Top-funded digital health companies offering lifestyle interventions for dementia prevention: Company overview and evidence analysis

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Abstract

Background and objective

Dementia prevention has been recognized as a top priority by public health authorities due to the lack of disease modifying treatments. In this regard, digital dementia-preventive lifestyle services (DDLS) emerge as potentially pivotal services, aiming to address modifiable risk factors on a large scale. This study aims to identify the top-funded companies offering DDLS globally and evaluate their clinical evidence to gain insights into the current state of the global service landscape.

Methods

A systematic screening of two financial databases (Pitchbook and Crunchbase) was conducted. Corresponding published clinical evidence was collected through a systematic literature review and analyzed regarding study purpose, results, quality of results, and level of clinical evidence.

Findings

The ten top-funded companies offering DDLS received a total funding of EUR 128.52 million, of which three companies collected more than 75%. Clinical evidence was limited due to only nine eligible publications, small clinical subject groups, the absence of longitudinal study designs, and no direct evidence of dementia prevention.

Conclusion

The study highlights the need for a more rigorous evaluation of DDLS effectiveness in today's market. It serves as a starting point for further research in digital dementia prevention.

Introduction

According to the World Health Organization (WHO), more than 55 million people worldwide currently suffer from dementia, and projections indicate a rise to 78 million in 2030 and a staggering 139 million people in 2050 (1). With a global prevalence of 6.9% in the age group above 65 years, dementia has become one of the leading causes of care dependence in old age and the seventh leading cause of global deaths (1).

The social and economic effects of dementia are severe, where a person with dementia (PWD) is significantly more likely to be hospitalized and have a substantially higher average length of stay in hospitals (2). In 2019, dementia incurred an estimated global cost of over USD 1.3 trillion, translating to approximately USD 24,000 per PWD (1). Informal care provided by family members, friends, and neighbors makes up almost 50% of total dementia-associated costs (1). Caregivers are often referred to as “invisible second patients” as they have a higher likelihood of experiencing depression and anxiety (3), along with an increased risk of developing cardiovascular diseases (4) due to their caregiving duties. To address the social and economic ramifications of dementia, modern societies must strengthen their capabilities of dementia prevention by leveraging scalable and cost-effective approaches. Amid the global demographic shift and increasing labor shortage in healthcare (5), digital health interventions (DHIs) could play a central role in prevention and in delivering scalable, personalized, and evidence-based interventions (6).

Since no effective treatments for dementia are available, prioritizing prevention strategies becomes a public health priority. Although dementia risk is strongly correlated with age, studies indicate that lifestyle significantly influences individuals’ susceptibility to developing the condition later in life (7). Modifiable risk factors that directly influence dementia risk include, among others, physical activity, diet, and cognitive training (8,9). It is estimated that 30% of all

Alzheimer's disease (AD) cases could be prevented through the targeted change of these modifiable risk factors (10). The WHO confirms the important role of prevention by making the capacity improvement of healthcare professionals for the proactive management of modifiable risk factors a main target in its global action plan against dementia (11).

DHIs are part of the broader concept of Digital Health and pose new opportunities to bridge the gap in care access and quality in health systems (12–14). They offer various benefits to all actors in the system (14) and an increasing body of evidence in various disease domains suggests positive effects of DHIs on costs and health outcomes (6).

Against the background of upcoming demand for digital dementia-preventive lifestyle services (DDLS) and an increasing number of companies in the field of DHIs, this study aims to comprehensively identify and analyze companies offering DDLS by answering the following research questions:

RQ1. What are the globally top-funded digital dementia-preventive lifestyle services?

RQ2. What is the clinical evidence of the identified solutions?

Materials and methods

In this section, we present the methodologies of two studies we conducted against the research questions. Following the procedure described in Safavi et al. (2019), study 1 provides an identification of DDLS companies through market screening, and study 2 provides an evidence analysis of published clinical studies by identified companies. This methodological approach provides us with the current state of clinical validation of the top funded DDLS companies (15) and is characterized by a continuous peer reviewing process to ensure reliable and credible results (16).

