepare a healthy meal. Third, a personalized email reminder system is built into the BAM that can be adjusted to the participants' individual needs. In their personal profile space, a participant can choose to receive daily, weekly, biweekly, or monthly email reminders. These reminders give an overview of current active goals and will link the participant directly to this goal after logging in. Fourth, during the registration process new participants can opt-in to receive BAM newsletters, which will be sent using the MailChimp engine. At any time, participants can opt-in or opt-out to the newsletter. Last, participants get a personal profile space with a quick and easy overview of their current lifestyle, they can make adaptations to their lifestyle, see the results of their goals, and they can adjust their settings.

Considering the field setting for this intervention, it is difficult to control for concomitant care, or better yet if the BAM inspires participants to make use of other platforms to alter their health behavior in a positive way, this accomplishes the BAMs goals. The BAM can and may function as a gateway to healthy behavior. Using the Goal Setting Module and the yearly follow-up, the BAM can track changes over time even if participants actively use outside help that the BAM refers them to.

Use of health behavior change theory

A description of the used behavior change techniques is given using the taxonomy provided by Abraham and Michie (Abraham & Michie, 2008). This paper provides researchers with 26 behavior change techniques based on behavior change theories to be used while designing an intervention. As the BAM is a self-guided, voluntary online intervention, the majority of participants will be in the last three stages of the Trans-theoretical Model (TTM); the preparation, action, and maintenance phases (Prochaska & Velicer, 1997). The BAM guides participants from preparation phase (informing), to action phase (goal-setting, short-term self-monitoring), to maintenance phase (long-term self monitoring). As participants enroll in the BAM, the three stages of the TTM are facilitated instantaneously and for every behavior the participant can choose the most appropriate phase to begin. When the preparation phase is chosen, the knowledge database for that behavior is the most suitable starting point. Providing a participant with information is in accordance with the Information-Motivation-Behavioral Skills Model.

When participants decide to enter the action phase of the TTM and become active goal-setters, they get an appropriate list of instructions and tips. Setting active behavioral goals is a part of most renowned behavior change theories such as the Theory of Planned Behavior (TPB; Fishbein & Ajzen, 2010) and the Social Cognitive Theory (SCT; Bandura, 1991). In line with the SCT, general encouragement is provided when goals are set and (partially) accomplished. While working with the tips and tools, participants will monitor their behavior. Bandura notes in his SCT that self-directed change can be promoted with features that allow program participants to set realistic goals, provide them with instructions and tips to reach these goals, and to allow for detailed self-monitoring of their own behavior over time (Adriaanse et al, 2009; Bandura, 1998). Using GAS prompts a participant to set specific lifestyle goals, the buddy system prompts the review of behavioral goals, the short-term monitoring system prompts self-monitoring of behavior, and evaluating their own performance gives the participant feedback on their own behavior. The instructions and tips, when of additional value, include a list of commonly heard behavioral barriers and reasons why these barriers are either invalid or on how to overcome them, which is part of the SCT. Another possible instruction was to set up a behavioral contract with a person

close to the goal-setter to create a form of peer pressure or control, which is in line with the theory of operant conditioning (Abraham & Michie, 2008). Among the instructions and tips, when applicable, is the suggestion to form if-then implementation intentions (Adriaanse et al, 2009). These if-then implementation intentions partially ease the transformation of behavior but also aid in relapse prevention, as these actively trigger the goal-setter to identify risk situations and come up with an appropriate action if the occasion arises (eg, IF my friends keep asking me to drink beer, THEN I will firmly tell them that I am drinking water this evening). Finally, the goal that can be set to reduce stress and optimize satisfaction with life aims at stress reduction through various methods (eg, yoga, mindfulness).

After the completion of a goal, follow-up is built into the system by automatically re-evaluating changed behavior on a monthly basis. Also, using an automated email reminder system, the BAM aims to maximize adherence to the program, providing follow-up prompts. To summarize, in accordance with the taxonomy by Abraham and Michie, 13 out of 26 behavior change techniques are used in the BAM (#1, 4, 5, 6, 8, 10-13, 16, 18, 23, and 24) (Abraham & Michie, 2008).

Research Questions and Outcome Measures

Our primary research questions are (1) Is successful health behavior change related to better cognitive aging patterns over time? Change scores will be calculated by subtracting baseline scores from scores at year 1 and year 2, (2) Does the BAM facilitate health behavior change? (see Appendix 7 for the construction of the overall lifestyle score), and (3) Does the BAM facilitate health behavior change in certain specific lifestyle areas better than others?

Our secondary research questions are (1) Is there a dose-response relationship between the number of goals participants set and the expected amount of health behavior improvement? and (2) Does the BAM increase feelings of self-efficacy in health-related behavior and a change in self-control scores from baseline to 1 and 2 years of intervention, as measured with the Self-Control Scale (SCS; Tangney et al, 2004). In other words, does the BAM increase feelings of being in control of one's life?

Our primary outcome measures are (1) cognitive change over time, (2) overall lifestyle change over time, and (3) specific lifestyle changes over time. The secondary outcome measures consist of (1) number of goals set, (2) change in self-efficacy, and (3) change in self-control.

Participant Timeline

The timeline for the BAM is straightforward (see Figure 4.1). Participants need to register only once. Immediately after registering, email validation, and the informed

consent form, the lifestyle questionnaires are available. Once the lifestyle questionnaires have been completed, the BAM-COG becomes available. Seven days after subscription, the personality questionnaires appear in the personal dashboard. Subsequently all these features are again presented to the participant 365 and 730 days after their baseline completion. The GSM, STMS, and LTMS are continuous processes from the moment they first become available to the participant. After 1 year (365 days), the data will be collected for preliminary secondary outcome analysis. After the 2-year follow-up (730 days), the data will be used for analysis of both primary and secondary outcomes. The nature of the grant requires that the intervention will remain online even after data collection is finished for the initial study period and that the BAM will remain open to the public after the study is completed. Adaptations to the program can be made at this time, according to study outcomes.

Sample Size

We aim for a group size of 200 to find a 15% reduction on the risk factors (power calculation based on $\alpha < .05$; power 0.8; two-tailed: $n=166$; $\pm 20\%$ dropout).

Recruitment

Different recruitment strategies will be implemented to reach the necessary sample size. First, we will recruit medium to large commercial or governmental organizations through their human resources department or company employed medical staff. The BAM can provide organizations with a concrete intervention program that can substantiate their health policy. Organizations will be recruited by direct inquiry through telephone calls, emails, and will be targeted during several symposia, workshops, and congresses where the BAM will be presented. Once an organization is recruited, the research team in collaboration with the human resources department will develop a tailored recruitment strategy that maximizes the use of existing communication channels within the organization. These organizations are expected to deliver approximately 50% of all study participants.

Next to organizational recruitment, the BAM will also recruit participants in the general Dutch population. A press release will be issued by the Radboudumc to reach mainstream media to generate national attention for the study. The BAM will be advertised at the website of a cooperative research consortium that draws national attention because researchers from four nationally spread out universities will promote this website. Also, we will present the BAM at (inter)national health care conferences. We estimate that approximately 50% of all study participants will result from this free recruitment strategy.

The enrollment period will take approximately 4-5 months. However, due to the nature of the grant no actual stop in participant influx will be enforced. Participants will be allowed to enter the study at any given time. We will monitor participant influx over time so we can keep estimating the relevance and need for an intervention such as the BAM. Unless individual organizations determine otherwise, no financial incentives are offered to potential participants. If this occurs, this will be disclosed in future publications.

Sequence Generation, Allocation Concealment Mechanism, Implementation, and Blinding

This pragmatic field trial does not use a control group. Therefore, sequence generation, allocation concealment, implementation, and blinding are not discussed.

Data Collection Methods

Data collection in the BAM is completely automated through its website. Therefore training of personnel is irrelevant. All data collection forms will be equal for each new participant that subscribes to the program. For collection of the descriptive lifestyle data, questionnaires have been used that accurately represent the relevant health norm or health behavior (full lifestyle questionnaires can be found in Appendix 6). For measuring cognitive functioning, the BAM program uses a validated online self-monitor for cognitive functioning, specially developed for use in the BAM, called the BAM-COG (Aalbers et al, 2013). We have deliberately chosen to keep the baseline assessment as concise as possible. Creating a complete overview of a participant's lifestyle can be a tedious task and with high risk of early dropout in eHealth interventions, the BAM's lifestyle assessment is meant to give a fast and easy overview of a participant's compliance to health norms, not a detailed description of all facets that make up healthy living.

The BAM intervention has multiple built-in mechanisms aimed at increasing retention to protocol. As described in the intervention section of this protocol, we will use blogs and recipes in the intervention to keep participants' focus on the program, as well as the deployment of the adjustable reminder system and the flexible use of newsletters. When the program has been online for 365 and 730 days, special newsletters will be sent out to all active participants reminding them of their annual follow-up measurement that becomes available on their personal dashboard.

Participants who want to exit the study can do so at any given moment in time. They can unsubscribe from their personal profile page using the unsubscribe instructions. Once this process is initiated by the participant, a short questionnaire will be used to identify the reason for dropout. Also, the BAM will ask the participant if they are still

willing to be reminded of the annual measurements. In this case, they would not actively participate in goal-setting and behavior monitoring but would be willing to come back and provide the program with follow-up data.

Data Management

Because of the eHealth nature of the intervention, all data entry and collection is done online and therefore is programmed to be completely automated. The intervention website is secured with up-to-date online security protocols and certificates safeguarding private information of participants. Users must sign in to get access to their profile and logged data. To sign in, a user name (email address) and password is required. Passwords are stored by using the MD5 hash algorithm. Each user gets their own session after signing in. This session will be killed when the user closes the browser or when the session times out. All data are stored in a MySQL database. To access this database, a password is required that contains digits as well as characters, randomly created. The site uses the HTTPS protocol and is secured by a Comodo SSL Certificate.

Data storage will be extensively tested in the pilot phase. All the participants are assigned an anonymous personal identifier that will be used for all the tables containing data during data collection in the MySQL database. The data will be stored on secure hosting servers for 20 years after the completion of the intervention period.

Statistical Analyses

Intervention Effects

Primary analyses will be unadjusted. Depending on the distribution of continuous, categorical, and interval outcomes, an appropriate distribution and relevant statistical models will be used. These models will assess intervention effect at end-of-intervention (1- and 2-year) as well as the difference between 1- and 2-year measurements. Baseline characteristics will be compared between groups using *t* tests for continuous variable and chi-square tests for categorical variables. Mann-Whitney tests will be used when baseline data are not normally distributed. If necessary, multivariate analysis, including multi-analysis of variance and multiple regression, will be performed to adjust potential confounders, including baseline demographic and behavioral characteristics. The covariates associated with outcomes or contributing to a significant part of variation of used multivariate models will be adjusted as potential confounders. The final model will include these covariates or remove those that do not affect estimates, if models show evidence of overfitting.

Secondary Analyses

Total set goals and specific lifestyle area goals will be reported descriptively. The changes of lifestyle within the goal setting group will be reported in absolute difference at end of intervention. The dose-response association between goals and change of lifestyle will be analyzed by multivariable linear regression model, and potential confounders will be adjusted. The change in self-efficacy and self-control scores will be reported in absolute difference at end of intervention. The association between the use of BAM and the increased feeling of self-efficacy or self-control will be analyzed by multivariate analysis.

Analysis will be performed per protocol. The dropout in this pragmatic field study is likely to be high but can be considered a separate outcome for the implementation and feasibility of these types of intervention. As such, it represents valuable data about the quasi-experimental study design.

Data Monitoring

There will be no Data Monitoring Committee for this intervention, as no adverse events are expected. No interim analysis will be performed for the same reason. No significant harm to the participants is to be expected for the BAM intervention program. If anything would occur, participants can contact the research team through the contact form on the website. Standard data monitoring procedures for the scientific Geriatric Medicine department at the Radboudumc apply.

Auditing

No auditing is planned specifically aimed at the BAM study. However, the BAM is part of the scientific branch of the Geriatric Department of the Radboudumc and therefore can be routinely audited internally.

Research Ethics Approval and Protocol Amendments

The program is largely implemented in medium-to-large corporations that transparently implement the program as part of their health policy. From individual participants, an online form of Informed Consent for their participation in scientific analysis is obtained during registration for the program. This study was deemed exempt from formal ethical evaluation by the local medical ethics committee (region Arnhem-Nijmegen, registration number: 2014-1268). Protocol amendments will be submitted, if necessary.

Informed Consent

Due to the online nature of this study, no personal informed consent can be obtained from participants. However, we do realize a substitute of online informed consent to make sure that participants are aware of their participation in scientific research.

Therefore an extra step has been added to the registration process. After email verification, before a participant can start the program a screen appears with an informed consent form. If informed consent is not provided by ticking the correct box, participation with the program becomes impossible. See Appendix 5 for a complete translation of the information provided and accompanying informed consent form is in.

Confidentiality

All information that is stored in online databases is random-password protected. Also all our websites use state of the art SSL-security certificates to ensure maximum safety of participant confidential information. MySQL data that contain names are stored in different tables as study results. Exported data from the MySQL online databases will be downloaded to local password-protected hard drives for analysis. Also, when databases are saved on local hard drives these databases will be stored anonymously, using only anonymous personal identifier codes for all participants. No print records will be kept at any point during the study. Participants' study information will not be released outside of the study without the documented permission of the participant.

Access to Data

Only principal investigators, post-docs, and PhD students involved in the study will have access to the full raw dataset. Other researchers interested in using the BAM dataset will get access to a cleaned dataset. Human resources departments of recruited companies will, at no point, get access to any form of dataset. They will receive anonymous overall group results of data analysis.

Ancillary and Post Trial Care

Participants can always contact the research team by phone or email with any questions they may have. Also, the BAM will remain available to them after the study closes since the BAM is part of a national Quick Results grant aimed at providing fully functional end products at the end of the study period.

Dissemination Policy

Study results, regardless of their direction of outcome, will be published in high standard, peer-reviewed scientific journals. Study publications will be written on primary and secondary outcomes and subgroup analysis. Researchers and health care professionals will be updated on study results during (inter)national conferences and workshops and with targeted tailored publications in relevant professional magazines.

Participants who unsubscribe to the program are given the option to stay updated on study results when these become publicly available in the form of a summary of the

research report or PhD thesis. Participants who stay in the program until the study period closes will be approached by email to probe their interest in study results. Furthermore, study results will be made public to the general public via a press release issued by the Radboudumc after publication of the primary outcomes. No publication restrictions apply and no ghost- or professional medical writers are involved in the study.

Discussion

To our knowledge, this is the first large study that aims at health behavior gains with a cognitive motivation and outcome measure in the general population. Furthermore, the BAM is one of the first studies launched in an era when almost everybody has an Internet connection. As such it can serve as a proxy for the feasibility of these type of interventions when specifically launched into the general population.

Enhancing the BAM with state-of-the-art, scientifically validated applied games gives the unique advantage of being capable of measuring cognitive functioning while maintaining all advantages such as reach and low cost that are associated with eHealth studies. The use of online applied games from the safety and comfort of one's home gives us another major advantage. It also provides a motivational edge, since playing games is considered more appealing than participating in standard neuropsychological testing. We decided to use self-reporting measures for the BAM instead of more objective clinical measures (eg, blood pressure, cholesterol) because use of these measures in a general community dwelling research population is either not feasible or expensive and a big logistic challenge. Moreover, using a participant's self-reported input closely matches the participant's perception of their own behavior, therefore, the goals a participant will set are more likely to be perceived as personally relevant and the participant will feel ownership over the goal and behavior change that needs to be achieved. Combined, we feel this increases the odds of successful implementation of the BAM.

We chose a quasi-experimental design as it seems more appropriate for a field setting in which it is highly impractical to initiate a randomized controlled trial, and blinding participants to the type of eHealth intervention they are receiving is practically impossible (Baker et al, 2010). Theoretically, it was preferable to use a step-wedge cluster-randomized controlled design, but this was not feasible with the current 2-year intervention period. Since recruitment of companies is not guaranteed, cluster randomizing from the start is also difficult, especially since organizations are not very likely to see the incentive of participating as a control group. There is also a pragmatic

side to the choice of the population. There is substantial theoretical background to select participants aged 40 and older (Singh-Manoux et al, 2012), since in this part of the working population cognitive decline can already be measured, and they are more likely to be triggered by a dementia prevention program. People under 40 are less likely to be triggered by cognitive decline or even dementia prevention, as it is a disease associated with old age, and only in later years a relevant threat to their health. Nonetheless, the BAM will allow participants under 40 to subscribe. However, lifestyle advice will be tailored to age cohorts starting at the age of 40.

Last, the use of a multimodal lifestyle perspective is a strength, as it gives potential participants a more integral overview of lifestyle. Providing a more comprehensive lifestyle overview allows the participant to prioritize one type of change over the other and take a holistic approach to their own lifestyle. Also, benefits from changing one behavior may transfer to improved outcomes on other behavior that would go unnoticed in single modal interventions. Since the BAM is an eHealth intervention, tailoring to the needs of the participant is cheap after initial development costs have been incurred. Zooming in on personally relevant lifestyle factors after providing a more general overview should improve program adherence because the participant becomes aware of why they are working on what risk factor. This is important as adherence often is the crucial factor in lifestyle improvement programs.



5

CHANGING LIFESTYLE RISK FACTORS FOR COGNITIVE DECLINE USING A SELF-MOTIVATED EHEALTH INTERVENTION IN DUTCH ADULTS

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Abstract

Background: Our labour force is aging, but aged workers are not yet coached how to stay cognitively fit for the job.

Objective: In this study we test whether a self-motivated, complex eHealth intervention can improve multiple health-related behaviours that are associated with cognitive ageing among working Dutch adults.

Methods: Design: Quasi-experimental, prospective study with a pre-post design. Setting: Employees of Dutch medium to large companies. Participants: All employees with Internet access, a good understanding of the Dutch language, and who provided digital informed consent were eligible. In total, 2972 participants (71.1% females) with a mean (\pm SD) age of 51.8 (\pm 12.9) years were recruited; 2305 became active users of the intervention, and 173 completed the one-year follow-up. Intervention: This self-motivated eHealth lifestyle intervention stimulates participants to set personally relevant, monthly health behaviour-changing goals using Goal Attainment Scaling and to realise these goals by implementing behaviour-changing techniques grounded in behaviour change theory. Main outcome measures: The primary outcomes were the goal-setting success rate and the change in overall lifestyle score from baseline to the one-year follow-up; the score was based on physical activity, diet, smoking, alcohol, sleep, and stress scores. The secondary outcomes were the changes in body weight, body mass index, specific lifestyle characteristics, and website usage.

Results: A total of 1212 participants set 2620 behaviour-changing goals; 392 participants assessed 1089 (47.6%) goals and successfully achieved 422 (38.8%) of these goals. Among the goal-setting participants in follow-up, this led to a +0.81-point improvement (95% CI: 0.49, 1.13; $p < 0.001$) in overall lifestyle ($d = 0.32$) and weight loss of 0.61 kg (95% CI: -1.16, -0.07; $p = 0.029$). These participants also showed significant improvement in eight out of eleven specific lifestyle components.

Conclusions: Among an adult Dutch population, this eHealth intervention resulted in lifestyle changes in behavioural risk factors associated with cognitive decline, and these improvements lasted over the period of one year. Given the general ageing of our workforce, this eHealth intervention opens new avenues for the widespread use of cost-effective self-motivated prevention programmes aimed at prevention of early stage cognitive decline, and more self-management of their risk factors.

Introduction

A number of large-scale longitudinal studies have shown that several behavioural risk factors are causally related to the onset and progression of disability and chronic diseases in later life, including diabetes, cardiovascular disease, stroke, and cognitive impairment (Artaud et al, 2013; Elwood et al, 2013; Goldstein, 2010). Moreover, studies have shown that the relative risk of developing these diseases increases when several risk factors are present (van Dam et al, 2008). Consequently, reversing unhealthy behaviours may significantly benefit one's health in later life. Three key unhealthy behaviours – a lack of physical activity, consuming an unhealthy diet, and tobacco use – are estimated to account for approximately 71% of the more than one million preventable deaths that occurred in the year 2000 in the United States alone (Mokdad et al, 2004; Mokdad et al, 2005). Moreover, a growing body of evidence suggests that good health during one's midlife years has a positive impact on cognitive ageing, and focusing on modifiable lifestyle-related risk factors can delay or even prevent the onset of Alzheimer's disease (Barnes & Yaffe, 2011; Evans et al, 2014; Solomon et al, 2014). Physical activity, nutrition, smoking, alcohol consumption, sleep, and stress have all been identified as lifestyle choices that can affect cognitive ageing (Anstey et al, 2009; Blondell et al, 2014; Di Marco et al, 2014; Goel et al, 2009; Horton et al, 2014; Jonsdottir et al, 2013; Polidori & Schulz, 2014; Wolf, 2009). A recent study even predicted that one-third of all global cases of Alzheimer's disease can be attributed to potentially modifiable risk factors (Norton et al, 2014), and according to a study by Barnes and Yaffe, even a 10-25% reduction in modifiable risk factors for Alzheimer's disease might prevent up to 3 million cases of Alzheimer's disease worldwide (Barnes & Yaffe, 2011).

Internet-based lifestyle programs

In a recent systematic review, we found that tailored Internet-based intervention programs provide an evidence-based means to effect large-scale change in modifiable risk factors (Aalbers et al, 2011). The efficacy and feasibility of web-delivered intervention programs for changing unhealthy behaviors is well-established with respect to the relevant health behaviors (e.g. increased physical activity, weight loss, smoking cessation, and reduced alcohol consumption; Bennett & Glasgow, 2009; Ritterband & Tate, 2009). Moreover, more recent research attempted to determine which types of interventions are the most effective. For example, recent meta-analyses revealed that some form of tailoring is necessary for improving the personal relevance and extent of health behavior-changing programs (Lustria et al, 2013) and for increasing the intervention's effectiveness (Krebs et al, 2010). However, to date, no published eHealth study has been designed to investigate the effect of lifestyle changes on cognitive ageing.

Our objective was to design an innovative eHealth intervention program that motivates ageing adults to adopt healthy lifestyle changes in order to help prevent cognitive decline. To facilitate feedback and to increase participant motivation, the intervention enables participants to monitor their own cognitive functioning over time by playing applied games (abbreviated here as the BAM-COG part of the intervention), which provide a valid measure of various cognitive functions (Aalbers et al, 2013). These games are part of the Brain Aging Monitor (BAM), an eHealth system with minimal barriers for participation, and they are sustainable in a wide range of practice settings. After developing and pilot-testing this eHealth intervention program, we initiated this study by asking whether using this self-motivated, complex eHealth intervention can effectively result in changing multiple health behaviors that are related to cognitive ageing over one year time. As people have to work longer, and work is more and more relying on cognitive capacity, we decided to conduct this among adult Dutch working employees 40 years of age and older.