Study 1: Company Overview

Search Strategy

To ascertain the globally top funded DDLS, this study combined data extraction from two leading financial databases, Pitchbook and Crunchbase, augmented by supplementary web searches on Google. This multi-pronged approach ensured a broad capture of the landscape, identifying enterprises with significant funding aimed at dementia prevention through digital lifestyle interventions. The search strategy was refined through an iterative process among the co-authors, with keywords in three categories: "Verticals, methods, and industries", "Dementia", and "Management and prevention". Due to limited keyword search masks in Crunchbase, "Dementia" and "Management and prevention" categories were merged. **S1 & S2 Tables** provide the selected search strategies and keywords used in both databases, which defer due to differences in the search functions of the two databases, where Crunchbase did not utilize OR/AND operators, and only predefined industries could be selected.

Inclusion & Exclusion Criteria

The inclusion criteria were stringently designed to focus on digital health technologies directly targeting patients or consumers with interventions capable of potentially modifying lifestyle factors associated with dementia risk. Essential for inclusion were technologies that demonstrated a clear application towards dementia prevention, articulated through their digital solutions. Exclusion criteria were carefully applied to omit companies not directly targeting dementia risk, lacking in necessary detail, lacking funding information, or not providing solutions in English, ensuring a focus on globally applicable and accessible services.

Selection Process

An intricate screening process ensued, beginning with the elimination of duplicates and a thorough review of database entries and company websites. Each company was evaluated

against the inclusion and exclusion criteria by a dedicated researcher (JP), with a subsequent independent review by a second researcher to ensure thoroughness and reliability (MN). Disagreements were solved through discussion and the interrater reliability was assessed through the calculation of the Cohen's kappa coefficient. This two-tiered review process was augmented by expert feedback, soliciting insights from academicians and industry specialists in dementia care and prevention. Experts were invited to assess the preliminary list and suggest additional companies, further enriching the dataset.

Data Collection

Based on previous research (15), the following data points were collected via Pitchbook (as available by January 30, 2023): Year founded, headquarter location, total amount raised, last financing size, last financing date, last financing type, years of funding rounds, number of financing rounds, number of investors and number of employees. Considered financing rounds included all deal types (Angel, Seed, Early-Stage VC, Later Stage VC, Equity Crowdfunding, PE Growth/Expansion, Corporate, Joint Venture, M&A) and were only included if completed by January 30, 2023. In case of unavailable funding information, corresponding information was retrieved from the Crunchbase database, or further from publicly available news articles to identify the last financing size as indicator for the overall funding amount.

Sample Characteristics

The search iteration yielded a cumulative outcome of 605 total results (Pitchbook: 341, Crunchbase: 262, Google: 2), and 16 duplicates were removed. The screening of the database company descriptions resulted in further exclusion of 573 additional companies. Out of the remaining 16 companies, funding information could not be obtained for one. In the collaborative coding process according to the pre-defined set of inclusion and exclusion criteria, six companies were excluded. The final list of nine companies were reviewed by four experts

who suggested 15 additional companies for review. On a scale of one (no expertise) to five (extremely high expertise), the experts assessed their market expertise at an average score of 2.6. Of those 15 expert-suggested companies, two were already included from the database results, and 12 were excluded in the collaborative coding process. This process provided us with a list of nine companies from the database search, and one company through expert feedback, resulting in a total of 10 companies (see **Figure 1**). The Cohens' kappa coefficient prior to expert validation was k_I=0.857 (93% agreement), and after expert validation was k_E=0.66 (86.6% agreement). These values align with a strong and moderate level of agreement (17), consequently establishing the reliability of the results.

[INSERT FIGURE 1 HERE]

Figure 1. Flow diagram for the included DHIs for the prevention of dementia in the systematic market analysis.

Data Analysis

Company data was extracted and analyzed with descriptive statistics by one researcher (JP).

Study 2: Evidence Analysis

Search Strategy

Peer-reviewed publications were identified by searching Google Scholar and PubMed for the company name and by retrieving study references on corresponding company websites as available by April 18, 2023. In case the name of the solution differed from the company name, databases were searched for both names using the OR boolean operator. If necessary (due to an unmanageable number of search results), Google Scholar searches were further limited through the publishing date after founding year of the corresponding company and/or with the keyword "Dementia" (using the AND operator), as additional search requirements.