Methods

Study design

This study used a pre-post design, in which newly enrolled participants chose their own time path, from registration to setting goals and monitoring their change in behavior. Randomizing the participants against a sham intervention in an occupational health promotion program, in which the stimulated behaviors are known to be advantageous, was judged to be insufficiently motivating for the participants and potential participating companies; therefore, we chose to use a pre-post design. Inclusion started in October 2012. This intervention was registered with the Dutch Trial Register (NTR4144) and was exempt from formal testing by the Medical Ethics Committee of the Radboud university medical center Nijmegen, which determined that the intervention was not invasive, risky, or burdensome.

Study population

Participants were recruited from medium to large companies and from the general population. Due to the Internet-based nature of the eHealth intervention, no regional restrictions applied. Although the intervention was primarily aimed at participants 40 years of age and older, no age restriction for registration applied, as this did not result in any additional logistics or cost. Participants were required to have regular Internet access at their work and/or home. This was not a relevant barrier to participation, as approximately 92% of individuals 45-75 years of age in the Netherlands have Internet access (Eurostat, 2012). Because the intervention was available in Dutch only, a good understanding of the Dutch language was a prerequisite for registration, and all

participants were required to provide electronic written informed consent. Because the presented outcomes are intermediate outcomes for the overall two-year follow-up data outcomes, no power analysis was performed specifically for the reported outcomes.

Assessment of risk factors related to cognitive ageing

At baseline, physical activity, nutrition, smoking, alcohol consumption, sleep patterns, and stress behavior data were collected using electronic questionnaires. For a detailed overview of the room for improvement in these six lifestyle factors in Dutch society, see Appendix 8: “Room for improvement in the Netherlands”. We monitored the participants’ cognitive functions (e.g. working memory, visuospatial short-term memory, and planning performance) using the BAM-COG, an online tool for self-monitoring cognitive functioning using applied games that we previously developed and validated (Aalbers et al, 2013). In addition, we administered the Dutch General Self-Efficacy Scale (DGSES; Schwarzer, 1995), lifestyle factor-specific self-efficacy questions (Kelly et al, 1991), the Positive and Negative Affect Scale (PANAS; Watson et al, 1988), and the Self-Control Scale (SCS; Tangney et al, 2004). A complete overview of these questionnaires are available from the protocol (Aalbers et al, 2015). Twelve months after starting the intervention, the participants were automatically prompted by e-mail to repeat the e-questionnaires and BAM-COG. We monitored the number of login events, the number of goals set, the number of goals assessed (i.e. the goals that were scored by the participant), and whether or not a goal was achieved. Goals were set using Goal Attainment Scaling (GAS; see the example in Table 5.1; Kiresuk & Sherman, 1968). The main features and strengths of using GAS are that it enables BAM to compare goals over different lifestyle modalities, it provides positive feedback regarding partially accomplished goals, and it stimulates the participant to consciously consider what goals are realistic within a given time frame.

Using these GAS scores, we measured both overall success and the success of each specific lifestyle area (as a percentage). To measure overall lifestyle change, we calculated an overall lifestyle score based on the following eight lifestyle measures: physical activity, exercise, healthy nutritional behavior, unhealthy nutritional behavior, smoking status, alcohol consumption, sleep status, and stress status. Each of these factors was categorical with a value of 1-3, thus summing to a total score that ranged from 8 (i.e. an unhealthy lifestyle) to 24 (i.e. a healthy lifestyle). Appendix 7: “Construction of the overall lifestyle score” provides more detailed information regarding how the values were defined for each lifestyle factor.

Table 5.1. Example of Goal Attainment Scaling for the goal “I want to exercise more”.

	Behavior frequency		Behavior duration	GAS-score
I fall short of my goal if I exercise:	2 times per week	For	45 minutes	-2
I fall a little short of my goal if I exercise:	3 times per week	For	45 minutes	-1
I reach my goal if I exercise:	4 times per week	For	45 minutes	0
I exceed my goal if I exercise:	5 times per week	For	45 minutes	+1
I greatly exceed my goal if I exercise:	6 times per week	For	45 minutes	+2

The Brain Aging Monitor intervention

Participants were able to register free of charge at the intervention website. After providing electronic written informed consent and receiving e-mail validation of their account, the participant could log on to a personalized ‘dashboard’. After completing the questionnaires (for their tailored intervention content), each participant received a personalized lifestyle overview indicating room for improvement, after which the participant was invited to complete the three validated online puzzle games to assess their baseline cognitive performance.

After the questionnaires were completed, the intervention components were unlocked, thus enabling the participant to begin setting behavioral goals using the GAS methodology (Kiresuk & Sherman, 1968) in the BAM interface. After a participant set a goal, positive reinforcement was provided, along with practical tips and tricks for how to accomplish that specific goal (for example, when a participant’s goal was to ‘start exercising’, the tips and tricks provided included training schedules building up to a 5-km run or 500-metre swim). Because using behavior-changing techniques that are based on evidence-based principles leads to better final scores (Webb et al, 2010), we incorporated 13 of the 26 behavior-changing techniques that were identified in the taxonomy by Abraham and Michie (Abraham & Michie, 2008). These techniques are grounded in the Social Cognitive Theory (Bandura, 1991; Bandura, 1998), the Trans-theoretical Model (Prochaska & Velicer, 1997), the Theory of Reasoned Action, and the Theory of Planned Behavior (Fishbein & Ajzen, 2010). Each goal was then transferred to the Short-Term Monitoring System (STMS), in which the participants could monitor their behavior on a daily basis; behavior was represented graphically in bar charts. After one month, the participants were asked whether or not the goal was achieved. If the participant answered this question (regardless of the answer), the goal was considered assessed. If the result was positive (i.e. a GAS score ≥ 0), the goal was registered as being achieved successfully, and the goal was transferred to the Long-Term Monitor System (LTMS); if the result was negative (i.e., a GAS score < 0), the

goal was deleted from the participant's profile. After a goal with a positive outcome was entered into the LTMS, it was monitored monthly in order to track the behavior and stimulate its maintenance.

The BAM automatically sent reminder e-mails to the participants each week. The frequency of these reminder e-mails could be changed by the participant to daily, bi-weekly, or monthly intervals. In addition to the goal-setting and monitoring components, the BAM also featured weekly blogs and healthy recipes (Aalbers et al, 2015).

Primary and secondary outcomes

We defined changes in risk factors for cognitive ageing and website use as the one-year outcomes. The cognitive outcome measures require longer follow-up (e.g. two years) and were not available at the time of publication (Aalbers et al, 2015). The first one-year primary outcome was the overall and lifestyle-specific goal-setting success rates, which were calculated as GAS scores of ≥ 0 . The second primary outcome was the change in overall lifestyle score from baseline to the one-year follow-up. The secondary outcomes were changes in body weight, body mass index (BMI), and the resulting changes in specific lifestyle areas.

Data analyses

The differences between the goal-setting group and the non-goal-setting group at baseline were analyzed using the independent-sample *t*-test (for interval variables) or the χ^2 test (for categorical variables). The Mann-Whitney U-test was used to compare differences in intervention usage. We used the paired-sample *t*-test to analyze within-group differences in overall lifestyle score, BMI, weight, and lifestyle-specific areas. An analysis of covariance (ANCOVA) was used to calculate the mean change in body weight, BMI, and lifestyle changes, as well as the 95% confidence interval (95% CI). For changes in body weight and BMI, the baseline values were adjusted as covariates in the ANCOVA in order to control for a potential regression-to-the mean effect. After adjusting for covariates, multivariate linear regression analyses were performed to assess the linear associations between the total number of goals set (as a proxy for intervention utilization) and the changes in lifestyle factors at the one-year follow-up. Unless stated otherwise, the outcome values are presented as the mean and standard deviation (SD); where possible, 95% CI is presented as well. Effect size (Cohen's *d*) was calculated for the overall lifestyle change. All *p*-values are based on two-sided testing, and all statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

A total of 2972 people registered via the website, and 2305 became active users (see the flowchart in Figure 5.1). The mean (\pm SD) age at registration was 51.8 ± 12.9 years, and 68% of the participants were female. After the baseline measurement, 1212 participants proceeded with setting behavior-changing goals. Thus, 1093 participants never set a behavior-changing goal. The goal-setters and non-goal-setters differed significantly with respect to gender, education, unhealthy nutrition behavior, and overall lifestyle score (Table 5.2).

Table 5.2. Baseline characteristics of the goal-setters and non-goal-setters.

	Goal-Setters (n=1212)	Non-Goal-Setters (n=1093)
Age (years)	52.34 \pm 12.21	51.28 \pm 13.73
Gender, female (%)	862 (71.1)	689 (64.6) ^c
Education Level, n (%)		
Secondary school or lower	391 (32.3)	397 (37.2) ^a
Vocational degree	537 (44.3)	421 (39.5)
University degree	284 (23.4)	249 (23.3)
Body Weight (kg)	75.5 \pm 14.4	75.6 \pm 14.8
BMI (kg/m ²)	25.2 \pm 4.2	25.0 \pm 4.4
Subjective Health, n (%)		
Poor	13 (1.1)	16 (1.6)
Fair	164 (13.5)	144 (13.5)
Good	796 (65.7)	654 (61.5)
Very good	187 (15.4)	188 (17.7)
Excellent	52 (4.3)	61 (5.7)
Physical Activity, n (%)		
Inactive	274 (22.6)	206 (19.7)
Sub-optimally active (1-4 days per week)	340 (28.1)	292 (27.9)
Norm active (\geq 5 days per week)	598 (49.3)	547 (52.3)
Exercise, n (%)		
Inactive	303 (25.0)	239 (22.9)
Sub-optimally active (1 day per week)	235 (19.4)	210 (20.1)
Norm active (\geq 2 days per week)	674 (55.6)	596 (57.0)
Healthy Nutrition (Range: 0 – 30)	23.6 \pm 4.6	23.6 \pm 4.8

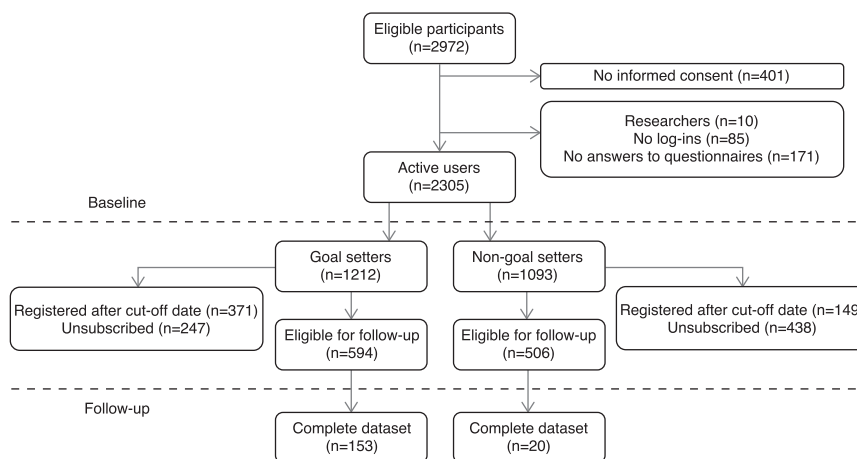
Table 5.2. Continued.

	Goal-Setters (n=1212)	Non-Goal-Setters (n=1093)
Smoking, n (%)		
Smoker	85 (7.0)	80 (7.7)
Ex-smoker	535 (44.1)	455 (44.0)
Non-smoker	592 (48.8)	499 (48.3)
Alcohol, n (%)		
Abstainer	257 (21.2)	223 (21.6)
Drinker (1-5 days per week)	702 (57.9)	571 (55.3)
Frequent drinker (≥6 days per week)	253 (20.9)	238 (23.1)
Sleep Pattern, n (%)		
Poor sleeper	268 (22.2)	208 (20.5)
Suboptimal sleeper	557 (46.1)	437 (43.1)
Good sleeper	384 (31.8)	369 (36.4)
Sleep Hygiene Score	10.6 ± 4.0	10.0 ± 4.2
Satisfaction with Life (Range: 5 – 35)	25.0 ± 6.3	25.2 ± 6.3
Overall Lifestyle Score (Range: 8 – 24)	17.4 ± 2.7	17.7 ± 2.6 ^a
Personality Questionnaires		
DGSES (Range: 10 – 40)	32.0 ± 4.3	32.3 ± 4.8
Positive Affect (Range: 10 – 50)	33.9 ± 5.2	33.7 ± 5.5
Negative Affect (Range: 10 – 50)	21.1 ± 6.1	20.4 ± 5.8
Self-Control Scale (Range: 36 – 180)	125.6 ± 13.2	126.7 ± 13.1

Mean (±SD) is presented for continuous and ordinal variables, and n (%) is presented for categorical variables. DGSES = Dutch General Self-Efficacy Scale; For Healthy Nutrition, Satisfaction with Life, Overall Lifestyle Score, DGSES, Positive Affect, and the Self-Control Scale, a higher score represents better performance; for Unhealthy Nutrition and Negative Affect, a lower score represents better performance; ^a $p < 0.05$, ^b $p < 0.01$, ^c $p \leq 0.001$.

Use of the Brain Aging Monitor for goal-setting

The 2305 participants logged on to the Brain Aging Monitor a total of 14,225 times. The non-goal-setting group logged on with a mean (±SD) of 2.6 ± 1.9 times per participant, which was significantly fewer than the goal-setting group (9.4 ± 21.3 visits per participant), even when twelve goal-setting participants who logged on >100 times each were excluded (resulting in 7.7 ± 10.0 visits per participant in the goal-setting group); $P < .001$, $r = 0.46$.

Figure 5.1. Flowchart of participants in the Brain Aging Monitor

The 1212 goal-setting participants set a total of 2620 lifestyle goals (with 2.2 ± 3.6 goals set per participant). Of these 2620 goals, 2288 were predefined lifestyle goals in the GAS method, and the remaining 332 goals were created without the use of GAS. Of the 2288 pre-specified behavior-changing goals, 1089 (47.6%) were assessed, and 422 of the completed goals (38.8%) were achieved. Interestingly, all 1089 completed goals were completed by a sub-group of 392 participants (32.3% of the goal-setting group); the remaining 820 (67.7%) participants did not complete their goals within the study period. Table 5.3 summarizes the number of goals that the participants set, categorized by lifestyle area; Table 5.3 also shows statistics for the goal-setters who reached their follow-up period and those who did not reach the follow-up period.

On the reference date for follow-up (March 9, 2014), 1785 participants had been registered for at least one year. However, 685 of these participants withdrew from the program, leaving 1100 participants who could provide follow-up data (see Figure 5.1). On descriptives in Table 5.2, at baseline the 153 goal-setters who reached the follow-up period had lower BMI ($P=.03$), had more education ($P=.04$), were more likely to exercise ($P=.02$), and were more likely to be non-smokers ($P=.04$) than the 1059 goal-setters who did not reach the follow-up period. However, together, these differences did not result in a significant difference in overall lifestyle scores ($P=.50$).

Table 5.3: Overview of goal-setting, goal assessment, and goal achievement among the 1212 participants in the goal-setting group

Lifestyle area	Goal-Setters (n=1212 participants) ^a	Goal-Completers (n=392 participants)	Achieved (%) ^d
	Set ^b	Completed (%) ^c	
Physical Activity	590	270 (45.8)	131 (48.5)
Weight Gain	7	1 (14.3)	0 (0.0)
Weight Loss	516	243 (47.1)	57 (23.5)
Healthy Nutrition	263	126 (47.9)	69 (54.8)
Unhealthy Nutrition	288	143 (49.7)	65 (45.5)
Smoking	21	6 (28.6)	2 (33.3)
Alcohol Consumption	184	114 (61.2)	47 (41.2)
Sleep	304	154 (50.7)	39 (25.3)
Stress	115	32 (27.8)	12 (37.5)
Total number of goals	2288	1089 (47.6)	422 (38.8)
	Goal-Setters in follow-up (n=153 participants)	Goal-Completers in follow-up (n=127 participants)	
Total number of goals	673	575 (85.4)	227 (39.5)
	Goal-Setters not in follow-up (n=1059 participants)	Goal-Completers not in follow-up (n=265 participants)	
Total number of goals	1615	514 (31.8)	195 (37.9)

^a = the number of participants in the group, ^b = the number of goals set for each specific lifestyle area, ^c = percentage of completed goals out of the number of goals set, ^d = percentage of achieved goals out of the number of goals completed.

Overall and lifestyle-specific lifestyle changes

After one year of BAM intervention, the participants in the goal-setting follow-up group had a significant improvement in their overall lifestyle scores (with a mean change of $+0.81 \pm 1.92$, 95% CI: 0.49-1.13; $P < .001$, $d = 0.32$). The overall improvement was even larger when only the participants who achieved their goals were taken into consideration (with a mean change of $+1.01 \pm 1.88$, 95% CI: 0.61-1.41; $P < .001$, $d = 0.39$). Thus, remaining in the program and successfully reaching one's goals translates to a higher overall lifestyle score over one year's time. Table 5.4 summarizes the changes in lifestyle factors in the goal-setting group after one year in the program. We found that body weight, BMI, physical activity, healthy nutritional habits, unhealthy nutritional habits, hours slept per 24-hour period, and sleep hygiene were positively affected after one year's participation in the BAM. With respect to smoking, no results can be reported, as none of the users in the follow-up group completed smoking-related behavior-changing goals. With the exceptions of the sleep outcomes and satisfaction with life, the participants who set a goal had significantly lower baseline values in each specific lifestyle area than the participants who did not set goals in that specific lifestyle area. For example, at baseline, the participants who set an exercise goal averaged 1.5 days of exercise per week, whereas the participants who did not set an exercise goal were already exercising an average of 2.3 days per week ($P = .001$).

Table 5.4. Change in the lifestyle factors within the goal-setting group (n=153)

Cognitive ageing risk factor	Baseline value (mean \pm SD)	Value at year one (mean \pm SD)	Mean change (95% CI) ^a	P-value
Weight (kg)	74.9 \pm 13.5	74.3 \pm 13.4	-0.62 (-1.16, -0.07)	.03
BMI (kg/m ²)	24.6 \pm 3.9	24.4 \pm 3.8	-0.20 (-0.38, -0.03)	.03
Physical Activity (p/w)	4.1 \pm 2.0	4.3 \pm 2.0	+0.27 (0.02, 0.52)	.04
Exercise (p/w)	1.9 \pm 1.4	2.1 \pm 1.4	+0.17 (-0.02, 0.37)	.08
Healthy Nutrition Score	23.7 \pm 3.9	24.8 \pm 4.0	+1.09 (0.63, 1.56)	<.001
Unhealthy Nutrition Score	5.7 \pm 3.7	5.0 \pm 3.7	-0.67 (-1.05, -0.29)	.001
Alcohol Consumption (p/w)	2.9 \pm 2.4	2.7 \pm 2.3	-0.13 (-0.31, 0.04)	.14
Sleep (hours/24-hour period)	6.8 \pm 0.9	6.9 \pm 0.9	+0.12 (0.01, 0.22)	.03
Sleep Hygiene (points)	10.3 \pm 4.1	9.0 \pm 4.5	-1.32 (-1.85, -0.78)	<.001
Satisfaction with Life	24.5 \pm 6.7	24.2 \pm 7.2	-0.16 (-1.86, 0.86)	.75
Overall Lifestyle Score	17.6 \pm 2.6	18.4 \pm 2.6	+0.81 (0.50, 1.12)	<.001

p/w = per week

^aeach mean change and 95% CI was adjusted for gender and age at baseline, and Weight and BMI were additionally adjusted for baseline Weight.

In addition, we investigated the association between the total number of goals set by each participant and the change in lifestyle from baseline to the one-year time point; this association was measured for the 173 participants who completed the one-year follow-up. Our analysis revealed that setting more goals was significantly associated with the participants' ability to achieve weight loss (adjusted for gender and age at baseline; $P=.01$), reduce BMI (adjusted for gender and age at baseline; $P=.01$), and reduce unhealthy nutritional behavior ($P=.01$). Setting more goals was also positively associated with an improvement in overall lifestyle ($P=.06$) and healthy nutritional behavior ($P=.06$). Finally, the total number of goals set was also positively correlated – albeit not significantly – with exercise, alcohol consumption, sleep hygiene and sleep pattern *pa* (data not shown); in contrast, no such trend was found with respect to physical activity or satisfaction with life.

Discussion

Here, we report that utilizing a self-motivated eHealth intervention program for one year can improve one's overall lifestyle scores by introducing lifestyle-specific health behavior changes that are relevant to cognitive ageing. Although the effect size on overall lifestyle score at the individual participant level can be considered moderate ($d=0.32-0.39$) for a therapeutic intervention, from a public health perspective, this effect size can be considered highly relevant and may deliver substantial added value to society (Webb et al, 2010).

Strengths of the study

The primary strength of this study is that the intervention can reach and select the participants who score sub optimally in specific lifestyle areas, thereby motivating these specific individuals to set – and reach – realistic lifestyle goals and facilitating long-term health-related changes in behavior. This study therefore demonstrates proof-of-concept for the BAM intervention, focusing on improving cognitive ageing risk factors among employees. Similar studies of other risk factors reported similar effect sizes (Schulz et al, 2014) and concluded that these effects are common among computerized interventions; moreover, evidence suggests that these small to medium effect sizes can translate to large public health gains when implemented on a wide scale (Lustria et al, 2013; Krebs et al, 2010). Therefore, the need for scalable lifestyle eHealth programs is clear, particularly given that smaller programs – although potentially more effective – lack the cost-effectiveness needed for large-scale public health implementation (Milat et al, 2013). This improvement in public health is necessary, because epidemiological studies have found that healthy living – characterized by adherence to multiple healthy behavioral modalities – promotes

positive physical and cognitive ageing, whereas unhealthy living has a clear negative impact on both (Artaud et al, 2013; Elwood et al, 2013; Goldstein, 2010). Because the Brain Aging Monitor is targeted to the working population (a group that is intrinsically self-motivated to stabilize and/or improve their working capacity, particularly in times of economic crisis), the BAM may benefit large populations during this important age window. From a scalability point of view, the costs needed to implement, recruit, and administer the BAM intervention likely favor eHealth over more traditional, expert-led face-to-face interventions (Elbert et al, 2014).