Inclusion & Exclusion Criteria

Identified studies were sought to be relevant if they were peer-reviewed publications that examine the potential effects of the identified solutions on clinical outcome, cost, or access to care in dementia care or dementia prevention (15). Exclusions were made for studies on non-dementia conditions (e.g., Parkinson's disease), non-risk groups (e.g., healthy individuals), non-English publications, protocols, proof-of-concept works, systematic reviews, or commentaries, due to their irrelevance for dementia prevention.

Selection Process

After the removal of duplicates, title and abstract screening of publications was conducted by one author (JP), and full-text review was conducted by two authors (JP and MN). In case of disagreements, consensus was achieved through discussion. Interrater reliability was again assessed through the calculation of the Cohen’s kappa.

Data Collection

In line with the procedure described in (15), publications were analyzed for evidence level, the number of clinical subjects, the purpose of the study, target condition or risk factor (if specifically targeted), and the demonstrated effect as per U.S. Preventive Services Task Force (USPSTF). USPSTF levels of evidence are: Level 1 (good) with at least one randomized trial, Level 2 (fair) includes non-randomized or well-designed studies, and Level 3 (poor) consists of expert opinions or descriptive studies (15).

The purpose of this categorization was to classify studies as: effectiveness, validation, or other studies. In the coding process, the journal and paper type, trial registration, and demonstrated changes in utilized proxies were retrieved in addition to the data from prior research (15). Moreover, on a scale of 1 (low) to five (high), subjective quality assessment scores (referring to the relevance for answering the research question), were assigned to each study.

Sample Characteristics

1,890 publications were identified from database search. After removing 129 duplicates, 1,784 unique articles underwent title and abstract screening. 1,693 articles were excluded based on the inclusion and exclusion criteria. After full-text review, 82 articles were further excluded, for instance, due to a missing relation to the identified companies or products (n=23), systematic reviews (n=19), or missing focus on dementia (n=13). Nine articles were deemed eligible for evaluation of clinical evidence (see **Figure 2**). A Cohens' kappa coefficient of k_0=1 was determined during the full-text review, while the following coding-based analysis led to an initial k_1= 0.57 (77% agreement) and a k_2=1 (100% agreement) after discussion.

[INSERT FIGURE 2 HERE]

Figure 2. Flow diagram for the included publications in the evaluation of clinical evidence.

Data Analysis

Data extraction and analysis was conducted by two authors (JP, MN) and followed a one-cycle coding process based on previously introduced publication-related aspects (15). In case of disagreement, consensus was reached through discussion and interrater reliability was reported.

Results

Top Funded Digital Health Technology Companies Offering Dementia Preventive Lifestyle Services

The systematic search and rigorous selection process culminated in identifying 10 DDLS companies (cf. **Table 1**), collectively amassing EUR 128.52 million in funding. This remarkable funding concentration, predominantly within three companies (more than 75% of the total funding), underscores the competitive and uneven landscape of digital dementia prevention initiatives. The diversity in the years of establishment among these companies

highlights an evolving field (i.e., 1999 – 2021), with both longstanding entities and new entrants driving innovation in dementia preventive services.

Geographical analysis revealed a significant European presence among the top-funded companies, alongside notable representations from North America and Asia. This geographical distribution emphasizes the global interest in digital solutions for dementia prevention, transcending regional boundaries to address a universal public health challenge. **Table 1** provides a summary of the 10 identified DDLS companies.

Table 1. List of all identified solutions that correspond with the pre-defined set of inclusion/exclusion criteria. (Extracted company and funding data is per January 30, 2023).