The multimodal nature of cognitive decline justifies choosing a multimodal intervention over single modality programs. Multiple behavior-changing programs address a broader scope of risk factors, delivering tailored and more comprehensive help to the participant. Moreover, the current public health status in the Netherlands (see Appendix 8: “Room for improvement in the Netherlands”) emphasizes the added value provided by multiple health behavior-changing interventions. For this reason, we analyzed the effect of the intervention on separate lifestyle factors, as well as the overall lifestyle score. Because one’s overall lifestyle affects cognitive function, measuring changes in overall lifestyle using an aggregated measure seems to make intuitive sense. In support of this approach, other studies measured overall lifestyle in order to create risk profiles for overall mortality, cardiovascular disease, cancer, and diabetes (Kirkegaard et al, 2010; van Dam et al, 2008). Compared to the relatively small average effect sizes reported by systematic reviews and meta-analyses of other tailored eHealth interventions that focus on more traditional health messages ($d=0.19$ (Lustria et al, 2013), $d=0.17$ (Krebs et al, 2010), and $d=0.16$ (Webb et al, 2010)), our effect size with respect to overall lifestyle change was large ($d=0.32-0.39$). Our participants’ weight loss was similar to previously reported interactive computer-based interventions, particularly given that most weight-loss interventions are aimed at overweight individuals instead of the general population that was targeted in this study (Wieland et al, 2012). This effectiveness may be explained – at least in part – by the fact that the Brain Aging Monitor uses a novel motivation for healthy living (e.g. self-monitoring of cognition with games), which by itself has been advocated for many years (Shephard, 1983). However, the general public is generally unfamiliar with the notion that healthy living can impact cognitive health in later life; indeed, to the best of our knowledge, the BAM is the first eHealth intervention that is aimed in this direction. Our results suggest a trend towards a dose-response effect between the number of goals set and lifestyle changes. This is consistent with other studies in which utilization of the intervention predicts outcome measures (Bennett & Glasgow, 2009; Schulz et al, 2014). Consistent with our results, a synthesis of meta-analyses and reviews found that single health behavior-changing programs were more effective at changing physical activity and dietary behavior, whereas multiple behavior-changing

programs were more effective at inducing weight loss (Sweet & Fortier, 2010). Given the results of our study, alternative routes to successfully change participants' physical activity and dietary behavior can be integrated into future eHealth interventions. Thus, although a program may initially be broad in its overall scope, it can subsequently focus on tailored behaviors. A systematic review by Nigg and Long revealed a lack of multiple health behavior-changing interventions in older adults (i.e. over the age of 55) for comparison with the effectiveness of single health behavior interventions, underscoring the need for interventions similar to BAM, so further effectiveness comparisons can be done (Nigg & Long, 2012).

Limitations of the study

This study also has some limitations. First, high dropout rates are a well-known limitation in eHealth research in general (Bennett & Glasgow, 2009; Eysenbach, 2005; Leslie et al, 2005; Schulz et al, 2014). Although study retention does not necessarily affect the study's outcomes (Lustria et al, 2013), low study adherence can hamper external validity. In our study, the average number of times each participant logged on to the BAM is higher than in a similar study (Schulz et al, 2014); however, the BAM should be improved further in order to increase adherence, thereby optimizing the public health impact. Initial tailoring, repeat notifications, and monitoring are important factors for increasing adherence; however, maintaining the participants' interest is difficult with eHealth interventions that run longer than a few weeks (Bennett & Glasgow, 2009). Making the program more interactive and increasing the overall attractiveness of the design are two logical steps towards achieving higher adherence rates and increasing societal impact (Baker et al, 2014; Kreps et al, 2010).

Second, our choice of a quasi-experimental pre-post design was driven by the predicted dropout rate and the setting of the study, this design was the most feasible option for this type of pragmatic field trial (Milat et al, 2013). Although a cluster-randomized trial would have been preferred, such a design was not feasible given the low number of participating companies. For practical reasons, the companies agreed to include the BAM in their healthcare policy only if all of their employees would be allocated to the experimental group. Randomizing the participants at each site into control and treatment groups would have posed many practical problems (e.g. blinding and allocation criteria; Baker et al, 2010). Therefore, given the dropout rate, maximizing statistical power by keeping the study group as large as possible justifies the use of a quasi-experimental design when performing longitudinal self-motivated eHealth research (Milat et al, 2013). However, we acknowledge the need for more controlled trials in order to further investigate the causal and dose-response relationship between the intervention uptake and lifestyle change.

Third, the results are based on self-reported measures, which may have introduced a reporting bias. However, because our study population did not differ from the general Dutch population (see Appendix 8: “Room for improvement in the Netherlands”), our sample likely reflects the general population. Moreover, self-reported measures provide a suitable reflection of the way in which participants view their own behavior and therefore serve as a suitable starting point for measuring behavioral changes that are perceived as personally relevant. Our recruitment strategies intentionally favored higher educated, ‘white collar’ participants, as these participants would benefit most from a program with cognitive outcome measurements; such participants are likely to notice a small decline in executive functioning performance at work at a relative young age. It may also be argued that the overrepresentation of women participants (71.1% of participants were female) may have affected the outcome of our study. However, this overrepresentation is expected in health-related online research studies, which average 64% women (Lustria et al, 2013); moreover, neither age nor gender was significantly associated with the intervention outcome.

Finally, one could argue that the construction of the overall lifestyle score was – at least to some extent – arbitrary. To the best of our knowledge, no unified method combines – and assigns appropriate weight to – multiple lifestyle outcomes in a way that optimally reflect its effect on cognitive ageing. Therefore, we combined six lifestyle areas that are known to have an effect on cognitive ageing, and we constructed the overall lifestyle score using lifestyle area-specific scores that reflect their respective impact on brain ageing. A similar approach has been used previously in other fields (Kirkegaard et al, 2010; Parekh et al, 2012; Yun et al, 2012).

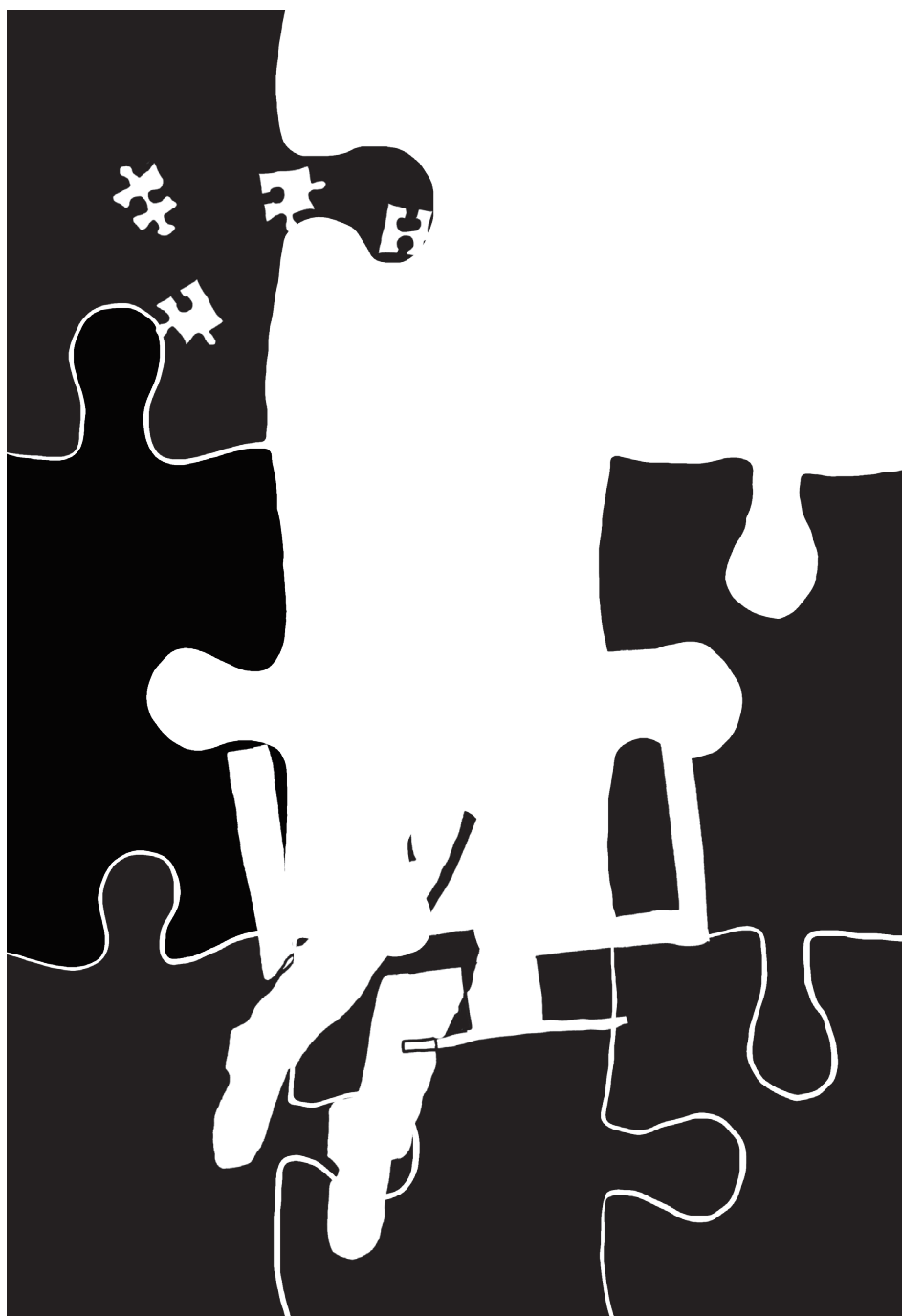
Unanswered questions and future research

Asking healthy people in the general population to participate in a lifestyle-improvement trajectory by following a predetermined intervention route that can last for a year (or longer) is notoriously difficult. Our most important recommendation for implementing an eHealth intervention and maximizing program adherence is to design public health programs that are highly flexible, enabling the participants to enter and exit the program freely and at their own convenience whilst still providing measurements at regular intervals. The ability to measure each participant’s success using a more flexible approach should be addressed in future studies. Methods should be developed to identify pre-follow-up dropouts, who reached a sort of self-aspired end state, as successful intervention completers. Adapted stepped wedge cluster-randomized trial designs may be well-suited to this purpose (Mdege et al, 2011). From a more practical perspective, long-term adherence might be increased by ‘gamifying’ future intervention programs. Adding game components to scientific research might provide the participant commitment and loyalty that many eHealth interventions currently lack (Baranowski

et al, 2013). The gamification of eHealth interventions can make the interventions more social, create competition, incorporate a reward system, and enhance motivation. Thus, within the constraints of playing a game, the working mechanisms of current eHealth components can be implemented (Miller et al, 2014).

Conclusions

In conclusion, we report adherence to and effectiveness of the Brain Aging Monitor program, and we report that this online, self-motivated and self-managed eHealth intervention, which is aimed at changing multiple health behavior risk factors for cognitive ageing, has a positive impact on public health. Given that the participants with the most room for improvement had the largest change in behavior, and given that the participants who were the most involved with the program had the largest benefit, we feel that future research with this tool is warranted. More globally, eHealth interventions can achieve more effective and more widespread primary prevention of cognitive decline, thus reducing the predicted strain of ageing-related cognitive decline on healthcare systems in the near future.



6

EHEALTH MEDIATED LIFESTYLE CHANGE AND COGNITION; PRIMARY PREVENTION OF COGNITIVE DECLINE DURING MIDLIFE IN DUTCH ADULTS OF 40 YEARS AND OLDER

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In preparation

Abstract

Background: In our aging societies, more people will develop a form of dementia in later life. Healthy lifestyle modifications at midlife appear to be a feasible and effective primary prevention strategy. Implementing online behavioural change programs gives health care systems the new opportunity to implement this primary prevention strategy while reaching large populations at low cost.

Objective: Aim of the present study was to examine the relationship between lifestyle change and cognitive aging as measured by an online, self-motivated eHealth platform: the Brain Aging Monitor.

Methods: The Brain Aging Monitor study was implemented using a quasi-experimental, prospective, pre-post design. Participants were recruited from both the general population and medium to large Dutch companies. In total, 3076 users registered, of which 2363 (68% women; 51.7 ± 13.0 years old), became active users and 247 participants completed the one-year follow-up. The Brain Aging Monitor intervention identifies room for improvement in a participant's lifestyle, stimulates participants to set monthly, personally relevant health behaviour goals, and provides them with practical tips to accomplish these goals while monitoring their own behaviour. Primary outcome measures were the change scores on three cognitive domains (working memory, planning, and visuospatial short term memory) after one-year of intervention.

Results: Out of the 247 participants in 1-y follow-up, 219 (88.7%) became active goal setters, setting a total of 939 pre-specified lifestyle goals, of which they assessed 795 (84.6%) goals and achieved 314 (39.5%). This resulted in a significantly improved overall lifestyle score ($+0.90$, 95% CI: 0.63 - 1.16 ; $P < 0.001$, $d = 0.35$), and improved scores on the working memory task ($+1.05$, 95% CI: 0.51 - 1.58 ; $P < 0.001$). Furthermore, an increase in lifestyle score was positively associated with improved scores on working memory ($\beta = .336$ $P = .04$). Although non-significant, weight loss showed the similar tendency ($\beta = -.183$ $P = .25$).

Conclusions: The Brain Aging Monitor is a feasible and low cost eHealth program to change participants' health behaviour through 1 year follow-up. Consequently, this increase in overall lifestyle performance was associated with less cognitive decline and even a slight improvement in working memory performance.

Introduction

The global number of people with dementia was 44.4 million in 2013 and is estimated to have doubled by 2030 to 75.6 million people (Prince et al, 2013; Prince et al, 2015). Therefore, primary prevention of cognitive decline and dementia is increasingly emphasized as a priority to reduce this large societal burden, even more as the FINGER randomized trial has shown that a combined life style intervention can very effectively decrease cognitive decline in older persons with increased risk for vascular cognitive decline (Evans et al, 2014; Mangialasche et al, 2012; Ngandu et al, 2015, Norton et al, 2014; Rodriguez-Gomez et al, 2014). Several systematic reviews also underlined that (un)healthy behaviour and modifiable risk factors, such as overweight or obesity, during midlife affect an individual's risk of cognitive decline and dementia in old age (Barnes & Yaffe, 2011; Dahl et al, 2013; Evans et al, 2014; Solomon et al, 2014). The most important and evidence based modifiable risk factors include physical inactivity, unhealthy dietary patterns, a too high alcohol consumption, smoking, lack of sleep, and psychological distress (Anstey et al, 2009; Blondell et al, 2014; Di Marco et al, 2014; Goel et al, 2009; Horton et al, 2014; Jonsdottir et al, 2013; Polidori & Schulz, 2014; Wolf, 2009). It is predicted that one-third of all cases of Alzheimer's disease may be attributed to these modifiable risk factors (Norton et al, 2014), and that a 10-25% reduction in modifiable risk factors for Alzheimer's disease might prevent up to 3 million cases of Alzheimer's disease worldwide (Barnes & Yaffe, 2011). Based on this evidence the call for effective, scalable public health interventions targeting modifiable vascular risk factors grows stronger (Norton et al, 2014). In order to develop and implement scalable and effective methods for primary prevention the use of technology and more specifically eHealth interventions is strongly advocated (Bennett & Glasgow, 2009).

Therefore, we propose a combined, multi-domain eHealth intervention offering participants to target multiple risk factors simultaneously, which has the best odds of being effective (Solomon et al, 2014). eHealth interventions are very suitable for this purpose, since they can be tailored to the individual participants' needs and wishes. Participants can choose what parts of the interventions they actively want to receive, and which parts they do not want to use. Both a simultaneous and sequential treatment approach can be effective depending on the type of health behaviour and personal preference (Schulz et al, 2014). Our Brain Aging Monitor (BAM) has shown promising results as an online eHealth behaviour change program in adults aged 40 and older (Aalbers et al, 2016). Participants in the BAM are capable of reaching their monthly behaviour change goals through easy-to-use instructions and can self-monitor their behaviour, which has shown to result in improved overall lifestyle scores, lowered weight and improved dietary patterns (Aalbers et al, 2016). Aim of the

present study is to determine whether the observed lifestyle changes in the Brain Aging Monitor also resulted in improvement of cognitive function.

Methods

Study design

This study used a pre-post design, in which newly enrolled participants chose their own time path, from registration to setting goals and monitoring their change in behaviour. This design was selected, since randomising the participants against a sham intervention in an occupational health promotion programme, in which the stimulated behaviours are known to be advantageous, was judged to be insufficiently motivating for the participants and participating companies. This intervention was registered with the Dutch Trial Register (NTR4144), and was exempt from formal testing by the Medical Ethics Committee of the Radboud university medical centre Nijmegen, given its non-invasive, risk-free and relatively burden-free nature.

Study population

Participants were recruited from medium to large companies (>100 employees) and from the general population in the Netherlands. Due to the Internet-based nature of the eHealth intervention, no regional restrictions were applied. Although the main analysis is aimed at participants of 40 years and older, no age restriction for registration were set, as participation of younger individuals did not result in any additional logistics or costs. Participants were required to have regular Internet access at their work and/or at home. This was not considered to be a relevant barrier to participation, as approximately 92% of individuals 45-75 years of age in the Netherlands have Internet access (Eurostat, 2012). Because the intervention was available in Dutch only, a good understanding of the Dutch language was a prerequisite for registration, and all participants were required to provide electronic written informed consent. We aimed for a group size of 200 to have the power to find a 15% reduction on the six targeted risk factors for cognitive decline (power calculation based on $\alpha < 0.05$; power 0.8; two-tailed: $n=166$; $\pm 20\%$ drop out).

Assessment of risk factors related to cognitive ageing

At baseline, physical activity, nutrition, smoking, alcohol consumption, sleep patterns, and stress behaviour data were collected using electronic questionnaires. We monitored the participants' cognitive functions using the BAM-COG, an online tool for self-monitoring cognitive functioning using applied games that we previously developed and validated (i.e. "Conveyer Belt" for working memory, "Sunshine" for visuospatial short-term memory, and "Papyrinth" for planning performance), on which higher

scores reflect better cognitive performance (Aalbers et al, 2013). To be able to analyse individual differences in behavioural change, we online administered the Dutch General Self-Efficacy Scale (DGSES; Schwarzer, 1995), lifestyle factor-specific self-efficacy questions (Kelly et al, 1991), the Positive and Negative Affect Scale (PANAS; Watson et al, 1988), and the Self-Control Scale (SCS; Tangney et al, 2004; see Aalbers et al, 2015). Twelve months after starting the intervention, all participants were automatically prompted by e-mail to repeat these e-questionnaires and BAM-COG. We monitored the number of login events, the number of goals set, the number of goals assessed (i.e. the goals that were scored by the participant), and whether or not a goal was achieved. Goals were set using Goal Attainment Scaling (GAS; see the example in Table 6.1; Kiresuk & Sherman, 1968). The main features and strengths of using GAS-scores are that it enables BAM to compare goals over different lifestyle modalities, it provides positive feedback regarding partially accomplished goals, and it stimulates the participant to carefully consider what goals are realistic within the given time frame.

Table 6.1. Example of Goal Attainment Scale for participant with the goal “I want to eat more fruit”

	Behaviour frequency		Behaviour duration	GAS-score
I fall short of my goal if I eat:	3 pieces of fruit	On	3 days per week	-2
I fall a little short of my goal if I eat:	3 pieces of fruit	On	4 days per week	-1
I reach my goal if I eat:	3 pieces of fruit	On	5 days per week	0
I exceed my goal if I eat:	3 pieces of fruit	On	6 days per week	+1
I greatly exceed my goal if I eat:	3 pieces of fruit	On	7 days per week	+2

^a each mean change and 95% CI was adjusted for gender and age at baseline, and Weight and BMI were additionally adjusted for baseline Weight

Using these GAS scores, we measured both overall success and the success of each specific lifestyle area. To measure overall lifestyle change, we calculated an overall lifestyle score based on the following eight lifestyle measures: physical activity, exercise, healthy nutritional behaviour, unhealthy nutritional behaviour, smoking status, alcohol consumption, sleep status, and stress status. Each of these factors was categorical with a value of 1-3, thus summing to a total score that ranged from 8 (i.e. an unhealthy lifestyle) to 24 (i.e. a healthy lifestyle). Appendix 7 provides more detailed information regarding how the values were defined for each lifestyle factor.

The Brain Aging Monitor intervention

Participants were able to register free of charge at the intervention website. After electronically providing written informed consent, the participant could log on to a personalised 'dashboard'. After completing the questionnaires (for their tailored intervention content), each participant received a personalised lifestyle overview indicating room for improvement, after which the participant was invited to complete the three validated, abovementioned online puzzle games to assess their baseline cognitive performance.

After the questionnaires were completed, the intervention components were unlocked, thus enabling the participant to begin setting behavioural goals using the GAS methodology (Kiresuk & Sherman, 1968) in the BAM interface. After a participant set a goal, positive reinforcement was provided, along with practical tips and tricks for how to accomplish that specific goal (for example, when a participant's goal was to 'start exercising', the tips and tricks provided included training schedules building up to a 5-km run or 500-m swim). Because using behaviour-changing techniques that are based on evidence-based principles promotes a better overall outcome (Webb et al, 2010), we incorporated 13 of the 26 behaviour-changing techniques that were identified in the taxonomy by Abraham and Michie (Abraham & Michie, 2008). These techniques are grounded in the Social Cognitive Theory (Bandura, 1991; Bandura, 1998), the Transtheoretical Model (Prochaska & Velicer, 1997), the Theory of Reasoned Action, and the Theory of Planned Behavior (Fishbein & Ajzen, 2010). Each goal was then transferred to the Short-Term Monitoring System (STMS), in which the participants could monitor their behaviour on a daily basis; behaviour was represented graphically in bar charts. After one month, the participants were asked whether or not the goal was achieved. If the participant answered this question (regardless of the answer), the goal was considered to be assessed. If the result was positive (i.e. a GAS score ≥ 0), the goal was registered as being achieved successfully, and the goal was transferred to the Long-Term Monitor System (LTMS); if the result was negative (i.e., a GAS score < 0), the goal was deleted from the participant's profile. After a goal with a positive outcome was entered into the LTMS, it was monitored monthly in order to track the behaviour and stimulate its maintenance.

The BAM automatically sent reminder e-mails to the participants each week. The frequency of these reminder e-mails could be changed by the participant to daily, bi-weekly, or monthly intervals. In addition to the goal-setting and monitoring components, the BAM also featured weekly blogs and healthy recipes. A more detailed description of the intervention was published separately (Aalbers et al, 2015).