#	Company	Year founded	Total number of employees	Total funding (mEUR)	Year of last funding
1	Neurotrack	2012	41	50.21	2022
2	Constant Therapy Health	2013	19	29.35	2017
3	NeuroNation	2011	25	19.06	2021
4	Emogoc	2021	30	13.31	2022
5	Cognifit	1999	55	6.21	2022
6	Five Lives	2019	36	6.18	2022
7	MindStep	2017	25	3.31	-**
8	Luci	2017	25	>= 0.47*	-**
9	OptiChroniX	2019	7	0.32	2022
10	Beynex	2020	6	0.1	2023
	Average	2015	27	12.85	2021

*Note: *Unable to retrieve total funding information, thus it is possible that the overall funding is higher; **No information regarding last funding round available*

A deeper dive into the business models and funding mechanisms of these entities revealed a rich tapestry of strategies aimed at sustainability and growth. Direct-to-patient models emerged as a prevalent approach, reflecting a direct engagement strategy with end-users. However, the

pursuit of insurance reimbursements, partnerships with insurers, and the ambition for governmental collaborations indicate a nuanced approach towards securing a broad base of support and legitimacy. Moreover, the strategic utilization of aggregated data for research signifies a forward-thinking approach to creating value beyond direct service provision.

The intervention strategies deployed by these companies exhibited a keen focus on cognitive engagement, aligning with contemporary understanding of lifestyle factors in dementia risk. However, the breadth of interventions varied, with some companies offering comprehensive platforms that address multiple lifestyle domains, demonstrating a holistic approach to dementia prevention. The integration of clinical insights and customizable treatment plans underscored a trend towards personalized, patient-centric services, enhancing the potential impact of these digital interventions.

Evidence Analysis

The analysis of nine publications revealed a skewed distribution of evidence across three companies: Cognifit (five publications), Beynex, and Constant Therapy Health (two each). This indicates that 7 out of 10 identified DDLS provided no evidence meeting our criteria. No direct link was found between a company's funding and its number of relevant publications. Despite Constant Therapy Health's significant funding (EUR 29.3 million), it did not lead in publication count, while Beynex, with only EUR 0.1 million in funding, matched its output.

The publication dates of studies ranged from 2013-2022. Eight studies were published as papers in journals and one as a poster presentation at a conference. Five publications are indexed in PubMed and six are published in papers with an assigned journal impact score (JIS). With an average JIS of 4.29, the lowest journal had a JIS of 2.31 and the highest 6.591. Three of the studies were officially registered trials, and three others were IRB approved and/or a published study protocol.

Out of nine studies, five did not fit the Clinical Effectiveness or Validation categories as previously defined (15), including three feasibility studies and two comparing interventions in tailored vs. untailored settings. Three studies aimed at clinical outcomes, focusing on clinical outcomes, and one validated outcomes against another solution. Seven publications showed level 1 evidence according to the criteria of the USPSTF, meaning that evidence was generated through at least one randomized-controlled trial. Out of all the publications, only one demonstrated level 2 evidence, while another publication presented level 3 evidence.

Average participation was n=59, ranging from n=2 to n=122, with most studies (7 out of 9) involving n<100 participants. Six of the studies targeted a study population with a condition and only two targeted participants with a disease risk factor. The most common targeted condition was Subjective Mild Cognitive Impairment (SMCI) and Mild Cognitive Impairment (MCI) itself, followed by dementia, primarily encompassing Alzheimer's disease (AD). The two targeted risk factors included diabetes and old age. None of the studies demonstrated any change in the targeted condition or risk factor.

Except for 1 study, all studies demonstrated shifts in study proxies, mainly showing improved cognitive and memory functions (see **Table 2**). Overall, the quality of the analyzed publications was assessed as rather mediocre with an average subjective quality score of 3.

274 **Table 2.** List of all included publications that correspond with the pre-defined set of inclusion/exclusion criteria. Different coloring represents company affiliation of study.