Primary and secondary outcomes

As primary outcome for this study we defined the change scores on three different cognitive domains, as measured with the BAM-COG, after one year of Brain Aging Monitor use. Secondary outcomes were the associations between overall lifestyle change and cognition, and individual lifestyle factor changes after one year of BAM use. Also the relation between Self Control and Self-Efficacy and lifestyle and cognition outcomes measures and the trends for these personality traits over time will be discussed.

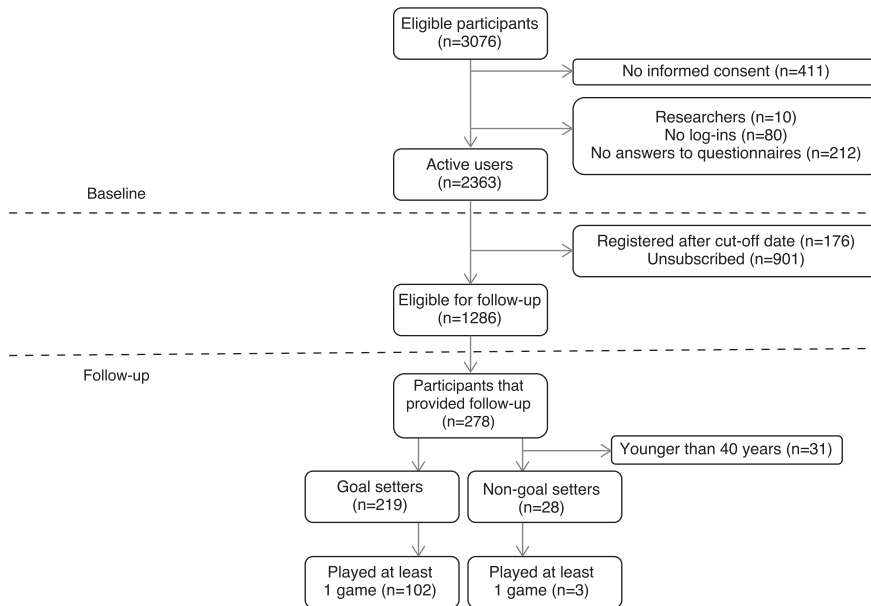
Data analyses

The differences between the goal-setting group and the non-goal-setting group at baseline were analysed using the independent-sample *t*-test (for interval variables) or the χ^2 test (for categorical variables). The Mann-Whitney U-test was used to compare differences in intervention usage. We used the paired-sample *t*-test to analyse within-group differences in overall lifestyle score, BMI, weight, and lifestyle-specific areas. An analysis of covariance (ANCOVA) was used to calculate the mean change in body weight, BMI, and lifestyle changes, as well as their 95% confidence intervals (95% CI). Changes in body weight and BMI were adjusted by using their baseline values as covariates in the ANCOVA in order to control for a potential regression-to-the mean effect. To test the association between lifestyle and cognition we performed multivariable regression analysis adjusting for age, weight and education at baseline. Unless stated otherwise, descriptive measures are presented as the mean and standard deviation (SD). Outcome values are presented with 95% Confidence Intervals (95% CI). Effect size (Cohen's *d*) was calculated for the overall lifestyle change and cognitive outcomes when appropriate. All *p*-values are based on two-sided testing, with alpha for statistical significance offset at 0.05, and all statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

A total of 3,076 people registered via the website, and 2,363 became active users. Mean age (\pm SD) at registration was 51.7 ± 13.0 years, and 1607 (68%) of the participants were women. On the reference date for follow-up (September 9, 2014), 2187 participants had been registered for at least one year. However, 901 of these participants withdrew from the programme, leaving 1,286 participants who could provide follow-up data (see Figure 6.1). Of these users, 278 took part in follow-up measurements. For the cognitive outcomes we were only interested in users aged 40 years or older ($n=247$), 219 of whom (88.7%) were active goal setters.

Figure 6.1. Flowchart of participants in the Brain Aging Monitor cognition study

Baseline characteristics for the goal-setters (GS) and non-goal-setters (NGS) are presented in Table 6.2, and did not show significant between-group differences, except for a worse score for unhealthy diets in the goal-setting group. At baseline the 219 goal-setters who reached the follow-up period were more likely to exercise ($P=0.02$) than the 856 goal-setters who did not reach the follow-up period. However, these differences did not result in a significant difference in overall lifestyle scores at baseline ($P=0.41$).

Use of the Brain Aging Monitor for goal-setting

The 219 goal-setters set 1,124 lifestyle goals in total (mean of 4.6 ± 9.3 goals per participant). Of these 1,124 goals, 939 were set using the predefined GAS method, the other 185 goals were created without the use of GAS. A total of 795 (84.6%) of the pre-specified behaviour-changing goals were assessed, 314 of which (39.5%) were achieved. Interestingly, all 795 completed goals were completed by a sub-group of 185 participants (84.5% of the goal-setting population); the remaining 34 (16.5%) participants did not complete their goals within the study period. A summary of the number of type of goals that the participants set, categorised by lifestyle area is given in Table 6.3.

Table 6.2. Example of Goal Attainment Scale for participant with the goal
“I want to eat more fruit”

	Goal-Setters (n=219)	Non-Goal-Setters (n=28)
Age (years)	54.9 ± 8.62	57.2 ± 5.6
Gender, female (%)	146 (66.7)	15 (53.6)
Education Level, n (%)		
Secondary school or lower	58 (26.5)	10 (35.7)
Vocational degree	102 (46.6)	13 (46.4)
University degree	59 (26.9)	5 (17.9)
Body Weight (kg)	75.2 ± 12.7	75.1 ± 15.0
BMI (kg/m ²)	24.9 ± 3.9	24.8 ± 4.8
Subjective Health, n (%)		
Poor	3 (1.4)	0 (0.0)
Fair	26 (11.9)	4 (14.3)
Good	136 (62.1)	15 (53.6)
Very good	42 (19.2)	6 (21.4)
Excellent	12 (5.5)	3 (10.7)
Physical Activity, n (%)		
Inactive	47 (21.5)	10 (35.7)
Sub-optimally active (1-4 days per week)	66 (30.1)	10 (35.7)
Norm active (≥5 days per week)	106 (48.4)	8 (28.6)
Exercise, n (%)		
Inactive	42 (19.2)	5 (17.9)
Sub-optimally active (1 day per week)	54 (24.7)	2 (7.1)
Norm active (≥2 days per week)	123 (56.2)	21 (75.0)
Healthy Nutrition (Range: 0 – 30)	23.8 ± 4.2	23.9 ± 4.9
Unhealthy Nutrition (Range: 0 – 14)	5.4 ± 3.8	3.8 ± 3.3 ^a
Smoking, n (%)		
Smoker	8 (3.7)	3 (10.7)
Ex-smoker	99 (45.2)	15 (53.6)
Non-smoker	112 (51.1)	10 (35.7)
Alcohol, n (%)		
Abstainer	42 (19.2)	3 (10.7)
Drinker (1-5 days per week)	125 (57.1)	16 (57.2)
Frequent drinker (≥6 days per week)	52 (23.7)	9 (32.1)
Sleep Pattern, n (%)		
Poor sleeper	46 (21.1)	7 (25.0)
Suboptimal sleeper	104 (47.7)	8 (28.6)
Good sleeper	68 (31.2)	13 (46.4)

Table 6.2. Continued

	Goal-Setters (n=219)	Non-Goal-Setters (n=28)
Sleep Hygiene Score	10.8 ± 4.2	9.4 ± 3.7
Satisfaction with Life (Range: 5 – 35)	25.1 ± 6.7	23.6 ± 6.7
Overall Lifestyle Score (Range: 8 – 24)	17.7 ± 2.6	17.6 ± 3.1
Personality Questionnaires		
DGSES (Range: 10 – 40)	32.3 ± 4.5	33.0 ± 4.4
Positive Affect (Range: 10 – 50)	33.8 ± 5.2	32.3 ± 6.7
Negative Affect (Range: 10 – 50)	21.2 ± 5.9	19.2 ± 6.3
Self-Control Scale (Range: 36 – 180)	126.6 ± 13.1	131.6 ± 11.3
BAM-COG Games		
Conveyer Belt (Range:4-10)	5.6 ± 1.4	6.7 ± 1.6
Sunshine (Range:3-10)	4.5 ± 1.2	4.4 ± 1.2
Papyrus (Range:4-7)	5.4 ± 1.6	6.1 ± 1.5

Mean (±SD) is presented for continuous and ordinal variables, and n (%) is presented for categorical variables.

DGSES = Dutch General Self-Efficacy Scale

For Healthy Nutrition, Satisfaction with Life, Overall Lifestyle Score, DGSES, Positive Affect, and the Self-Control Scale, a higher score represents better performance; for Unhealthy Nutrition and Negative Affect, a lower score represents better performance.

^a=p<.05

Overall and lifestyle-specific changes

After one year of BAM intervention, the goal-setting participants that reached follow-up had a significantly improved overall lifestyle score (mean change of +0.90, 95% CI: 0.63-1.16; $P<0.001$, $d=0.35$). This improvement was even larger when only the participants who achieved their goals were analysed (mean change of +1.03, 95% CI: 0.70-1.37; $P<0.001$, $d=0.39$). Table 6.4 summarises the changes in lifestyle factors in the goal-setting group after one year in the programme. We found that all self-reported measures except for alcohol consumption and satisfaction with life were positively changed after one year participation in the BAM. There are no smoking outcomes that can be reported, as none of the users in the follow-up group completed smoking-related behaviour-changing goals.

Table 6.3. Overview of goal-setting, goal assessment, and goal achievement among the 1264 participants in the goal-setting group

Lifestyle area	Goal-Setters (n=219 participants) ^a	Goal-Completers (n=185 participants)	
	Set ^b	N completed (%) ^c	N achieved (%) ^d
Physical Activity	214	179 (83.6)	91 (50.8)
Weight Gain	4	1 (25.0)	0 (0.0)
Weight Loss	206	166 (80.6)	46 (27.7)
Healthy Nutrition	107	92 (86.0)	51 (55.4)
Unhealthy Nutrition	121	107 (88.4)	53 (49.5)
Smoking	3	3 (100.0)	0 (0.0)
Alcohol Consumption	101	91 (90.1)	33 (36.3)
Sleep	154	136 (88.3)	33 (24.3)
Stress	29	20 (68.9)	7 (35.0)
Total number of goals	939	795 (84.6)	314 (39.5)

^a= the number of participants in the group, ^b=the number of goals set for each specific lifestyle area,

^c=percentage of completed goals out of the number of goals set, ^d=percentage of achieved goals out of the number of goals completed.

^a=p<.05

The total number of behaviour change goals set by a participant were correlated with overall lifestyle change ($r=.143$; $P=.04$). Weight change was significantly correlated both with the number of logins and the number of goals set by a participant ($r=-.187$; $P=.01$, and $r=-.188$; $P=.01$ respectively).

Table 6.4. Change in the lifestyle factors and cognitive function within the goal-setting group (n=219)

Cognitive ageing risk factor	Baseline value (mean \pm SD)	Value at year one (mean \pm SD)	Mean change (95% CI) ^a	p-value
Weight (kg)	75.2 \pm 12.7	74.2 \pm 13.1	-0.64 (-1.10, -0.19)	0.007
BMI (kg/m ²)	24.9 \pm 3.9	24.5 \pm 3.8	-0.23 (-0.38, -0.07)	0.005
Physical Activity (p/w)	4.3 \pm 2.0	4.5 \pm 2.0	+0.29 (0.08, 0.50)	0.008
Exercise (p/w)	1.9 \pm 1.5	2.1 \pm 1.5	+0.28 (0.11, 0.45)	0.001
Healthy Nutrition Score	23.8 \pm 4.2	25.3 \pm 3.9	+1.38 (0.96, 1.80)	<0.001
Unhealthy Nutrition Score	5.4 \pm 3.8	4.7 \pm 3.5	-0.83 (-1.14, -0.52)	<0.001
Alcohol Consumption (p/w)	3.0 \pm 2.5	2.9 \pm 2.3	-0.11 (-0.25, 0.03)	0.107
Sleep (hours/24-hour period)	6.8 \pm 1.0	6.8 \pm 1.0	+0.11 (0.02, 0.20)	0.017
Sleep Hygiene (points)	10.8 \pm 4.2	9.3 \pm 4.6	-1.41 (-1.87, -0.95)	<0.001
Satisfaction with Life	25.1 \pm 6.7	24.6 \pm 7.2	-0.61 (-1.53, 0.32)	0.196
Overall Lifestyle Score	17.7 \pm 2.6	18.6 \pm 2.5	+0.90 (0.63, 1.16)	<0.001
BAM-COG Games				
Working Memory (n=43)	5.8 \pm 1.5	6.8 \pm 1.5	+1.05 (0.51, 1.58)	<0.001
Visuospatial Memory (n=81)	4.6 \pm 1.2	4.5 \pm 1.3	-0.09 (-0.19, 0.36)	0.54
Planning (n=44)	5.5 \pm 1.5	5.1 \pm 1.5	-0.34 (-0.14, 0.82)	0.16
Personality Questionnaires				
DGSES (n=178)	32.3 \pm 4.4	32.8 \pm 4.6	+0.52 (-0.06, 1.10)	0.08
Self-Control Scale (n=177)	126.3 \pm 12.8	127.0 \pm 13.4	+0.72 (-0.54, 1.98)	0.26

p/w = per week

^a each mean change and 95% CI was adjusted for gender and age at baseline, and Weight and BMI were additionally adjusted for baseline Weight

Lifestyle and cognition

For the cognitive outcomes we found a statistically significant positive change of +1.05 item (95% CI: 0.51-1.58) on the working memory task ($d=1.22$) in the 43 subjects who completed this cognitive testing over one year. We did not find any change on the visuospatial and planning tasks (see Table 6.4). To investigate which factors contributed to the change in working memory performance, we performed a multivariable regression analysis (see Table 6.5). Between total lifestyle change and weight change there was no significant correlation ($r=-.09$; $P=.20$), and therefore these were used as separate factors in the model. When only the change scores for lifestyle and weight were used in the model, lifestyle change was significantly associated with a positive change for working memory scores. However, when corrected for age, baseline weight and level of education this effect disappeared

($P=0.06$; see Table 6.5). For both visuospatial memory and planning the covariates did not change the outcome of the model.

Table 6.5. Multivariable regression analysis for lifestyle and weight change on the cognitive domains in all subjects who completed the cognitive testing over one year (standardized coefficients and their p-values)

	Working Memory (n=45)		Visuospatial Memory (n=83)		Planning (n=46)	
	Model I	Model II	Model I	Model II	Model I	Model II
Lifestyle change	.336 (.04)	.319 (.06)	.009 (.94)	-.020 (.87)	-.046 (.78)	-.077 (.66)
Weight change	-.183 (.25)	-.186 (.29)	-.009 (.94)	-.037 (.77)	-.371 (.03)	-.391 (.03)

Model I: unadjusted model includes Lifestyle change and Weight change as dependent variables

Model II: Model I subsequently adjusted for age, education, and weight at baseline

Running the analysis with only goal setters (losing only two participants on all three games) only slightly improved the models (data not shown). Using the separate lifestyle factors to build separate regression models did not improve the model in comparison to the overall lifestyle and weight measures. Adding the personality scores (general self-efficacy, self control, positive and negative affect) at baseline, or the measures of intervention uptake (the number of logins and number of goals set by a participant) to the models did not improve the model either.

Two year adherence to the Brain Aging Monitor

The Brain Aging Monitor program was meant to be a two-year intervention program because of the expected slow changes in the primary cognitive outcome measures. However, calculating dropout rates for the preliminary results after one year revealed that the analysis of the two-year results was not feasible. Out of 1,760 participants who could have finished the second year follow-up (based on subscription date), 745 had unsubscribed, leaving 1015 (57.7%) participants that could have provided second year follow-up data. However, only 26 (2.6%) participants completed all questionnaires over two years, none of whom played all the BAM-COG games, rendering it impossible to perform a 2-year follow-up analysis.

Discussion

Modifying lifestyle factors is likely to reduce later life dementia risk (Ballard et al, 2011; Di Marco et al, 2014; Ngandu et al, 2015). Assisting people in promoting healthy lifestyle during midlife thus may have a profound beneficial influence on public health both for physical and cognitive functioning. This study shows that a 5.5% improvement of overall lifestyle and a slight reduction in body weight, as a result of a multimodal eHealth intervention approach, is significantly related to a positive change on working memory after one year follow-up. The effect size (Cohen's d of 0.39) on overall lifestyle improvement after one year of this intervention, is quite large, specifically in the public health domain in which the intervention is positioned, where small changes over time may lead to considerable favourable long term health outcomes.

Due to the pragmatic study design, the current study sample was representative of the Dutch general population, and was not at specific high risk for cognitive decline. Thus, finding a direct effect on cognitive tasks was even more challenging than in the FINGER study, in which older persons with high cardiovascular risk scores were recruited (Ngandu et al, 2015). The improved overall lifestyle performance, and a positive association with improved cognitive performance in a sample with a relatively modest room for improvement, could even have larger implication in selected groups with higher baseline risk from primary prevention perspective.

As in the FINGER study, our study supports the multi-domain approach. This approach chooses to reflect on the sum of smaller changes across the board instead of intervening on a single modality, like dietary behaviour alone. In this study after one-year follow-up, the changes of separate lifestyle factors were not significantly associated with cognitive outcomes. However, when accumulated, overall lifestyle showed positive effects on cognitive performance. In order to prevent dementia in older adults, which is most likely a multi-causal syndrome, a multimodal intervention thus may be preferable over single modality interventions. Furthermore, a multi-domain intervention has an advantage taking into account the influence of the frequent co-occurrence of healthy and unhealthy behaviours (Hofstetter et al, 2014).

Consistent with our findings but implemented more rigorously in a single modality, a recent short-term intervention study consisting of a 12-week exergaming intervention (including a total of 24-hour aerobic exergaming) also showed a positive effect on executive functioning (eg. working memory) but not on visuospatial tasks (Maillot et al, 2012). Another intervention study in healthy middle-aged men with subjective memory complaints showed that a 14-day lifestyle intervention program (which also included brain teasers) had positive effect on working memory tasks and brain

metabolism in areas associated with verbal working memory (Small et al, 2006). Regrettably, the authors failed to report how much lifestyle change did occur over the 14-day period. Thus, working memory appears to be susceptible to training (Brehmer et al, 2012; Morrison & Chein, 2011), but the evidence comes from studies with suboptimal methodology (Shipstead et al, 2012).

Primary prevention of dementia during midlife encounters several methodological challenges. In a prospective study design, it typically requires follow-up periods ranging between 10 to 20 years (which is much longer than in the prevention of cardiovascular disease and diabetes (Tuomilehto et al, 2011)) to observe the influence in later life cognition. Therefore, it becomes relevant to address the long term potential of BAM in preventing dementia through direct and indirect effects of lifestyle modifications during midlife. It is estimated that a third of all cases of Alzheimer's Disease are attributable to seven potentially modifiable lifestyle risk factors; physical inactivity, smoking, diabetes, midlife hypertension, depression, low educational attainment and midlife obesity (Norton et al, 2014). In an epidemiological model built for the European population, physical inactivity was by far the most important risk factor followed by smoking and low educational attainment. A 10% decrease of these combined risk factors is estimated to result in a 9.1% decrease in AD prevalence over 40 years (Norton et al, 2014). Although the BAM does not directly measure or intervene in all vascular risk factors, it could indirectly modify these common risks by possible interlinked risk factors, such as body weight and physical activity. For physical activity the BAM shows improvements around 5-10%, for weight a modest 0.85% weight loss was achieved. Although small, these effects are in the opposite direction of what is considered as typical weight gain during aging (Mozaffarian et al, 2011). Based on the proposed European model of population-attributable risk, the overall lifestyle improvement of 5.5% has great potential to contribute to the long term prevention of dementia.

Strengths of this study

The public health relevance of pragmatic trials like the Brain Aging Monitor is becoming increasingly obvious. Scientific knowledge and insights gained in more strict controlled trials needs to be disseminated and implemented in real-world health care systems using cost-effective platforms such as eHealth in which self-delivered formats play a role (Dunkley et al, 2014; Schwarz et al, 2012). eHealth platforms excel at reaching large populations at low cost but also struggle to improve adherence (Bennett & Glasgow, 2009; Schulz et al, 2014). The novelty and importance of the Brain Aging Monitor lies in the fact that these are real-life effects in a representative sample of Dutch adults, whom are facilitated in capitalizing on their internal motivation to change. The intervention was not limited to a controlled experimental setting and no other interactions or consultations took place with the researchers than IT support,

which makes these results externally valid. This study provides interesting and important results on the association between lifestyle and cognition, and also provides real-world insights into program adherence for holistic, self-motivated eHealth lifestyle interventions that uses a novel primary motivator for behavioural and cognitive changes, compared to regular lifestyle programs aimed at the prevention of cardiovascular risk factors.

Another strength of the current approach is the new perspective it offers participants on the transfer effect of healthy living on cognitive outcomes. Whereas cognitive training alone, does little good for the overall health of a participant, health behaviour change is beneficial to both physical and cognitive health. Another advantage of this translational effect is that it circumvents testing problems that arise in cognitive training studies, where the pre- and post test often closely resemble the training tasks which decreases validity through the danger of measuring direct training effects (Lovden et al, 2013). Modifiable lifestyle factors are likely better primary prevention methods and cognitive training can be added in secondary prevention (Mowszowski et al, 2010), although the impact of cognitive training is still debated (Bahar-Fuchs et al, 2013).

Limitations of this study

Overall adjusted lifestyle change showed an interesting tendency, albeit not significant, in association with the change in working memory performance. The lack of statistical significance may be attributable to a lack of statistical power with too low sample sizes of subjects remaining compliant to the cognitive game testing, but the model gives reason to be optimistic before adjustment for covariates.

One could argue that the positive effect on the current working memory task is due to a test-retest effect instead of an actual improvement (Salthouse, 2014). However, this is not very likely for several reasons. First, if this effect was just due to learning or test-retest error, the same pattern could be expected for all three games. Second, we validated three different batches of tasks per game consisting of unique trials, making sure that the same trials were never given twice. As a result, participants played completely different trials in all tasks at baseline and year 1 follow-up (Aalbers et al, 2013). Finally, practicing the games was neither possible in the BAM, nor encouraged elsewhere.

The absence of a control group in this study renders a methodological challenge to evaluate the intervention effect, and without doubt makes it harder to interpret the outcomes of the study. However, the current pragmatic trial was firmly based on (behaviour change) theory developed in previous controlled experimental research.