#	Company	Reference	Purpose	# clinical subjects	Condition / risk factor targeted	Change in incidence	Change in proxy	Level of evidence	Publi-cation quality
1	Beynex	(18)	Clinical effectiveness	120	– AD – Subjective memory complaint	No	Improved MoCA scores Bayer-ADL scores indicated improvement in ADL.	1	1
2	Beynex	(19)	Clinical effectiveness	60	Subjective CI	No	Improved memory related cognitive parameters	1	1
3	Cognifit	(20)	Other (Tailored / untailored setting for subjects & self-efficacy / no self-efficacy)	84	Diabetes	No	Improved global cognition and memory composite scores	1	4
4	Cognifit	(21)	Other (Tailored / untailored setting for subjects)	44	– MCI – MrNPS	No	Improved performance on composite measures of global cognition, learning, delayed episodic memory	1	4
5	Cognifit	(22)	Validation	47	CI	No	Improved performance of global cognition, working memory, divided attention, processing speed	1	4
6	Cognifit	(23)	Other (feasibility combined with effectiveness)	18	– Episodic memory dysfunction – MCI	No	Improved working memory and speed	2	3
7	Cognifit	(24)	Clinical effectiveness	122	Old age	No	Improved visual-spatia information processing, visual scanning, global visual memory, naming, hand-eye coordination, visuospatial learning, and visuospatial working memory	1	5
8	Constant Therapy	(25)	Other (feasibility)	2	Dementia	No	No	3	2
9	Constant Therapy	(26)	Other (feasibility)	19	AD	No	Improved visual & auditory memory, attention, arithmetic, processing speed, adaptability	1	3
			Average	59					3

Discussion

The aim of this work was to not only identify the globally top-funded DDLS but to also analyze the corresponding body of published clinical evidence. 10 companies with a total funding of EUR 128.52 million, headquartered in eight different countries have been identified. Funding ranged from EUR 0.1 million to EUR 50.21 million, with the top two companies accounting for over half of the total funding. No clear correlation between a company's founding year and its funding was found.

Clinical evidence meeting our criteria was scarce, with only nine studies from three companies found. Many studies did not focus on clinical effectiveness or validation, three focused on feasibility, three on clinical effectiveness, and one on validation against alternatives. Most studies involved subjects with MCI or AD, with only two targeting subjects at risk. While 78% of the studies used randomized-controlled trials, sample sizes were small, and findings mainly showed changes in proxies rather than direct impacts on targeted conditions.

Interpretation of Results

Companies offering DDLS

The aging global population is making the social and economic impacts of dementia increasingly severe, with the WHO highlighting the urgency of prevention through lifestyle changes (1,11), and the provision of digital health interventions (DHIs) could significantly contribute to those efforts. Despite this, DHIs for dementia prevention seem underfunded compared to other areas, such as depression DHIs, which received more funding for the fifth-best funded initiative than all analyzed dementia companies combined (27). The impression of low overall funding of DDLS companies is confirmed when considering the staggering USD 23,796 estimated global societal cost of dementia per person with dementia in 2019 (28).

Since the underlying reasons for those findings are beyond the scope of this study, it should rather briefly be touched upon potential causes: A potential explanation are the relatively young medical findings that set the foundation for the offered interventions. A landmark study showed the positive impact of a multi-domain lifestyle intervention on dementia risk in 2015 and thus is not much older than a major part of the identified companies (29). On the other side, however, many of the identified companies strongly leverage brain games as a way to foster cognitive engagement. The idea of utilizing cognitive training to prevent or delay dementia has been widely discussed before (30–33). The companies' recent establishment may explain the modest funding levels, challenging the assumption that funding correlates with company age. Monetization uncertainties and the prevalence of local champions, suggesting a fragmented market with limited global commercial potential, could also impact funding. These hypotheses underscore the need for further research in this area.

Clinical Evidence

The limited number of publications meeting our criteria, primarily from just three companies, is unexpected. This is particularly striking considering the companies' professed strong scientific orientation and their extensive citation of scientific papers on their websites (34–39). Besides the challenging application of traditional evidence generation methods in Digital Health (40), a potential reason for this could be the relatively low funding of the identified companies since the conducting of clinical studies is associated with substantial financial costs (41). Despite Beynex's low financing, it managed to produce two eligible studies, indicating no strong link between a company's funding and its research output, aligning with previous research findings (27). The lack of publications may also be due to the young age of the companies. Many studies are still underway and unpublished. This could also explain why some solutions are preliminarily accepted for insurance reimbursement, like NeuroNation, without meeting the eligibility criteria. Finally, the drive for clinical research may be influenced by

companies' revenue models: As a large proportion of solutions are also directly targeted at uninformed patients through marketing and sales activities, trials may be less demanded from a target audience perspective.