The fact that healthy living, as advised in the Brain Aging Monitor, is beneficial to the general population is beyond discussion, and the lifestyle advice itself was not the core topic of interest. In maximizing the outreach of the study, together with several practical and technical difficulties (i.e. keeping participants from signing in twice under different e-mail or IP addresses to escape the control condition), we chose not to include a control group. Therefore, the current study may be interpreted as an example of the Hawthorne effect. We expect that the absence of subject-experimenter interaction, and the completely self-motivated nature of both subscribing and participating in the e-intervention, makes it less likely that participants would change or report change for anyone else but themselves. Also, the general tendency within the goal-setting group was that participants with more goals had more accumulated overall lifestyle change, hinting at a dose-response relationship. Moreover, although selection bias clearly could be an issue (even though the demographics appear quite representative of the general Dutch population), researchers were not directly involved in recruitment, and strategies to improve adherence and compliance were equal for all participants, never favouring those more likely to succeed.

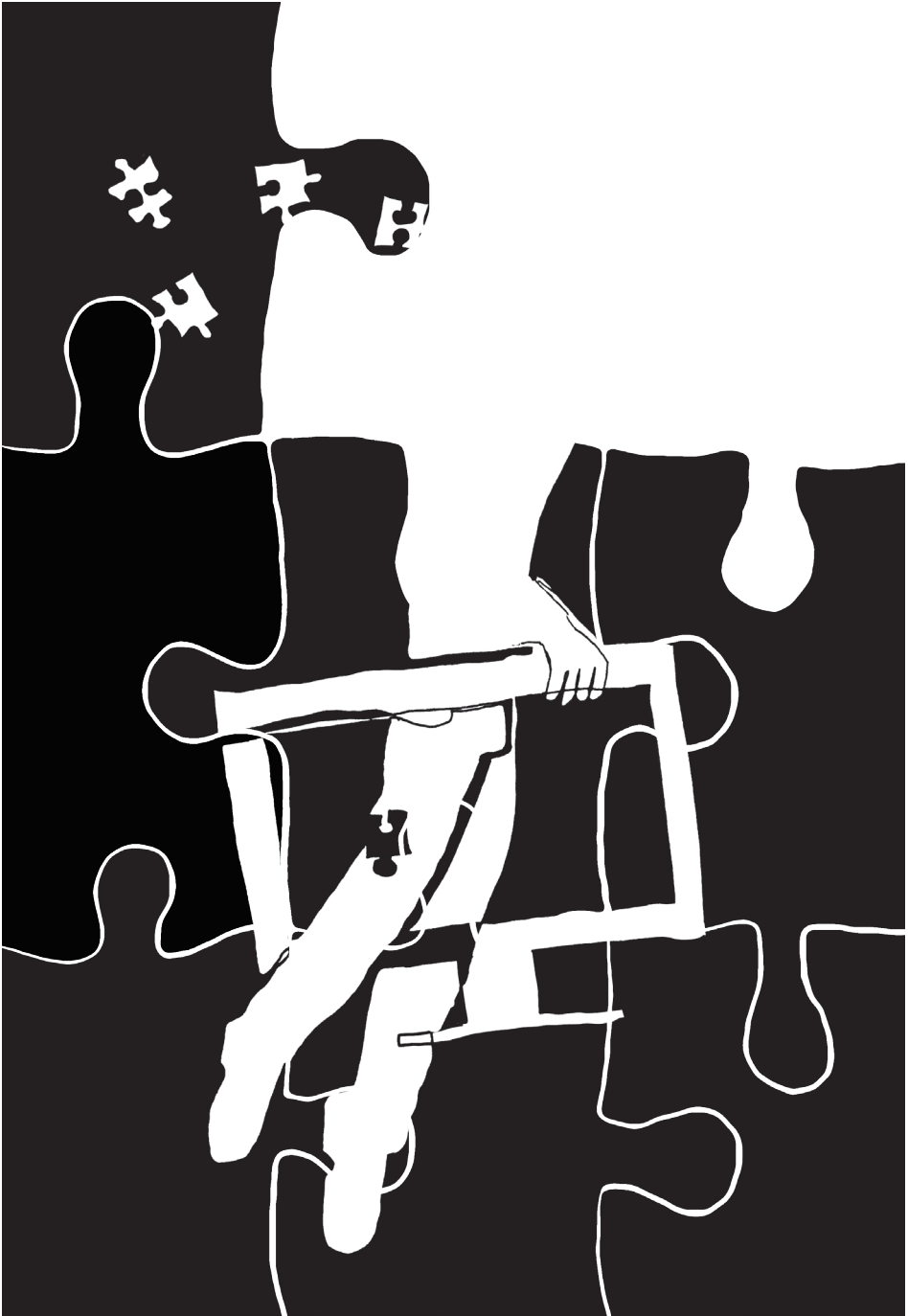
Future research

A low intensity, self-motivated intervention with low implementation and maintenance costs resulted in a moderate lifestyle improvement. Intensifying the intervention by having more health care professionals involved may sound attractive to reduce attrition rate, but scaling up the current format may be an even better choice since this will reach larger populations at almost the same cost, instead of spending more resources on professional support with possible marginal improvement on outcomes. Second, with the speed of current technological improvements and changes in the telecommunications landscape, a huge challenge is arising to improve and adapt trial methodology to keep it feasible for these quickly changing e-health interventions (Saner, 2013; van Gemert-Pijnen et al, 2011). This will probably require a paradigm shift from conventional randomized controlled studies in this domain to more flexible pragmatic field trials.

Conclusion

After having evidenced the efficacy of the Brain Aging Monitor's use as an eHealth lifestyle and behaviour change tool (Aalbers et al, 2016), we now have generated the first preliminary evidence, that this gain in overall health is associated with less cognitive decline or possibly even a gain in working memory function over a one year period. Although it remains difficult to provide evidence for primary prevention of cognitive decline in midlife, we clearly showed that eHealth applications such as the

Brain Aging Monitor shape very promising research routes to follow towards more global prevention of cognitive decline. The cognitive assessment by applied online games is a promising and feasible example of methodological innovations that are also required to demonstrate and compare the added value of such eHealth innovations, of which many are underway, and are marketed commercially.



7

SUMMARY AND DISCUSSION



Based on previous chapters, it can be concluded that using eHealth interventions on modifiable lifestyle risk factors for neurodegenerative diseases, specifically Alzheimer's disease, appears to be a viable option. Based on both the theoretical background and on the results of the empirical research described in the previous chapters, it becomes clear that the advantages of eHealth interventions may outnumber the drawbacks for a substantial target group. Participants who may benefit are generally looking for an easily accessible, personally relevant platform, providing them with the knowledge and tools to change their lifestyle for the better, with both their physical and cognitive wellbeing in mind. The next few paragraphs will briefly summarize the research I have done and discuss what I have learned along the way. I will conclude with five recommendations for future research in e- and mHealth that may assist and evaluate the next generation of digitalized and personalized life style interventions.

The systematic review in **chapter 2a** resulted in twelve articles from the period 1995-2010, all using web-based techniques in controlled samples and mediating one or more modifiable lifestyle risk factors for cognitive decline. The result of this review showed that on average more women subscribe to online health programs than men and that, overall, men tend to drop out more. Furthermore, the identified studies showed a wide variety of intervention components adding up to numerous simple (one intervention component), and complex (combinations of intervention components) online interventions. We concluded that complex interventions, using intervention components that were tailored to the participant, were more effective from both an outcome perspective as well as from an attrition perspective. One drawback of complex interventions is that identifying individual effective intervention components is not possible. Rather, research is done on the system, making it difficult to build a step-by-step guide to help other researchers in developing effective online interventions. In spite of the challenges that still needed to be resolved, these combined eHealth interventions showed positive results in changing multiple lifestyle risk factors.

In **chapter 2b** we present another example of the difficulty of identifying singular effective intervention components, in this case of the Mediterranean diet. There is cross-sectional evidence that this diet may play a neuroprotective role throughout the lifespan, and several intervention studies (RCTs) are underway. However, the effect of adherence to all parts of the Mediterranean diet does appear greater than the sum of the individual components (eg. nuts, olive oil, red wine, little red meat). Furthermore, we criticize a paper by Kesse-Guyot and colleagues in chapter 2b, who drew conclusions about the lack of neuroprotection of the Mediterranean diet that were not justified by their data.

Chapter 3 describes the validation of a new online, fast-to-play self-monitor instrument aimed at four cognitive functions that are susceptible to deterioration due to neurodegeneration. These cognitive functions are related the domains of working

memory, pattern recognition, visuospatial short-term memory, and planning (as part of executive function), all crucial for optimal wellbeing and independent living. This Brain Aging Monitor – Cognitive Assessment Battery (BAM-COG) was specially developed in close collaboration with game developers to give its users a fast indication of four important cognitive domains in a gaming environment. We developed the BAM-COG because at the start of this research project no other online, Dutch, validated gamified tools were available for research purposes. The BAM-COG was specifically not developed to be a diagnostic or prognostic instrument. Major advantages of this tool are that it increases and expands the possibilities of classical neuropsychological tests, and that it also extends the reach of online cognition research. In a sample of 397 adults aged 40 or older, three out of four of the puzzle games were shown to have adequate to good results for alternate-forms reliability, convergent- and divergent validity. Based on these results it can be concluded that the BAM-COG is a unique and valid evidence based online tool, which allows researchers and lay public (research participants) to measure working memory, visuospatial short-term memory, and planning, and that it was justified to use it in our eHealth intervention research with the Brain Aging Monitor.

Chapter 4 describes the design of the Brain Aging Monitor evaluation study, with all related background information on the behavior change theory and the relationship between healthy living and cognitive functioning underlying the rationale for the Brain Aging Monitor study. This paper provides full disclosure of the questionnaires and behavior change techniques used in the intervention. It describes the Goal Setting Module, using Goal Attainment Scaling, and gives a more detailed overview of recruitment and data management.

The 1-year outcome on modifiable lifestyle risk factors in participants who actively used the BAM is described in **chapter 5**. At the start of this evaluation period 2972 unique participants were recruited for using the BAM. Participants were drawn to the study through a number of middle- to large-sized companies in the Netherlands that participated in the study as part of their human resources management strategy, or through conventional or social media outings. After completing the baseline questionnaires, 1212 participants actually set their personally relevant behavior change goals. In total 2620 lifestyle goals were created, 1089 goals were assessed a month later, and out of the assessed goals 422 were completed successfully. After one year, 153 participants showed an overall lifestyle improvement in follow-up measurements that was mainly caused by improvements in exercise, dietary, and sleep outcomes. A major strength of the study was that it recruited participants who had suboptimal lifestyles, and as such had enough room for improvement. However, major drawbacks were that the BAM was not able to prevent high dropout rates (91.5% after one year), and the fact that the pragmatic study methodology did not allow for a control group.

Added to the positive health and lifestyle outcomes on the modifiable lifestyle factors in **chapter 5**, we describe the cognitive outcomes from the BAM-COG in **chapter 6**. Because the BAM participation was ongoing, the population that completed 1-year measurements had grown to 219 participants, showing altogether similar lifestyle changes as the 153 participants described earlier. From the data collected in the subsample of participants who completed the games a positive change in working memory performance was demonstrated, which was correlated with the overall improvement in lifestyle score of 5.5% and the slightly decreased body weight (0.5 kg). This improvement in working memory amounted to a full additional level of the working memory task. No changes were found on visuospatial short-term memory or planning, the other cognitive functions assessed by the BAM-COG.

Overall, the study described in this thesis provided interesting and relevant data on the feasibility of this type of eHealth field trials that allows dissemination and evaluation of innovations to large populations at lower costs and in a shorter time than more strictly controlled designs. Since dropout rates were high in the present study, yet comparable to those reported in most other longitudinal eHealth intervention studies, future studies will require shorter follow-up periods, to quickly and repeatedly assess the changes in modifiable lifestyle factors, preferably at midlife, and in the cognitive effects. New technologies (e.g., improved gamification) are needed to improve adherence to the studies. The BAM and BAM-COG results are sufficiently promising to conclude that it is worthwhile to further develop public health interventions to stimulate healthy brain aging by means of eHealth and mHealth innovations.



General discussion

Flash back and flash forward

Over the period that the studies of this thesis were carried out, the primary prevention of cognitive decline and dementia, through lifestyle improvement during middle and late life, received a lot of scientific and societal interest (e.g. Andrieu et al, 2015; Barnes & Yaffe, 2011). Large epidemiological, cohort and intervention studies have been published and are likely to be published in the coming years (Elwood et al, 2013; Gill & Seitz, 2015). The potential of a healthy lifestyle on late life mental and physical health slowly starts to enter into the crosshairs of the public (Norton et al, 2014). This active, self-directed and prevention oriented lifestyle also fits very well with the new definition of health as established by Machteld Huber, in which health is defined as “the ability to adapt and self-manage in ever changing circumstances” (Huber et al, 2011). Acknowledging this definition may also mean that it is healthy to adapt one’s lifestyle to the growing body of knowledge that you may be able to prevent or delay chronic diseases of old age, especially dementia. Self-management and self-dependency, or independence, are highly praised values nowadays, both from a humane, societal and economic perspective. Using individualized e-health interventions at home facilitates ‘adapting to new and ever changing circumstances’.

However, it is important to note that it is not only the definition of health that changed during the period of working on the thesis, but also the method by which we disseminate our thoughts on health through ICT, which is explained by the rapid pace in which overall ICT industry is changing. Driven by Moore’s Law of computing power that predicts the annual doubling of power of computing technology, ICT and e-/mHealth set their own standards in the landscape of changing health care demands in our aging societies (Naslund et al, 2015). Importantly, a recent cohort study among older men concluded that those men using computers had an average delayed onset of dementia by 8.5 years (Almeida et al, 2012). This points at synergy between lifestyle changes and eHealth intervention effects. However, the development of ICT solutions in the health domain remains a complex and long lasting task that requires close collaboration between many stakeholders with different backgrounds from technology, to marketing and social sciences, and medicine (König et al. 2015). Providing proof of efficacy and building towards evidence based medicine does not come easy (Black et al, 2011), but it still expected nonetheless (Lewis, 2015).

A major finding of this study, although not identified as a primary outcome measure in the protocol, was that the planned two-year follow-up never took place, because the dropout was so substantial that performing any analysis on the remaining 26 participants would provide results too much flawed by attrition bias. This high dropout

rules out the possibility of intention-to-treat analysis, because for example imputing average data would still not allow for sound analysis (Grossman & Mackenzie, 2005). Therefore, we decided to withdraw from this original plan. Because of this strong attrition bias, we propose to measure the effect of primary (e-)prevention of cognitive decline in middle aged adults by measuring the effect of interventions on cardiovascular and other physical intermediate risk factors and biomarkers (Elwood et al, 2013; Norton et al, 2014). High attrition rates, however, cannot conclusively be taken as evidence for a lack of efficacy. The chosen follow-up time may have simply been 'inconvenient' to those participants that dropped out after initially succeeding at changing their behavior. The success rate of achieving goals for participants who quit the study also was equal to that of those participants who adhered to the follow-up testing in our study. The more rigid designs such as RCTs with in-person contact with the research participants, or the more innovative designs, where subjects themselves are governing the data collection, might be in a better position of reducing attrition, increasing compliance to the intervention, and thus allowing for a sufficiently powered longer lasting trial. However, the RCT method has also been criticized for its limitations, especially when implementation research and the required external validity for the average community of participants are concerned (Nallamothu et al, 2008). When answering questions of effectiveness instead of efficacy, RCTs are often not the optimal choice because of their predefined selection bias. Notwithstanding the value of RCT-based research, alternative methodologies should be considered as complementary evidence, instead of being excluded in reviews and guidelines (Nallamothu et al, 2008). Rather than developing longitudinal interventional eHealth studies that have difficulty overcoming adherence issues, hybrid designs (e.g., embedding randomized trials in large observational cohort studies using real-world participants) for wellness research, as suggested by Naci and Ioannidis may be an alternative methodology for future trials especially in the domain of e- and mHealth (Naci & Ioannidis, 2015). From a more practical point of view, in this particular study blinding would have been next to impossible, and the so called 'bleeding of effects' by cross contamination of co-workers or family members being allocated to different intervention groups would have imposed a problem similar to the current design limitations (Grossman & Mackenzie, 2005). We also experienced the disincentive for a more rigid evaluation design firsthand, as the largest company that implemented the BAM as their routine health program refused to use the BAM if their employees could be randomized into the control group.

The Brain Aging Monitor study: a pragmatic or explanatory design?

A pragmatic trial, a design first described in 1967 by Schwartz and Lellouch (Schwartz & Lellouch, 2009), can be one of these very worthwhile alternatives for the more strict RCT approach. The idea of pragmatic trials received more formal recognition in 2008

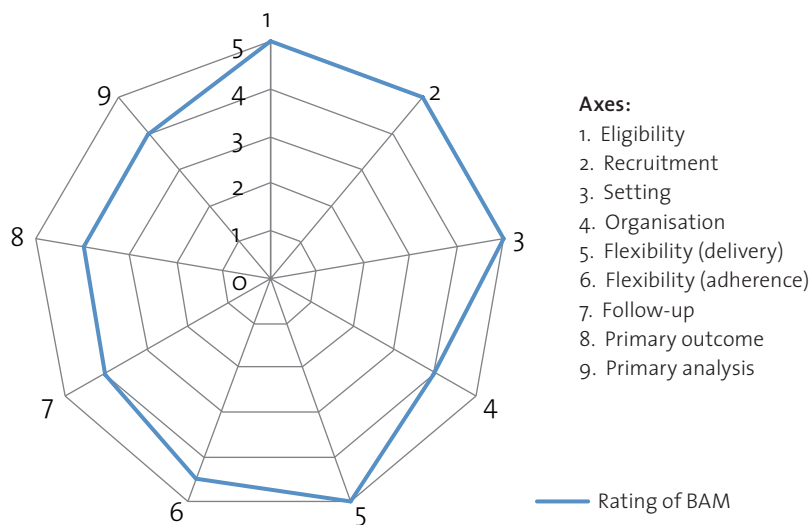
when the CONSORT statement extension for pragmatic trials was published in the *British Medical Journal* (Zwarenstein et al, 2008). Shortly thereafter the pragmatic trial quality assessment, abbreviated as the PRECIS tool (Pragmatic – explanatory continuum indicator summary), was published (Thorpe et al, 2009), which was recently followed by the PRECIS-2 (Loudon et al, 2015). The PRECIS-2 tool aims to help researchers to design their research methodology on nine axes relevant for designing pragmatic or fundamental/explanatory studies. The characteristic that distinguishes a pragmatic trial from explanatory trials is the question “how well does this intervention work in a real life setting?”, as opposed to “the ideal conditions” of an RCT answering the question “can this intervention work in the ideal circumstances and subjects” (Schwartz & Lellouch, 2009; Thorpe et al, 2009). Pragmatic trials use clinically relevant comparisons, from a broad study population, enrolling from diverse clinical environments, and apply evaluating strategies of complete treatment rather than single drug effects, and moreover measure multiple clinically relevant health outcomes, instead of one primary endpoint in RCTs (Nallamotheu et al, 2008).

The pragmatic trial approach fits perfectly with the ambition of the Quick Results Program of the National Initiative Brain & Cognition, of which the BAM project was a part, which aimed to disseminate available knowledge to large populations in their daily lives and in usual care. Following these overall program aims, pragmatism guided a lot of design choices, both implicitly and explicitly. As a result, not all choices are optimal pragmatic design decisions. Therefore I will use the PRECIS-2 (i.e. the improved and validated version of PRECIS; (Loudon et al, 2015) framework to reflect on the Brain Aging Monitor study, and thereby gain more insight in why the BAM worked in some ways, had trouble in other areas, and to show how different frameworks could be optimized for use in pragmatic eHealth trials. For a full and detailed description of PRECIS-2 I refer to the recent landmark paper of Loudon (Loudon et al, 2015), and the preceding papers on this highly relevant methodological debate of how to support innovation in trial methodology. Although it was not originally designed as an evaluative tool after a trial has been closed, it has been used as such before (Glasgow, 2013; Glasgow & Riley, 2013; Loudon et al, 2013).

Rating BAM with PRECIS-2

The Brain Aging Monitor is visualized as a pragmatic trial according to the PRECIS-2 tool for pragmatic design rating in the spider chart in Figure 7.1. In this spider or wheel chart, scores on the outside represent a more pragmatic approach and scores towards the core represent an explanatory (classical RCT like) approach (Loudon et al, 2015; Thorpe et al, 2009). I will subsequently briefly discuss our Brain Aging Monitor study on the nine criteria selected by Thorpe, Loudon and over 80 international trial designers, clinicians, and policymakers, who participated in the developmental process

Figure 7.1. BAM scored according to the Pragmatic-Explanatory Continuum Indicator Summary-2



Note: for more information on the PRECIS-2 tool see Loudon (2015)

of PRECIS-2. After discussing these methodological trial criteria in the light of our own eHealth intervention, I will conclude this chapter with recommendations for future innovation and research in this field of eHealth in primary prevention of cognitive decline.

On the first criterion of eligibility, we score the Brain Aging Monitor study as having a very open selection and recruitment (score 5 out of 5). To be included in the analysis on cognitive performance a participant had to be older than 40 years, but for our first outcome study on lifestyle changes, no such age criterion was applied. The subjects only had to speak Dutch, which is not very restrictive in a Dutch trial, and had to have regular access to the internet, which in the Netherlands is even less restrictive (94% of all Dutch households have regular internet access). Therefore, we granted the BAM the highest score on this criterion. With regard to recruitment (criterion 2), we again gave the BAM a score of five out of five. Recruitment for any public health program can be done by ways of press releases, conference talks and visits to companies. No additional effort was made by the research team after these announcements were made to include participants to the study, closely complying with other public health initiatives. The setting criteria (criterion 3) as well scores the maximum of five, since the BAM was disseminated through HR-departments just like other lifestyle programs

would, and the BAM reached the general Dutch population through national or regional media, just like any other public health initiative would. Subsequently, participants would partake from their homes or office, making it exactly like life as usual or 'usual care', giving the results very high generalizability. Therefore, implementing the BAM after the trial is possible and may be presumed to result in similar effects. This only takes a little additional effort, because it once more needs to generate attention for participants to start subscribing. However, organizations already using the Brain Aging Monitor can continue to do so without any additional burden to their organization. The only possible limitation or burden to the organization could lie in the need to update content like blogs and recipes once the research team no longer provides these. Still, such an easy route to further implementation probably is the strongest point in favor of a pragmatic trial.

With regard to the fifth criterion, all participants were free to choose their own path towards a healthier lifestyle after registering and completing the questionnaires (flexibility of delivery). They could choose their own goals, and their own tips and tricks to use and adhere to, and were even actively supported to use other aids outside the intervention to encourage the proactive change of behavior. Because the BAM is a self-management intervention, after HR makes the program available, the rest is up to the user. Normally the practitioner and participant are two different entities, but this is not always true in the case of self-management interventions. As discussed earlier, self-management and self-dependency are increasingly important in health care, and new technologies facilitate this type of uptake of health care, maximizing the flexibility of delivery. Also, employers, who from a delivery perspective can be perceived as the practitioners providing a service to their employees, were not followed-up on their adherence to the Brain Aging Monitor. We collected data from their individual employees but did not further inquire about how implementation was going. In pragmatic trials it is important to measure participant compliance (flexibility in adherence), but this should not be enforced in a too rigid manner. We did measure compliance of individual participants by means of number of logins and subscription status. However because the Brain Aging Monitor was fully automated no special action was taken accordingly, other than the predefined reminder system, which results in a score of four out of five on this sixth PRECIS criterion.

Since adherence (seventh criterion) to intervention programs is such a big part of the eHealth challenge, we consider the use of some adherence improving measures part of routine care in the BAM. The effort that was put in to gathering follow-up data from the participants and/or dropouts was, in the BAM design, the reminder system of e-mail notification, which was an inherent part of the intervention, comparable to dentist-appointment notifications, which are part of routine care. Apart from this, only one additional spike in effort of follow-up was used outside the intervention

protocol, because we send out one additional e-mail to all participants that had so far not responded to the follow-up measurements. However, this may have been perceived as just another regular reminder e-mail by most (former) participants. The reminder system was flexible (it could be set to daily, weekly, biweekly or monthly) and its activation did not depend on the participant's compliance pattern, and as such cannot be described as specifically targeting those participants at risk of dropping out. The eighth criterion judges the methodological rigidity of the primary outcome. Our endpoints were formed by questionnaires, which are in essence self-reported lifestyle changes, and by the BAM-COG which was partially validated before use. This reflects our opinion that we had to be flexible and could not only rely on well known and rigidly validated instruments, because they were not compatible (i.e. offline) with the rest of the intervention, which probably would have caused even greater adherence issues and not have resulted in measuring a relevant signal of change. So we 'sacrificed' psychometric rigidity to stay relevant and feasible (Glasgow & Riley, 2013). That is why we rated the criterion for primary outcomes with a three out of five, as also pragmatic trials are required to measure more objectively.

The final criterion dictates that a purely pragmatic trial should perform intention-to-treat analysis and thus just should look to what is happening after starting the intervention, including all drop out cases. However, because of the high dropout (which should be allowed according to criterion 6 and 7), intention-to-treat analysis was not feasible for the one- and two-year follow-up data. The strategy to impute missing values would result in a non conclusive trial because of this high dropout rate. Therefore we decided to perform a per-protocol analysis, which introduced a bias-by-selection, but still made it possible to find a signal of relevant change in lifestyle among those who adhered to the intervention. More specifically, this criterion, when judged in the BAM context of primary prevention, may be more directed at the 'ability-to-reach' a participant with the advice than at intention-to-treat, as the participant had to make the intervention happen by him- or herself. It also is up for debate whether participants who dropped out straight after subscribing or straight after performing the pre-test should be considered as participants at all. In the analyses we wanted to explore whether the BAM intervention had any effect on the individuals we reached and who motivated themselves to perform an intervention in practice, not on the people we could not reach. Thus, one may argue that a pure intention-to-treat does not fit very well with pragmatic trials (Grossman & Mackenzie, 2005). Rather arbitrary, we scored four out of five here.

Overall, the PRECIS-2 scoring of BAM proves that on the pragmatic – explanatory continuum, this was a trial more directed at showing the pragmatic effectiveness, than explaining the mechanistic efficacy. This means that the results from the

previous chapters should be interpreted as pragmatic results, mainly giving valuable knowledge about what to expect when an intervention like the Brain Aging Monitor is disseminated in a Western society like the Netherlands.

The pragmatic participant

After starting BAM it quickly became obvious that some people are still looking for the ‘magic pill’ that will make their unhealthy habits disappear. The anecdotal example is that I received a similar e-mail by several new subscribers who were midway through the intake questionnaires stating something along the lines of “if living healthy takes this much work, I do not think it is for me...”. All in all, they may have spent around ten to fifteen minutes on the website. These people show that online curiosity (which may or may not be intrinsic motivation) is very fragile and easily shattered. The fact that approximately 60% of subscribers dropped out before, during or straight after completing the questionnaires clearly points out that people will quit their enrollment without hesitation, if the perceived value of the intervention does not meet their expectation. And thus, pragmatic design and pragmatic measurements will not be ‘pragmatic enough’ for everybody. However, the pragmatic attitude of online participants requires a pragmatic study design, which is not the same as a call for methodological weakness. It is a call for the right methodology, and next to judge the results on its merits and not always from a RCT standpoint. A perspective by which, the question is addressed whether a program will work in day-to-day practice, and with what expected benefits, harms and costs, which after all is the most important question to the pragmatic participant or policy makers (Zwarenstein et al, 2008).

The pragmatism of IT innovations

This thesis is a product of its time. Maybe it is part of the last generation of research that was e- but not mHealth, yet part of the first generation of researchers witnessing and starting to conceive the possibilities and impact that eHealth and mHealth can have on society. During this research project, the *why* of online lifestyle interventions never changed but the *how*, and *what* rapidly did.

The relevant trends I noticed in these changes, during the last few years are:

1. Public health, healthcare systems and the health improvement definition are making a strong plea for more time and resources for prevention, also in cognitive decline.
2. In accordance with the law of accelerating returns (Moore’s Law), information technology, the Internet (of things), and fields like eHealth and mHealth have been rapidly and vastly expanding their public health reach and therefore generated new scientific opportunities and possibilities such as the scientific citizen. These innovations make participants conductor and principle investigator,

being in control of their data collection and data storage in very innovative ways. Data sharing with other participants and the professional researchers via the 'cloud' is becoming accepted and may be importantly facilitated by the rise of eHealth and mHealth (Friend, 2015).

3. Prevailing scientific methodology is not sufficiently equipped to keep up with these trends. While the new definition of health may be future proof, the same cannot be said for the health care system it is currently implemented and validated for. Therefore, successful eHealth and mHealth innovations have to find their own innovative niche in a quickly changing health care system.

Recommendations for future eHealth studies

Reflecting on the Brain Aging Monitor research, renders some new valuable insights in performing eHealth research in general. At the end of this thesis, I will describe five points of attention for future studies in this domain, without being able to provide definite answers in this quickly changing environment.

1. Gamification

Dropout and attrition have been a big part of the eHealth-related research challenges so far (Aalbers et al, 2015; Bennett & Glasgow 2009; Eysenbach, 2005). Especially when more longitudinal research is concerned, like that of the Brain Aging Monitor, keeping participants engaged and interested remains difficult. This is where two ways of design come in. First, the methodological design of a study has little or nothing to do with the *effectiveness of the study*. It does, of course, have an influence on the ease of analysis and statistical sturdiness of the results. But it is not primarily directed at limiting dropout rates. Second, the design of the actual intervention is all about limiting dropout rates. This second interventional design may be improved substantially by applying more gamification as the best way of reaching more meaningful and enriched user experiences (Anderson & Rainie, 2012). As such, gamification is defined as "those features of an interactive system that aim to motivate and engage end-users through the use of game elements and mechanics" (Seaborn & Fels, 2015). This prioritizes the user's needs over those of the organization, or the research project. First one needs adherent participants, and only after one is able to perform a study. Previous studies have shown that game-based learning is effective when educating kids at elevated risk of dropping out of school (Schmitz, 2014), which underlines the potential of gamification in improving adherence. Games also have been used successfully to identify older individuals at risk of cognitive decline in the pre-dementia stage (Sirály et al, 2015), which emphasizes that gamification can also be applied in frail older persons in a diagnostic route, which otherwise needs intense personal interaction. Thus, gamification is an evidence based method of improving compliance, and may also work in older individuals.

In the search to adapt gamification to the preferences of older people, Diaz-Orueta and colleagues used focus groups to identify success factors for elderly to adopt and play educational games. The successful gamification factors were: social engagement (mainly intergenerational), experiencing a challenge, combining cognitive and physical activity, and acquiring specific skills (Diaz-Orueta et al, 2012). Not surprisingly, these critical factors are very similar to critical factors for enticing gameplay in youths. A systematic review by Hall and colleagues concluded that most preliminary study results showed positive physical and mental health outcomes through videogame play in elderly populations (Hall et al, 2012). That being said, researchers should be aware of the fact that gamification and applied gaming is a young and emerging field of research still plagued by many methodological limitations (Hamari et al, 2014). Regardless, from a pure game perspective, the gaming industry is the biggest and thus fastest growing multimedia industry in the world, captivating millions of players for even far more hours, and the first scoping review on recommendations for the application of serious games in elderly with diverse (risks of) disability has already been published (Robert et al, 2014). Therefore, the average gamer can no longer be stereotyped as an “anti-social 18 year old adolescent, stuck in his parents’ basement, playing violent shooters for 12 hours straight,” but it is increasingly often a woman over the age of 35 playing quick online puzzles. Also, the number of target audiences for gaming are quickly expanding, including the aging population.

First recommendation

In order to conduct a successful eHealth trial, the first and foremost precondition is that user experience in and user friendliness of the intervention should first be optimized to enable participant adherence. Meaningful gamification should always be considered to reach this goal. Poorly designed digital intervention tools will result in quick failure, specifically failure of adherence resulting in high drop-out rates.

2. Big Data and Citizen Scientists

eHealth and mHealth have the potential to rack up astonishing numbers of users. The ever increasing number of wearables and Smartphone sensors everybody is using on a day-to-day basis provides a treasure of data (Naci and Ioannidis 2015). Best practices already exist for the potential effectiveness of ‘citizen-scientist’ scenario, in which the common citizen is having an independent role as researcher with one’s own big data; alone or in collaboration with fellow-citizens.

EyeWire, an MIT (Massachusetts Institute of Technology) based applied gaming project has over 190,000 players worldwide who map the 3D shapes of neurons in a mouse retina. This provides valuable insights in form and function of how the retina processes visual information. Another example: *Foldit* is a game in which over 57,000 players assist researchers in unravelling protein structures in the name of science.

Human players, because of our good pattern-recognition skills, still outperform the most sophisticated software package available to date. The added value of this endeavor was convincingly realized in 2011 when *Foldit* players in less than 3 weeks modeled the enzyme for the Mason-Pfizer monkey-virus that had left scientists baffled for 15 years (Khatib et al, 2011).

The roadmap 1.2 drawn by the UK National Health Service states that when it comes to consumer eHealth “popularity of applications does not necessarily equal quality” (National Information Board, 2015). Although this is undeniably true, the other side of the argument is just as likely. “Lack of popularity of applications equals bad quality of e-intervention design”. Unfortunately this is ignored rather easily. Popularity, means the idea is striking a chord with a large audience. From a retention and data-collection perspective the impact this has is enormous (Friend, 2015). This is not the same as saying that health research information in popular applications is by default correct, as one should always scrutinize the results for the sources of bias. But, using the biosensors that surround us on a daily basis in this way does allow us to analyze our live, in real time, as being ongoing longitudinal studies (Friend, 2015).

Second recommendation

Since dropout is a really large factor that can be negated by popularity of an intervention and its trial, and since popularity grows the communities so desperately needed for most application-evaluations to succeed, I recommend that eHealth trials should make a serious attempt to make data collection a popular and rewarding part of the study. Popularity of the trial is one of the main factors determining the success of e- and mHealth evaluation studies.

3. Collaboration

The upside that technology offers when it comes to increased interactivity comes at a price. Where normal one-to-one human interaction comes naturally to most of us (learned by trial and error from childhood onwards), designing human-computer interaction for the same purpose requires a set of skills that can only be realized by specific training and years of experience that most of us don't have nor aspire to get. From a research perspective I see many programs and interventions, like the Brain Aging Monitor, that may better be labeled as ‘data collection methods’ than actual behavior change programs that deliver a user experience stimulating a research participant to realize his or her goals. Again, in order to design pragmatic trials, when it comes to data collection we need to let the user perspective prevail over anything else (Agbakoba et al, 2015; Glasgow, 2013). Although BAM was fuelled by participant experiences, we might have ended up with better implementation results by using more outside help from a user perspective: What does the intervention ask and offer?

What is the 'look and feel' of this program? Oftentimes we do not need more information from a mere content and theoretical point of view, but from an interventional design perspective (Glasgow & Rabin, 2014). We not only need piloting but also co-designing and prototyping (Agbakoba et al, 2015). Entrepreneurs are focusing on providing their users with a valuable and meaningful user experience. This is where a disconnect occurs. eHealth evolves around technology; however, programming and designing is not the main area of expertise for a researcher. In eHealth studies, researchers are fighting an uphill battle when competing with design and programming professionals, if they fail to work together. Their potentially theoretically sound program gets outcompeted by the more applicable, pragmatic commercial products. Having learned from these expensive lessons, the first research groups are adopting a more commercial way of designing and implementing (Agbakoba et al, 2015; Lassen et al, 2015). Even though Lassen and colleagues (2015) advocate pre-financed commitments of several years, they do so without pre-defined solutions and pre-defined problems, enabling the consortium to be flexible and to take shape in the process of "creating more empowered, active and health-conscious citizens of all age" (p.16), which is another way to be pragmatic. Even more so for eHealth implementation research than for other fields, the end result preferably is a product that is about market ready. This is not the main focus nor expertise for university medical centers. Having a launching customer or commercial party on board from the start of a research project greatly increases the odds of a scientifically sound product reaching the market. Both parties should be in the lead in their respective design field. Let science handle data collection, within the framework of the user experience developed by commercial partners. Even a new type of research professional is advocated in an attempt to bridge this gap: 'the knowledge engineer in health' (Beck et al, 2012). However, these innovative ideas are not yet widely supported and require a culture change in the scientific community to allow for more diverse types of research to be performed alongside each other (Glasgow, 2013).

Third recommendation

From the start, eHealth innovations should be based on a consortium in which market oriented entrepreneurial expertise and commitment should be linked to innovation and evaluation expertise from academia. Both are essential for good trials and subsequent implementation.

4. A change of pace

In the short life cycle of eHealth, focusing on scientific evaluation of eHealth proved to be a deviating field of research, because the medium through which the field implements its added value (ie. technology), changes at a rate much faster than scientific trajectories (Glasgow et al, 2014; Hussein, 2015). This potentially makes the

results obsolete by the time they get published, which diminishes their value to policy makers and society (Glasgow & Riley 2013). This higher speed of change from within the business world in comparison to academia is also noted by other research groups (Devlin et al, 2015). The Financial Times stated that “WhatsApp Messenger has done to SMS on mobile phones what Skype did to international calling on landlines” (2011, p.1: <http://www.webcitation.org/6dneyucgK>). With 30 billion daily messages since January 2015, WhatsApp has quickly overtaken SMS messaging (global 20 billion per day) as primary form of instant messaging. Regardless, science is still validating SMS messaging as potential useful method of communicating with participants (Hall et al, 2015), concluding that “[a]lthough strong evidence supports the value of integrating text-messaging interventions into public health practice, additional research is needed to establish longer-term intervention effects, identify recommended intervention characteristics, and explore issues of cost-effectiveness” (p.393). In sharp contrast, in the last five years, only thirteen articles indexed in PubMed made use of WhatsApp, nine of which were published in 2015, even though WhatsApp was launched as early as 2009. In 2016, the Journal of the American Medical Association (JAMA) will publish a series of publications that describe innovations in health care delivery. By itself this initiative sounds very promising. However, both of the following statements can be found in the same call that announces the series; “Because innovations, by their nature, are supposed to be surprising and unexpected, a closed list of topics of interest would be self-defeating” (p.675) and “In this series, JAMA is not seeking theoretical papers, but rather rigorous studies and systematic reports on outcomes based on innovations that have been developed and tested. ... Evidence-based systematic reviews and scholarly Viewpoints on topics relevant to the clinical, implementation, entrepreneurial, and policy aspects of innovation in health care delivery also would be of interest.” (Berwick et al, 2015); p.676). This still breathes the classical and slow path of efficacy and effectiveness evaluation according to the traditional evidence based medicine rules, instead of promoting the use of an e-Health intervention. This will definitely get IT guided innovation and medical research out of phase, instead of realizing synergy.

Fourth recommendation

Next to the more traditional evaluation of efficacy of e-Health and mHealth innovations, we advocate to develop, validate and use quicker and shorter evaluation methods, also using the Rapid and Relevant Research Paradigm by Glasgow and colleagues (see Table 7.1).

Table 7.1. Short overview of the Rapid and Relevant Research Paradigm

Issue	Traditional Pipeline	Rapid and Relevant Research Paradigm
Speed	Slow to very slow	Rapid, especially early on
Intervention and “protocol” flexibility	“Frozen” early and standardized	Iterative, evolves during the study, adaptive
Adaptation	No change along the way, which is a compromise to integrity	Encouraging flexibility and change is regarded as necessary to “fit”
Design used	Predominantly RCTs, explanatory aim	Several, interactive, convergent: pragmatic research paradigm is dominant
Cost and feasibility of research and products produced	Feasibility and implementation is not a primary concern, and costs are usually high	Feasibility is central along the complete R&D pathway; MINC ^a approach considered before, during and after innovation start
Stakeholder engagement	Little and usually only responding to research ideas	Throughout, essential part of the project
Reporting	CONSORT criteria, primary outcome oriented with few other outcomes reported	Broad, transparent, perspective of adoptees and experiences of participants are as relevant
Role of context	De-emphasized, assumed to be independent of context	Context is central, critical and studied as well

^aMINC; Minimal Intervention Needed for Change

Fifth and final recommendation

eHealth does not exist as just one field of research, but is largely considered, discussed and criticized as such. But we cannot really talk about it like it is (Lewis, 2015). Is it aimed at prevention, curing, monitoring, intervening, chronic disease management or anything else? Future evaluation strategies should take the specific aims and features of the eHealth and mHealth applications as the key factors that can lead towards relevant, scientifically and societal sound and feasible research and policy making. Researchers should use and score the PRECIS-2 criteria for their research proposals from the start of their endeavor and adapt their trial design to the life cycle of the IT product, the users pragmatism, as well as to the requirements of the available and valid research methods. To answer the question “does this work in real life?” in my opinion is far more interesting than the question “does this work under ideal circumstances?”.

Concluding remark

At the end of this thesis it fits to quote a well-known quote about gaming; “*I am a gamer. Not because I don't have a life, but because I choose to have many*” (source unknown). This reflection gives warning when we feel inclined to stick to one perspective on developing and evaluating behavior change from a scientific, an entrepreneurial, or an information technology point of view. This single life perspective will not be able to cover the many faces eHealth innovations have to offer. Obviously we just have one life, but if anything, behavior change is a rocky road, one with ups and downs, that is infested with trial and error, where the concept of having multiple lives would be both practical and comforting. When gamers fail a level, a quest or a puzzle, they get up and try again. But all too often people who want to change their habits try, fail, and give up.

As Bernard Suits adequately put it, the challenge in gaming lies in *voluntary overcoming unnecessary obstacles*. Games are not about having fun, they are not even fun to begin with. Everyone who has ever picked up a game has at some point thrown it into a dark corner, just to crawl after it a minute later and start all over. Games are about overcoming these *unnecessary obstacles*, and in doing so gain self-worth and pride. For me, this is a perfect metaphor for what behavior change researchers and health care professionals should aspire to accomplish in their programs, their research, and with their users, no matter whether they are players or patients. Allow people to throw their behavior into a dark corner, but make it impossible not to go after it eventually, with even greater determination and perseverance.

Table 7.2. List of recommendations on future eHealth research**List of recommendations:**

- User experience and user friendliness are a prerequisite to successful eHealth interventions.
- Use gamification or applied games in eHealth interventions; data collection should be similarly rewarding to participants.
- eHealth implementation research needs commercial parties and academia to team up to ensure optimal development and implementation strategies.
- “eHealth” comes in many shapes, form and sizes, and eHealth evidence should be collected and judged individualized accordingly.
- The PRECIS -2 tool should be used in the design phase of each eHealth evaluation study.



NEDERLANDSE SAMENVATTING

Introductie

In de afgelopen jaren zijn er een aantal trends zichtbaar geworden in de Nederlandse zorg. Twee daarvan, komen samen in dit proefschrift. De eerste is dat mensen steeds ouder worden, dat meer mensen (erg) oud worden en dus dat het aantal mensen met een dementie stijgt. Hierdoor maken ook steeds meer mensen zich zorgen over de ziekte, en rijst de vraag of zij hier zelf in preventieve zin iets aan kunnen doen. Ten tweede staat het huidige zorgstelsel zwaar onder druk om te innoveren en vernieuwen en wordt de roep om goede zelfmanagement oplossingen steeds luider. Dit is noodzakelijk om de stijgende zorgkosten in de toekomst te kunnen drukken en de zorg betaalbaar te houden. In dit proefschrift vinden twee mogelijke oplossingsrichtingen elkaar.

Er wordt de laatste jaren steeds meer onderzoek gedaan naar de relatie tussen een gezonde leefstijl op middelbare leeftijd en een goede hersenfunctie op latere leeftijd. Het wordt daarbij steeds duidelijker dat voldoende beweging, gezonde voeding, geen overmatige alcoholconsumptie, niet roken, voldoende slaap en ontspanning, het risico op cognitief verval verkleinen. Dit is nieuw ten opzichte van het lang gangbare idee dat cognitie per definitie afnam met het ouder worden, en dat hier weinig tot niets aan te doen was.

Daarnaast maakt de voortschrijdende technologie steeds meer mogelijk. eHealth, oftewel het inzetten van digitale middelen om gezondheid te verbeteren, wordt steeds belangrijker in de zorg. Met name omdat eHealth op voorhand vaak als kosten- en tijdbesparend wordt gezien. Zoals gezegd worden eHealth en leefstijlbevordering als primaire preventie strategie tegen cognitieve achteruitgang in dit proefschrift met elkaar verbonden op zoek naar het antwoord op een drietal vragen:

1. Kan de ontwikkeling en implementatie van een website, specifiek gericht op het veranderen van “gezond hersengedrag”, succesvol leiden tot gedragsverandering bij Nederlandse volwassenen? (Hoofdstuk 2, 4 en 5);
2. Is het betrouwbaar en valide testen van cognitief functioneren mogelijk, met behulp van online te spelen spelletjes (zogenaamde toegepaste ‘games’) als een soort digitale hersenfunctiemonitor? (Hoofdstuk 3);
3. Leidt het gebruik van deze website over de tijd op deze speelse, digitale hersenfunctie monitor tot meetbare verbeteringen van cognitie? (Hoofdstuk 4 en 6). In de hierop volgende pagina’s zullen de resultaten van vijf jaar onderzoek kort worden samengevat.