The prominence of companies focusing on cognitive engagement through brain exercises (Constant Therapy Health, Cognifit, Beynex) in our findings is notable. Brain training has been a significant research focus, making it more probable for these solutions to have accumulated evidence. Cognifit, the oldest company (founded in 1999), leads with five publications, including two from 2013 (42). However, the newer companies, founded in 2013 (i.e., Constant Therapy Health) and 2020 (i.e., Beynex), along with the more recent average publication year of 2020 for remaining studies, suggest another reason for this trend. By requiring subjects to perform only game-based brain training with relatively little effort (compared to changing diet and exercise habits), drop-out rates could be lower, adherence rates higher, the trial more manageable and short-term effects potentially faster to detect. Thus, the failure rate of those studies is lower (43) and the overall risk due to extensive existing research diminished.

The evidence quality from the limited publications is mediocre, with most studies using randomized-controlled trials (evidence level 1 according to previously determined research (15), but involving small groups and showing changes only in utilized proxies. Solutions aimed at reducing the risk of MCI progressing to AD targeted subjects with MCI but only showed improved cognitive performance, not prevention of conversion. A potential reason for this could be the additional financial and non-financial resources necessary to conduct longitudinal studies at a large-scale.

The low number of scientific studies and identified methodological issues are in line with previous findings (44), where researchers systematically analyzed clinical evidence of mobile health solutions for people suffering from dementia and their relatives. On this basis, it was

concluded that there is no evidence for the clinical effectiveness of the analyzed solutions (44). Considering the few publications and their methodological limitations, this work suggests an insufficiency of evidence for the effectiveness of top funded global DDLS.

Theoretical Contributions

Overall, the results align with the complex definitions found in existing literature. Despite clear theoretical guidelines for analysis, comparing services highlights blurred distinctions between terms. Notably, a managerial aspect supports clinicians with non-clinical tasks, such as documentation, following the Digital Medicine Society (DiMe)'s framework (45). This indicates that digital health components can be part of digital medicine offerings, challenging the clear differentiation suggested by initial terminology. This relates to strategies like those of Constant Therapy Health and Cognifit, which aim to integrate into existing care processes rather than just complement them, raising questions about the adequacy of assumed definitions and the potential need for new concepts.

The foundation of DHIs is notably their evidence base. The results of the systematic review found that evidence supporting identified DDLS is scarce, with many companies focusing on general reviews rather than assessing their products' clinical effectiveness or comparing them to other interventions. This highlights a need for more precise definitions within DHI and Digital Medicine fields. While it is challenging to reclassify these solutions as merely lifestyle or wellness apps without medical relevance, the current definitional framework lacks specificity. A more holistic approach to classification is suggested, one that not only evaluates evidence but also considers business models, offering a broader perspective on DHIs' role and impact. In addition to the previously mentioned benefits of clarity of definitions, this could also further strengthen the bridge between the role of evidence generation and business model building and scaling in digital health: When digital medicine companies operate at the

crossroads between regular technology companies and pharmaceutical companies, obtaining clinical evidence is paramount (46).

Clinical Implications

The current manuscript undertakes a critical exploration into the realm of DDLS, scrutinizing the clinical evidence that underpins these emerging interventions. This inquiry is paramount, not only due to the growing investments and interest in DHIs aimed at staving off dementia but also because it addresses a significant gap in existing literature. The pressing need for effective dementia prevention strategies, in the absence of disease-modifying treatments, underscores the importance of this study.

Evaluating the relevance and novelty of this research, it becomes evident that it fills an essential void by systematically identifying and analyzing the top funded companies within the DDLS domain. This approach not only sheds light on the current landscape of digital interventions but also critically assesses the extent and quality of clinical evidence supporting their efficacy. In doing so, the study brings forth new perspectives on the role of digital health in preventing dementia, challenging existing paradigms by questioning the robustness of the purported benefits of these interventions.

The study's findings on the limited clinical evidence supporting the efficacy of DDLS highlight the urgent need for more rigorous and longitudinal research in this area. Such evidence is crucial for informing clinical guidelines, shaping public health policies, and guiding future research directions. The identification of this gap not only signals the necessity for further empirical inquiry but also posits the manuscript as a cornerstone for subsequent investigations aimed at validating and enhancing the clinical utility of digital interventions for dementia prevention.