Resultaten

Voor we aan het ontwerpen van onze eigen interventie website, ‘de Brain Aging Monitor’ begonnen, hebben we in **hoofdstuk 2** literatuuronderzoek verricht naar eHealth studies gericht op leefstijlverbetering. Hierbij waren we met name geïnteresseerd of men er op dat moment (2010) al in was geslaagd gedrag te beïnvloeden met behulp van digitale middelen, en in het vinden van effectieve interventiecomponenten. Uit deze studie bleek dat het effectief beïnvloeden van gezondheidsgedrag al met succes was gedaan. Een minstens net zo belangrijk resultaat was de diversiteit in het type interventies dat was ontwikkeld. Dit varieerde van kort- tot langlopend onderzoek, met intensieve of beperkte begeleiding van professionals, en van op maat gemaakte adviezen tot algemene gezondheidsinformatie. Wat met name duidelijk werd, was dat het gebruik van een theoretisch raamwerk de effectiviteit ten goede kwam en dat het gebruik van persoonlijke doelen en het monitoren van het eigen gedrag effectieve strategieën waren.

Om deze kennis toe te kunnen passen in onze eigen Brain Aging Monitor studie en om de tweede onderzoeksvraag te kunnen beantwoorden, moesten we eerst de beschikking hebben over een betrouwbaar instrument om het cognitief functioneren van onze deelnemers te meten. Om deze reden beschrijven wij in **hoofdstuk 3** de ontwikkeling en validering van ons eigen meetinstrument voor cognitief functioneren; de Brain Aging Monitor – Hersenfunctiemeter (BAM-COG). In deze studie onder bijna 400 Nederlandse volwassenen vergeleken we de BAM-COG met bestaande tests om cognitie mee te meten. Na vergelijking bleken drie van de vier taken uit de BAM-COG voldoende precies en accuraat te zijn. Daarmee is de BAM-COG geschikt om in eHealth onderzoek in te zetten om 1) werkgeheugen, 2) ruimtelijk geheugen en 3) planningsvermogen te meten. Dit zijn drie functies van de hersenen die bij cognitieve achteruitgang relatief in een vroeg stadium aangedaan kunnen worden. De BAM-COG hebben we hierna ook toegepast in de planning en uitvoer van de Brain Aging Monitor studie.

De resultaten van de in **hoofdstuk 4** in detail beschreven studie met de Brain Aging Monitor (BAM) worden in **hoofdstuk 5 en 6** nader toegelicht. De Brain Aging Monitor is een online, zelfmanagement platform voor volwassenen die gezonder willen leven. De BAM is tot stand gekomen door slim gebruik te maken van bestaande gedragsveranderingstheorie, gecombineerd met de lessen uit hoofdstuk 2. Op de website kunnen deelnemers een persoonlijke profiel aanmaken en met een zestal snelle, eenvoudige vragenlijsten inzicht krijgen in hun eigen leefstijl. Hierbij wordt met name gelet op lichamelijke activiteit, voeding, alcohol consumptie, roken, slaap en stress. De gezonde normen die iedereen kent in relatie tot overgewicht, hoge bloeddruk, diabetes en

verschillende typen kanker zijn eigenlijk allemaal ook van toepassing op het gezond verouderen van de hersenen. Alleen over de hersenen is heel lang gedacht dat deze, naar mate iemand ouder wordt, steeds minder capaciteit krijgen. Tegenwoordig weten we steeds beter dat we de kans op het krijgen van dementie zelf aanzienlijk kunnen verkleinen door tijdens onze jeugd en op middelbare leeftijd gezonde gewoontes aan te leren. Na het in beeld brengen van de eigen leefstijl wordt de deelnemer uitgedaagd en begeleidt in het stellen van persoonlijk relevante gedragsdoelstellingen. De deelnemer wordt in dit proces begeleidt door de website en krijgt per doelstelling een aantal praktische handvatten om mee aan de slag te gaan. Vervolgens wordt de deelnemer gevraagd zijn eigen gedrag nauwgezet te volgen.

Van de ongeveer 3000 mensen die zich inschreven bij de BAM namen er na ruim een jaar looptijd ruim 200 actieve gebruikers deel aan de nameting. Deze deelnemers scoorden op verschillende leefstijlgebieden beter dan toen zij begonnen. Dit uitte zich ook in een verbetering in een algemene leefstijlscore van 5.5% ten opzichte van het jaar daarvoor. Met name op het gebied van voeding en beweging werd goede vooruitgang geboekt. Deze leefstijlverbetering hield ook verband met een verbetering van het werkgeheugen op het daarvoor ontwikkelde BAM-COG spel. Hoewel een verbetering van 5.5% misschien niet groot klinkt kan deze kleine persoonlijke verbetering maatschappelijk gezien zeer belangrijk zijn. Wanneer veel mensen net iets gezonder gaan leven, kan dit de nodige verlichting in ons zorgsysteem opleveren. Daarnaast zou het over verloop van jaren voor een deelnemer veel betekenen om elk jaar 5% gezond te gaan leven. Daarmee is de Brain Aging Monitor voor de mensen die hier korte of langere tijd gebruik van maken een geschikt instrument om te werken aan gezond gedrag.

Discussie

Het doen van eHealth onderzoek is een bijzonder uitdagende vorm van onderzoek. Deelnemers aan eHealth onderzoek zijn wegwijs op het internet en weten wat ze zoeken. In een (digitale) omgeving waar vele prikkels om voorrang vechten, is een aantrekkelijk en laagdrempelig aanbod aan onderzoeksprojecten nodig. Hierbij moeten onderzoekers zich niet alleen de vraag stellen 'wat vind ik interessant om te onderzoeken?', maar ook 'hoe houd ik mijn deelnemers gemotiveerd en bied ik hen een positieve en relevante ervaring als onderzoeksdeelnemer?'. Met ideeën uit de digitale spel industrie, door gebruik maken van de menselijke nieuwsgierigheid en het aangaan van waardevolle samenwerking met private partijen, zijn aantrekkelijke onderzoeksvoorstellen goed mogelijk. Om dit te kunnen realiseren zijn een aantal aanpassingen in de wetenschappelijke methode wenselijk zodat technologische

ontwikkeling en het verzamelen van wetenschappelijke evidentie met elkaar in de pas kunnen blijven. eHealth gaat over het toepassen van gezondheidskundige kennis in digitale techniek en vaak over de vraag ‘werkt dit of is dit toepasbaar in het echte leven?’. Het is een grote wetenschappelijke uitdaging om bij te blijven met deze snelle veranderingen in dit ‘echte leven’. Om bruikbare, gezonde adviezen te geven, juist ook gericht op het behoud van de hersenfunctie. Hersenfuncties die in onze gedigitaliseerde maatschappij een steeds belangrijkere rol spelen.



DANKWOORD

Dankwoord

De puzzel is compleet en het laatste stukje is gelegd. De metafoor van de puzzelaar zal mij, niet geheel onterecht, voor de rest van mijn leven blijven achtervolgen. Ook promoveren is puzzelen. Voor jezelf, het team, de deelnemers en de omgeving. Sommige puzzelstukjes vielen wat makkelijker dan andere en voor sommige heb ik goed moeten zoeken. Gelukkig lagen de hoekjes en de meeste randjes, er al voor ik aan dit traject begon en hoefde ik “alleen nog maar” verder in te kleuren.

Een onderzoek is geen onderzoek zonder **deelnemers**. Hoewel ik slechts enkelingen echt gesproken heb, is het dankzij jullie allemaal dat dit proefschrift tot stand is gekomen. In het bijzonder wil ik hier graag mijn deelnemer **Minke** bedanken voor alle leuke, serieuze, dankbare en enthousiasmerende e-mails die wij de afgelopen jaren hebben mogen versturen naar elkaar. Hierin heb ik altijd houvast gevonden dat de Brain Aging Monitor impact heeft gehad.

Al die deelnemers heb ik kunnen werven, coachen en analyseren dankzij een begeleidingsteam dat mij de afgelopen jaren veelvuldig heeft bijgestaan. **Marcel**, als eerste promotor en houvast door de jaren heen heb ik ontzettend veel van je mogen en kunnen leren. Vanaf een zeer prettig sollicitatiegesprek af aan heb ik veel vertrouwen van je gekregen en kunnen leren van onze duopresentaties. De track-changes waar stukken altijd ontegenzeggelijk van verbeterde, het feit dat ik je altijd even kon strikken voor een snelle werkbepreking op de gang en jouw drang naar innovatieve interventies zijn voor mij altijd het teken geweest dat Geriatrie verre van stoffig is.

Roy, ik heb in de afgelopen jaren veel geleerd van jouw nuchtere kijk op het doen van onderzoek en ontzettend genoten van de praatjes tussendoor. Praatjes tussendoor die altijd twee minuten leken te gaan duren maar steevast eindigde in gezellige, staande werkbeprekingen. Het feit dat je beperkt aanwezig maar altijd beschikbaar was, was zeker naar het einde toe van grote waarde. Jouw aversie tegen alles wat met sport te maken heeft onderstreepte dagelijks het belang van programma's zoals de Brain Aging Monitor.

Li, regardless of the fact that you only stepped in later on in the project you have been able to coach me a lot. You have shown a very high tolerance for my statistical stupidity and were always there when I needed to nag about how reviewers are most likely the dumbest people on earth. Assuming that Google Translate will not screw me over: 非常感谢在过去几年.

Annet, wij hebben elkaar gevonden in de wil om verschillende werelden, specialismen en type mensen met elkaar te verbinden. Jouw kijk op nieuwe samenwerkingen in het onderwijs en het bedrijfsleven hebben bijgedragen aan de manier waarop ik nu tegen werken aan kijk. Daar ben ik je uitermate dankbaar voor. Bij jou kon ik altijd terecht juist als ik even uit de waan van alledag gehaald moest worden.

Lia, lang geleden zijn we hier samen aan begonnen, inmiddels ben ik op eigen benen aan de finish gekomen. Dank je wel voor jouw steun in de fase dat alles nog verzonnen en uitgedacht moest worden. Daar ligt uiteindelijk de basis voor dit proefschrift.

Ook wil ik hier graag even stilstaan bij alle onderzoekers van het consortium waar de Brain Aging Monitor onderdeel van uitmaakte. **Martin**, dank je wel dat jij als consortium-leider onze projecten altijd op koers hebt weten te houden en nadrukkelijk naar de verbinding hebt gezocht. **Jennifer, Jessika, Jaap, Richard, Tessa, Hannie** en **Kelly** onze consortia meetings hebben mij echt gedwongen kritisch naar de studie te kijken, vroegtijdig veranderingen door te voeren, maar ook altijd vol enthousiasme over de ontwikkelde producten. Hopelijk zien we elkaar in de toekomst via andere routes nog!

Dank aan mijn **manuscriptcommissie**: Pim van Assendelft, Koos van der Velden en Jaap Murre en de leden van mijn **promotiecommissie** voor jullie enthousiasme en de tijd die jullie hebben genomen om mijn proefschrift te lezen en in de corona plaats te nemen.

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Bridgeclub 't Hartje, beter bekend als de **BLUP-groep**, gevreesd waren de dagen dat ik hard moest werken omdat ik dan onherroepelijk vierhonderd appjes verdeeld over vijf groepsapps "miste". Vele mooie herinneringen liggen achter ons en er is nog geen eind in zicht als het op ondoordachte, vreselijk impulsieve actieplannen aankomt. **Miel, Ilonka, Linnie, Loes, Alex, Bart, Ies, Wouter, Dre, M-i-r-e-i-l-l-e** en **Laura** jullie waren de beste surprise act van de afgelopen jaren!

Stijn mooie kerel speciaal voor jou een zin zonder al te veel interpunctie omdat wij nou eenmaal houden van ellendig lange zinsconstructies die elke draad nog lijn binnen de kortste keren volledig kwijt (dreigen) te raken Er zijn weinig mensen met wie rampzalige onzin produceren zo'n fantastische vorm aan kan nemen als met jou en ik

vertrouw erop dat dit een vaste waarde in ons repertoire zal blijven. **Joost**, dat we nog maar veel dwaze projecten mogen opstarten waarvan we er zo af en toe ook nog eens eentje afmaken. Hoewel ik al bijna net zoveel plezier heb in het aanleggen van een verzameling half afgeronde hobbyprojecten! **Marcel** en **Renée**, jullie zijn op de afdeling menigmaal aanleiding tot behoorlijke spraakverwarring geweest als Miriam en ik 'lekker bier waren gaan drinken met Marcel en Renée'. Het promoveren is nu klaar, het bier drinken hopelijk niet! Mijn nichtje **Lieteke**; ik denk niet dat iemand anders zo heerlijk oprecht kon vragen "en hoe gaat het nou met jou?", als jij. Ik heb te weinig gebruik gemaakt van het aanbod om 'te komen eten als ik geen zin had om te koken', maar hoop dit in de toekomst nog vaak te mogen doen.

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List of publications

Peer-reviewed articles:

- Aalbers T, Baars MAE, Olde Rikkert MGM. Characteristics of effective Internet-mediated interventions to change lifestyle in people aged 50 and older: a systematic review. *Ageing Res Rev* 2011;10(4):487-97.
- Aalbers T, Baars MAE, Olde Rikkert MGM. The Mediterranean diet as prevention strategy for dementia as a multicausal geriatric syndrome. *American Journal of Clinical Nutrition* 2013;97(6):1411-11.
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- Aalbers T, Baars MAE, Qin L, de Lange A, Kessels RPC, Olde Rikkert MGM. Using an Internet-mediated eHealth intervention to stimulate health behavior for the prevention of cognitive decline in Dutch adults aged 40-67 years: study protocol for the Brain Aging Monitor (BAM). *JMIR Res Protoc* 2015;4(4):e130.
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- Aalbers T, Qin L, Baars MAE, de Lange A, Kessels RPC, Olde Rikkert MGM. eHealth mediated lifestyle change and cognition; primary prevention of cognitive decline during midlife in Dutch adults of 40 years and older. *Ready to submit*.

Book chapters:

- Aalbers T and de Lange A. (2013) De Brain Aging Monitor als interventie. In: de Lange, A and van der Heijden B. (eds). *"Een leven lang inzetbaar? Duurzame inzetbaarheid op het werk: interventies, best practices en integrale benadering"*. Alphen aan de Rijn; Vakmedianet. ISBN:9789462150973.
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About the author

Teun Aalbers (1985) studeerde in 2005 af aan de Hogeschool Arnhem en Nijmegen aan de opleiding Sport, Gezondheid en Management en behaalde in 2009 zijn master “Gezonde Veroudering” van de studie Bewegingswetenschappen aan de Rijksuniversiteit van Groningen. Het gebruik van eHealth interventies en online/mobiele applicaties om de gezondheidszorg te verbeteren ziet hij als een grote uitdaging. Naast een onderzoekspositie aan de afdeling Geriatrie van het Radboudumc, waar hij onderzoek doet naar leefstijlverbetering van voetbalsupporters, heeft hij een eigen bedrijf dat applied games ontwikkeld in de zorg.

Teun Aalbers (1985) graduated in 2005 from the University of Applied Sciences Arnhem and Nijmegen as a Sports, and Health Manager. After which he continued to study at the Rijksuniversiteit Groningen doing a masters in Healthy Aging at Human Movement Sciences. He looks upon the development of eHealth and mobile applications as a very interesting and important next step in creating and maintaining a healthy society. In addition to a senior research position at the Department of Geriatric Medicine at the Radboudumc, he owns an applied gaming studio that develops games for diverse health care settings.



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Appendix 1. PubMed search strategy

Search strategy: created by TA

Date search: 15 September 2010

Limits: English, Dutch, Humans

Hits: 1876

Search strategy:

1. "Internet" [Mesh]
2. "Internet*" [ti]
3. "computer*" [ti]
4. "Web-based" [tiab]
5. "eHealth" [tiab]
6. "e-Health" [tiab]
7. "e-learning" [tiab]
8. OR/1-7
9. "Intervention Studies" [Mesh]
10. "Program Evaluation" [Mesh]
11. "Evaluation Studies" [Publication Type]
12. "Evaluation" [tiab]
13. "Randomized Controlled Trial" [Publication Type]
14. "Randomized Controlled Trial" [tiab]
15. "Effective*" [tiab]
16. "Monitoring" [tiab]
17. "Self management" [tiab]
18. "Implementation" [tiab]
19. "Review" [tiab]
20. "Meta-analysis" [tiab]
21. "Intervention" [tiab]
22. OR/8-21
23. "Life Style" [Mesh:NoExp]
24. "Life Style" [tiab]
25. "Lifestyle" [tiab]
26. "Health Promotion" [Mesh]
27. "Health Promotion" [tiab]
28. "Primary Prevention" [Mesh:NoExp]
29. "Primary Prevention" [tiab]
30. "Risk Reduction Behavior" [Mesh]
31. "Risk Reduction Behavior" [tiab]
32. "Behavior* change" [tiab]
33. "Quality of Life" [Majr]
34. "Exercise" [Mesh]
35. "Exercise" [tiab]
36. "Physical activity" [tiab]
37. "Nutritional Sciences" [Mesh:NoExp]
38. "nutrition" [tiab]
39. "Diet" [Mesh]
40. "Diet" [tiab]
41. "Obesity" [Mesh]
42. "Obesity" [tiab]
43. "Hypertension" [Mesh]
44. "Hypertension" [tiab]
45. "Diabetes Mellitus" [Mesh]
46. "Diabetes Mellitus" [tiab]
47. "Cholesterol" [Mesh]
48. "Cholesterol" [tiab]
49. "Alcohol Drinking" [Mesh]
50. "Alcohol Drinking" [tiab]
51. "Smoking" [Mesh]
52. "Smoking" [tiab]
53. "Smoking Cessation" [Mesh]
54. "Smoking Cessation" [tiab]
55. "Socioeconomic Factors" [Mesh]
56. "Depression" [Majr]
57. "Sleep" [Mesh]
58. "Sleep" [tiab]
59. "Sleep Apnea, Obstructive" [Mesh]
60. "Stress, Psychological" [Mesh]
61. OR/22-60
62. Child [tiab]
63. Children [tiab]
64. Infant [tiab]
65. Infants [tiab]
66. Adolescent [tiab]
67. Adolescents [tiab]
68. Student [tiab]
69. Students [tiab]
70. College [tiab]
71. Teenager [tiab]
72. Teenagers [tiab]
73. Youth [tiab]
74. Young [tiab]
75. OR/61-74
76. 8 AND 22 AND 61 NOT 75



Appendix 2. Overview of BAM-COG games

The four puzzles used for the BAM-COG are online at www.spellenonderzoek.nl (website in Dutch). The description in this appendix should provide the reader with a fair overview of what the puzzles contain. A new version of this website can be found at www.expeditiecognitie.nl.

Conveyer Belt

Conveyer belt, a puzzle game relying mostly on working memory, shows a participant a grocery list on screen. After one second the conveyor belt turns on. Groceries run down the belt and participants need to select only those products that are on their list.

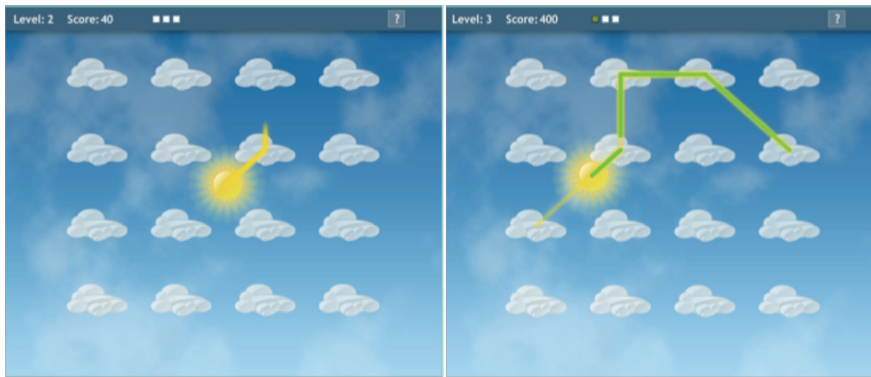


Conveyer Belt Instructions:

1. In the game 'conveyer belt' you get to see a list of groceries. You have to select the groceries on this list when they come down the conveyer belt.
2. You can select a product by clicking it on the conveyer belt. Make sure to click them before they drop into the box at the end of the belt!
3. Make sure that you do not select too many groceries or that you don't select all the groceries
4. We start out with a short practice round with only three types of groceries.
5. When you don't succeed in successfully completing two out of three trials you will be game over.

Sunshine

Sunshine, a puzzle game relying mostly on visuospatial short-term memory, creates visual patterns in a 5x5 matrix. This visual pattern dissolves gradually and after it is completely gone from the screen participants are asked to reproduce this pattern in the exact same order as it initially appeared on screen.



Sunshine Instructions:

1. The game 'sunshine' starts with a sun drawing a line between several clouds in a 4x4 grid. It is up to you to memorize the pattern of the line drawn.
2. It is your task to draw the exact same line as the sun did as soon as the sun disappears from the screen. You can do this by clicking the clouds in the correct order.
3. Please note: make sure that when you start your clicking sequence that the first cloud is actually selected (it will light up slightly).
4. You cannot take back steps. The trial end as soon as you have drawn an equal number of line pieces as drawn by the sun. We start out with a short practice round with a short line of only three line pieces.
5. When you don't succeed in successfully completing two out of three trials, the game will be over.

Viewpoint

Viewpoint, a puzzle game relying mostly on episodic recognition memory, presents a 5x5 matrix filled with stimuli to the participant. The participant gets three seconds to memorize this presented pattern before it disappears from the screen. After three seconds, three possible answers appear on screen from which the participant is to pick the answer that is an exact match to the previously shown matrix.

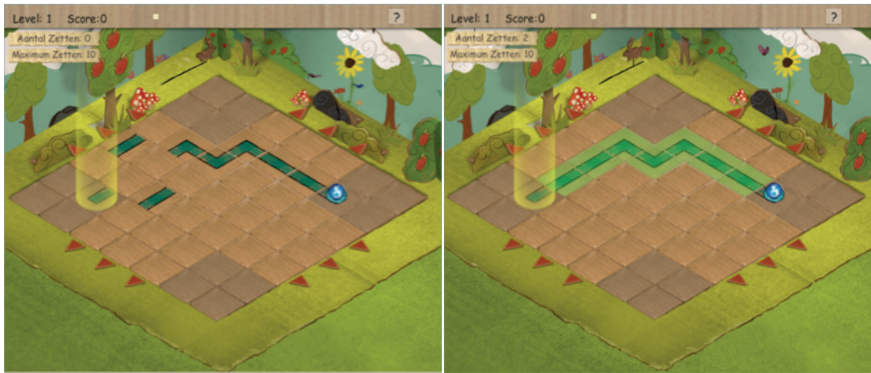


Viewpoint Instructions:

1. In the game 'viewpoint', you get to see a 5x5 matrix that contains a predetermined pattern made out of asterisks. You need to memorize this pattern.
2. After three seconds, the pattern disappears from the screen and the screen goes blank.
3. The blank screen is replaced with three answer possibilities. Only one of these three patterns is an exact copy of the originally shown pattern. You're supposed to select the exact copy.
4. We start out with a short practice round with only three groceries.
5. When you don't succeed in successfully completing two out of three trials, the game will be over.

Papyrinth

Papyrinth, a puzzle game relying mostly on planning, starts with presenting a scrambled route to the participant. The participants task is to complete the route so their pawn can move from start to finish unobstructed. Clearing the route is done by sliding the columns and rows in such an order that all pieces of road end up connected to each other.



Papyrinth Instructions:

1. In Papyrinth, you have to complete a route that is scrambled.
2. The goal of Papyrinth is to complete the route so that there is a unobstructed path from the start (the logo) to the finish (the yellow pillar).
3. You can complete the path by clicking the red arrows on the side of the rows and columns. Try to complete the pathway in as few moves as possible.
4. You can only move the entire row or column at once. Plan the moves you need to make strategically before actually clicking the arrows.
5. For every level, Papyrinth tells you the maximal amount of moves you are allowed to make before you should have solved the puzzle.
6. When you don't succeed in successfully completing two out of three trials, the game will be over.

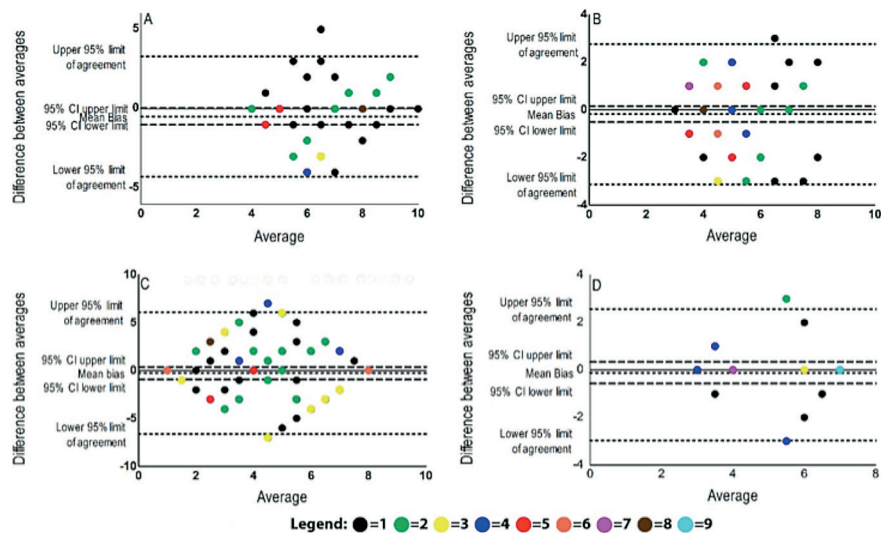
Appendix 3. Videos of the BAM-COG games

On the following link you can find a short trailer for the original BAM-COG games:
<https://www.youtube.com/watch?v=XV84wcNUbnY>



Appendix 4. Bland-Altman plots for Alternate Forms Reliability

In these Bland-Altman plots the differences in scores between two sessions (session 2 and 3) are plotted against the mean score in these two sessions. Furthermore, the scores means and limits of agreement are calculated as the mean of the difference between the two measurements $\pm 2SD$ of these differences. The standard error of measurement and the 95% confidence intervals for the mean difference between the two measurements are also calculated. If the 95% confidence interval does not include zero, this indicates a systematic and undesirable change in the mean. Also, if the mean bias is included in the 95% confidence interval this means the absence of a systematic difference between the means. Therefore, alternate forms reliability can be assumed.



Panel A = Conveyer Belt

Panel B = Sunshine

Panel C = Viewpoint

Panel D = Papyrus



Appendix 5. Digital informed consent form for BAM participants

Informed Consent form

The Brain Aging Monitor is a study about the brain of the Radboudumc in Nijmegen. The results of the research will be used to learn more about the workings of the brain.

We therefore ask you to agree that we use your answers to the questionnaires and measurement results. If you agree, you can participate in the Brain Aging Monitor program. Before you agree, you must have read the written information about what the research entails. This information is provided below:

What is the Brain Aging Monitor?

The Brain Aging Monitor is a lifestyle program developed by the Radboudumc. The Brain Aging Monitor (BAM) gives you insight in your lifestyle, makes you more aware of your behavior and supports you in making healthy choices. The BAM supports you in acquiring and maintaining healthy behaviors. For example, exercise, diet, alcohol consumption and smoking. But also sleep and relaxation.

The Brain Aging Monitor challenges participants to live healthy and responsible. You will gain insight in your own lifestyle. The BAM compares your personal lifestyle to the standards for healthy living by the World Health Organization and the National Food Centre. Based on these results you set personal and achievable monthly goals. The BAM provides you with a number of tools that make it easier to achieve your goals. For example, the BAM uses monitoring systems for the amount of exercise performed or the number of units of alcohol you have drunk. On the basis of this information, the BAM gives you insight into your progress to reach your goals.

In order to combine the performance of your brain with these lifestyle changes, the Radboudumc has specially developed a new online self monitor for cognitive performance for the Brain Aging Monitor. We developed a new way of using online puzzles. Thus, the BAM can map your memory and planning ability over the course of time. When we link the data about healthy living and your brain aging we can draw conclusions about how healthy living affects brain aging.

The Brain Aging Monitor is the subject of Teun Aalbers' PhD thesis. Aalbers is a PhD at the Department of Geriatric Medicine at the Radboudumc. For his study he tries to answer two questions. The first question is "What is the effect of a healthy lifestyle on the aging process of our brain?". The second question is "Is it possible to support

participants in making healthy lifestyle choices using a standalone website?”. The BAM therefore aims to follow you for two years. This may seem very long at first. But breaking unhealthy habits and patterns is not easy. Especially since we’re interested in observing if health behavior changes persist over time and become new healthy habits we need to follow you for a longer period of time. Furthermore, the decline of cognitive functions during our lifespan is a slow and gradual process. To see if making healthy behavioral choices influences this gradual decline the follow up period needs to be several years.

In order to optimally do this the Brain Aging Monitor administers a number of questionnaires. These questionnaires are about your current lifestyle. In addition, the Brain Aging Monitor asks you a number of questions that maps your perspective on behavior change and how you cope with difficult situations. This way, over the course of time, we can see if participants who deal with difficult situations in different ways also change their behavior in different ways.

The Brain Aging Monitor also asks you to play four puzzle games. This allows us to globally map the performance of your brain. By repeating these games after one year and two years we see how and if you have changed.

We hope that you continue to take part in the study for the duration of at least two years. However, you are free to stop your participation in the study at any given moment in time without providing an explanation. This can be done by clicking the “unsubscribe” button on your personal profile. After this you will receive no further information from the Brain Aging Monitor.

Your information will be kept strictly confidential by the Brain Aging Monitor and Radboudumc. Your personal information will not be provided or released to any third party under any circumstances. All your data is treated and analyzed anonymously and will in no way be traced back to your person. If you participate in the Brain Aging Monitor through your employer, your employer will not receive feedback on your results that can be traced to your person. Anonymous results will only be provided when there are sufficient participants from the same employer participating to guarantee anonymity.

If, for whatever reason, you are under the care or supervision of a physician, dietitian, physical therapist or other health care professional, you need to follow the advice you have been given by this health care professional at all times. If the advice of the Brain Aging Monitor are contradictory to the advice you receive from your therapist, you can discuss this with said health care professional. The advice of your therapist, however, is completely customized to your situation. So always follow the advice of your health care professional over advice by the Brain Aging Monitor.

1. I have read the written information concerning the study
2. I am satisfactorily informed about the study
3. I have had time to think about my participation in the study
4. I know that participation is completely voluntary. I know I can decide not to participate at any given moment in time. I don't need to provide a reason for my discontinuation of the study.
5. I give the administrators of the Brain Aging Monitor permission to access my account when I request assistance.

I hereby consent to the use of my data for scientific purposes, provided that my privacy is guaranteed:

- ☐ Yes, I have read the informed consent of the Brain Aging Monitor and agree to these terms.



Appendix 6. Overview of all lifestyle questionnaires in the BAM

1. Demographics

1. What is your age?
_____ years old
2. Gender:
Male / Female
3. What is the highest education you have enrolled in?
answers provided in Dutch as our system differs from the English or US system, ranked from low to high, starting with 'no formal education' up to 'university'
 - ☐ Geen opleiding gevolgd / afgemaakt
 - ☐ Basisonderwijs
 - ☐ MAVO
 - ☐ Voorbereidend beroepsonderwijs
 - ☐ HAVO / VWO
 - ☐ Middelbaar beroepsonderwijs
 - ☐ Hoger beroepsonderwijs
 - ☐ Wetenschappelijk onderwijs
4. Height:
Approximately _____ cm
5. Weight: (preferably today or otherwise a recent measurement)
Approximately _____ kg
6. How would you describe your general health?
 - ☐ Not good
 - ☐ Moderate
 - ☐ OK
 - ☐ Very good
 - ☐ Excellent
7. Do you find yourself forgetful?
 - ☐ Yes
 - ☐ No

8. How much do you worry about your forgetfulness?

- ☐ Not at all
- ☐ Very little
- ☐ A little
- ☐ A lot
- ☐ Very much

9. How many hours per week do you work under contract?

_____ hours

10. How much overtime do you work on a weekly basis? (Please include both paid and unpaid overtime but at home or at work. Exclude time commuting)

_____ hours

11. How many hours of your total working hours do you spend behind a computer?

_____ hours

2. Lifestyle questionnaires

2.1 Physical activity:

The next question is about physical activity like walking, or cycling, gardening, working out or other physical activity at school/work, around the house or during leisure time. Please include all physical activities that are at least as intense as walking briskly or cycling.

1. How many days a week do you at least perform 30 minutes of this type of physical activity?

Please consider the average number of days of an average week in the last month.

_____ days per week

The next question is about intense physical activity that noticeably raises your heart rate, respiration and lasts long enough to start perspiring, like exercise or other intense activities at school/work, around the house or during leisure time.

2. How many times per week do you take part in intense exercise or heavy physical activities that last long enough to start perspiring? Please consider physical activity that lasts longer than 20 minutes per bout. Consider an average week in the last month.

_____ days per week

3. Do you know the Dutch Norm for Healthy Physical Activity?

☐ Yes

☐ No

4. According to you, how much physical activity is necessary to increase your health status? This means something different from maintaining your health status.

☐ 1 time per week 10 minutes of moderate intense activity, like brisk walking or cycling (15 km/hr)

☐ 3 times per week 10 minutes of moderate intense activity, like brisk walking or cycling (15 km/hr)

☐ At least 5 times per week, but preferably daily, 30 minutes of moderate intense activity, like brisk walking or cycling (15 km/hr)

☐ 3 times per week at least 20 to 30 minutes of intense physical activity like running

5. According to you, how fit are you on a scale from 1-10?

1 2 3 4 5 6 7 8 9 10

2.2 Nutrition:

1. On an average week, how many days per week do you have breakfast?

_____ days per week

2. How many days per week do you have 3 regular meals (breakfast, lunch, dinner) a day?

_____ days per week

3. How many days per week do you eat 2 portions of fruit?

_____ days per week

4. How many days per week do you eat 200 grams of vegetables?

_____ days per week

5. How many days per week do you eat fish?
 - ☐ None
 - ☐ 1x per week
 - ☐ 2x per week or more
6. How many days per week do you eat after you had dinner?
 _____ days per week
7. How many days per week do you have unhealthy snacks in between the three main meals?
 _____ days per week

2.3 Smoking:

1. Are you a smoker?
 - ☐ Yes, I currently am a smoker
 - ☐ No, I have quit in the last six months
 - ☐ No, I have quit longer than six months ago
 - ☐ No, I have never smoked

Applicable for smokers only:

2. During last year, how many times did you quit smoking for a period longer than 24hours?
 _____ times
3. Are you seriously considering quitting smoking?
 - ☐ Yes, I consider quitting smoking within the next 30 days
 - ☐ Yes, I consider quitting smoking within the next 6 months
 - ☐ No, I don't considers quitting smoking at the moment
4. How much do you smoke on a day to day basis? (multiple options possible)
 - ☐ Less than 10 cigarettes
 - ☐ 10-20 cigarettes
 - ☐ More than 20 cigarettes
 - ☐ Less than 5 cigars/pipes
 - ☐ 5-10 cigars/pipes
 - ☐ More than 10 cigars/pipes

2.4 Alcohol:

1. How many days per week do you consume alcohol?
☐ 0 (go to 2.5)
☐ 1
☐ 2
☐ 3
☐ 4
☐ 5
☐ 6
☐ 7
2. How many standard drinks of alcohol do you have on a typical day that you consume alcohol?
☐ 1 glass
☐ 2 glasses
☐ 3-5 glasses
☐ 6 glasses or more
3. On the day of the week that you drink most alcohol, how many standard drinks of alcohol do you consume?
☐ 1 glass
☐ 2 glasses
☐ 3-5 glasses
☐ 6 glasses or more
4. How many standard drinks of alcohol do you consume weekly?
☐ 1-5
☐ 6-10
☐ 11-15
☐ >15

2.5 Sleep:

1. On average, how many hours do you sleep per night? Don't count the hours you spent in bed but those that you're actually asleep.
_____ hours
2. On average, how many hours of sleep do you think you need per night to function properly the next morning?
_____ hours

3. At what time do you normally go to bed?

4. At what time would you preferably go to bed on a normal night?

5. On average, how long does it take you to fall asleep?

6. On average, at what time do you wake up in the morning?

7. At what time would you preferably wake up on a normal morning?

8. How many times do you wake up during the night?

_____ times

The following short questionnaire are on your sleep during the night and attentiveness during the day time. Please indicate for every statement what is most appropriate for your situation when you look back at the last four weeks.

0 = never

1 = sometimes, but less than 3 times per week

2 = often, more than 3 times per week

3 = daily

Situation during the last 4 weeks	Never	Sometimes	Often	Daily
1 Do you have trouble getting to sleep?	0	1	2	3
2 Do you wake up multiple times during the night and have trouble getting back to sleep?	0	1	2	3
3 Do you experience tension and stress while trying to fall asleep?	0	1	2	3
4 Thoughts are racing through your head while you are in bed?	0	1	2	3
5 Are your muscles tense while trying to fall asleep?	0	1	2	3

6 Do you have the feeling that you sleep restlessness?	<input type="radio"/>	1	2	3
7 Do you snore?	<input type="radio"/>	1	2	3
8 Do you experience pain or cramps during the day and/or night time?	<input type="radio"/>	1	2	3
9 Do you wake up with a headache or painful muscles?	<input type="radio"/>	1	2	3
10 Do you get enough sleep to wake up refreshed?	<input type="radio"/>	1	2	3
11 During the day, do you feel drowsy or sleepy?	<input type="radio"/>	1	2	3
12 Do you take naps longer than 5 minutes during the day?	<input type="radio"/>	1	2	3

2.6 Relaxing:

1. Satisfaction with Life Scale:

Below are five statements that you may agree or disagree with. Using the 1 - 7 scale below, indicate your agreement with each item by placing the appropriate number on the line preceding that item. Please be open and honest in your responding.

- ☐ 7 - Strongly agree
- ☐ 6 - Agree
- ☐ 5 - Slightly agree
- ☐ 4 - Neither agree nor disagree
- ☐ 3 - Slightly disagree
- ☐ 2 - Disagree
- ☐ 1 - Strongly disagree

_____ In most ways my life is close to my ideal.

_____ The conditions of my life are excellent.

_____ I am satisfied with my life.

_____ So far I have gotten the important things I want in life.

_____ If I could live my life over, I would change almost nothing.

2. Can you estimate how many hours per week you spend on the following activities during a regular week?

- | | |
|---|----------------------|
| <input type="checkbox"/> Watch TV | _____ hours per week |
| <input type="checkbox"/> Reading; books, magazines, newspapers, etc | _____ hours per week |
| <input type="checkbox"/> Being part of a group / clubs | _____ hours per week |
| <input type="checkbox"/> Sports: ball sports, endurance training etc | _____ hours per week |
| <input type="checkbox"/> Light sports: hiking, cycling, gardening, etc | _____ hours per week |
| <input type="checkbox"/> Think sports: checkers, chess, puzzles, etc | _____ hours per week |
| <input type="checkbox"/> Doing groceries, cooking, physical hygiene | _____ hours per week |
| <input type="checkbox"/> Hobbies, making music, driving | _____ hours per week |
| <input type="checkbox"/> Learning new skills: language, courses, etc | _____ hours per week |
| <input type="checkbox"/> Social gathering with friends, family, acquaintances | _____ hours per week |

Appendix 7. Construction of the overall lifestyle score

Lifestyle area	Health Norm Division	Score
Physical Activity	Not active (0-2 days of physical activity per week)	1
	Sub-active (3-4 days of physical activity per week)	2
	Norm active (5-7 days of physical activity per week)	3
Exercise	Not active (0 days of exercise per week)	1
	Suboptimal active (1 day of exercise per week)	2
	Norm active (≥ 2 days of exercise per week)	3
Healthy Nutritional Behaviour	Lowest tertile of Health Nutrition scores	1
	Middle tertile of Health Nutrition scores	2
	Highest tertile of Health Nutrition scores	3
Unhealthy Nutritional Behaviour	Lowest tertile of Unhealthy Nutrition scores	1
	Middle tertile of Unhealthy Nutrition scores	2
	Highest tertile of Unhealthy Nutrition scores	3
Smoking status	Current smoker	1
	Ex-smoker	2
	Non-smoker	3
Alcohol consumption status	Frequent drinker (≥ 6 days per week)	1
	Abstainer	2
	Average drinker (≤ 5 days per week)	3
Sleep status	Poor sleeper	1
	Suboptimal sleeper	2
	Good sleeper	3
Stress status	Lowest tertile of Satisfaction with Life scores	1
	Middle tertile of Satisfaction with Life scores	2
	Highest tertile of Satisfaction with Life scores	3
Total score:	Ranging from 8-24	



Appendix 8. Room for improvement in the Netherlands

In the Netherlands, the rate of adherence to the Dutch Public Health Physical Activity Guidelines (which calls for a minimum of 30 minutes of moderate physical activity at least 5 days per week) has been stable at approximately 60% of the general population since 2006. However, since 2000, the middle-age population (55-64 years of age) has increased adherence to this guideline. From the year 2000 to 2011, Dutch adults increased the total number of minutes spent daily in physical activity by approximately 19% (from 169 minutes/day to 202 minutes/day); this increased activity primarily reflects increased activity at work, school, and home, but not sports (Hildebrandt et al, 2013). In contrast, only approximately 50% of elderly individuals (i.e. ≥ 65 years of age) adhere to the physical activity guidelines. Moreover, in the Dutch workforce, employees reportedly spend 7 hours engaged in sedentary behavior (Jans et al, 2007); this fact alone is cause for alarm, as it reflects a clear negative impact on physical and cognitive health (Lee et al, 2012; Owen et al, 2010; Voss et al, 2014).

The average Dutch male consumes 2390-2647 kcal per day, and the average Dutch woman consumes 1849-1956 kcal per day; these values are in accordance with the national guidelines for energy intake. However, only 70% of Dutch adults over the age of 30 eat breakfast on a daily basis. On average, Dutch adults consume 127 grams of vegetables and 97 grams of fruit (and 80 grams of fish on days in which fish is consumed); older women tend to have the healthiest dietary patterns, and younger men tend to have the unhealthiest dietary patterns (van Rossem et al, 2011). Approximately 90%, 84%, and 70-80% of Dutch adults do not meet the nutritional guidelines for consuming vegetables, fruit, and fish, respectively. Finally, it is estimated that 5.2% of total disease burden can be attributed to obesity (Hoeymans et al, 2014).

From the year 2000 to 2013, the prevalence of smoking among Dutch adults has declined from 30.6% to 19%, and this decrease can be attributed primarily to several large public health policy changes implemented by the Dutch national government (Verdurmen et al, 2014). However, 13.1% of total disease burden can be attributed to smoking cigarettes (Hoeymans et al, 2014). Nagelhout and colleagues estimated that from 2011 to 2040, one million Dutch citizens will die of smoking-attributable deaths, and nearly 15% of these deaths might be prevented by introducing an appropriate set of tobacco-controlling laws (Naghelout et al, 2012).

Approximately one in ten Dutch adults between the ages of 40 and 65 are considered heavy drinkers (van Laar et al, 2013). However, although the prevalence of heavy drinkers has decreased steadily since 2001, more than 80% of Dutch adults between the ages of 40 and 65 drink alcohol, and 2.9-4.5% of the Dutch population suffer from

alcohol dependency (van Laar et al, 2013). As more data emerges supporting the putative 'J-shaped' association between alcohol consumption and (for example) cardiovascular health and all-cause mortality becomes available, researchers struggle with the 'right' recommendations (Bellavia et al, 2014). In total, 2.8% of the total disease burden may be attributed to alcohol consumption (Hoeymans et al, 2014).

Insomnia – although less prevalent in the Netherlands compared to most European countries – is a problem in the Netherlands; the prevalence of insomnia in the Dutch workforce is approximately 14%, with peak prevalence among adults between the ages of 45 and 64 (Narayanan et al, 2009).

In the Netherlands, one in three cases of absenteeism from work is caused by work-related stress, making working-related stress the leading occupational disease in this country. One in ten employees has been absent from work for two consecutive weeks due to work stress-related issues, making these employees more vulnerable to depression and anxiety disorders (Hoeymans et al, 2014; Hupkens, 2004).



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