Moreover, the interdisciplinary nature of the manuscript, which intersects medical science, digital technology, and health policy, exemplifies the complex and multifaceted approach required to tackle dementia prevention. The manuscript's exploration of the funding dynamics and the technological underpinnings of the DDLS, coupled with its analysis of clinical evidence, reflects a comprehensive understanding of the ecosystem surrounding DHIs for dementia. This interdisciplinary perspective is vital for devising holistic and effective prevention strategies that can be seamlessly integrated into public health frameworks and clinical practice.

The manuscript also acknowledges the paramount importance of patient and public involvement in the research and development of DDLS. This recognition aligns with contemporary research ethics, emphasizing the co-creation of health interventions that are not only scientifically sound but also resonate with the needs, preferences, and realities of those they aim to serve. Such an approach not only enhances the relevance and applicability of research findings but also ensures that digital health interventions are grounded in the lived experiences of individuals at risk of dementia, thereby maximizing their potential impact.

Lastly, the manuscript's call for transparency and availability of data is a testament to its commitment to the principles of open science. By advocating for the unrestricted sharing of research data and methodologies, the study sets a standard for future research in the field, facilitating the replication and validation of findings, and fostering a collaborative research environment that accelerates the advancement of knowledge and the development of effective dementia prevention strategies.

In summary, the clinical implications of this manuscript extend beyond the mere analysis of current DDLS. It lays the groundwork for future research, encourages interdisciplinary collaboration, and underscores the importance of patient and public involvement in the creation

of DHIs. Furthermore, it champions the principles of transparency and open science, essential for the robust, ethical, and impactful advancement of dementia prevention research.

Limitations

One limitation of the global market analysis is its focus on English-language solutions, excluding companies targeting non-English markets, potentially overlooking well-funded entities. Additionally, only companies with publicly available funding information were analyzed, possibly omitting other significant players. Data completeness also affects the accuracy of funding-based rankings, as market intelligence databases may not have full funding details.

The publication analysis has two main limitations in relation to our second research question. Firstly, strict inclusion and exclusion criteria meant that studies on assessment/or diagnostic tools and those not focused on dementia prevention were excluded, possibly indicating a lack of clinical evidence for the companies reviewed. Second, while study duration was considered, the specific length of interventions wasn't, leaving some potential explanations unexplored. Finally, our analysis did not compare the clinical effectiveness of the solutions directly but evaluated the quality and results of each study independently, without comparing them to one another.

Suggestions for Future Research

Despite the promising strides in developing and funding DDLS, the study highlighted a critical gap in the clinical evidence underpinning these interventions. The limited scope of published studies, small participant groups, and the absence of longitudinal research point to an emergent field still grappling with establishing a robust evidence base. The disconnect between the proliferation of funded initiatives and the paucity of rigorous clinical validation underscores the

nascent stage of digital interventions in dementia prevention, marking a crucial area for future research and development.

Avenues for further research also include the screening of the global landscape with a focus on local champions, since the identification process showed that there are several highly interesting solutions which are only offered in a local language and setting. This research may open new possibilities for studying the blending of lifestyle interventions into local surroundings like hiking areas (physical activity) or community clubs (cognitive engagement). This could significantly contribute to the development of best practice reference models in the field of clinical evaluation itself as well as company building and business model development as a whole.

Acknowledgements

A substantial part of work has been conducted by JP as part of his master's thesis at the University of St. Gallen.

Conflict of interest

RV, PH, TK, and MN are affiliated with the Centre for Digital Health Interventions (CDHI), a joint initiative of the Institute for Implementation Science in Health Care, University of Zurich, the Department of Management, Technology, and Economics at the ETH Zurich, and the institute of Technology Management and School of Medicine at the University of St. Gallen. CDHI is funded in part by CSS, a Swiss health insurer, Mavie Next, an Austrian healthcare provider and MTIP, a Swiss investor company. TK is also a co-founder of Pathmate Technologies, a university spin-off company that creates and delivers digital clinical pathways. However, neither CSS nor Pathmate Technologies, Mavie Next, or MTIP was involved in this research. All other authors declare no conflict of interest.

References

1. World Health Organization. Global status report on the public health response to dementia [Internet]. 2021 [cited 2024 Mar 13]. Available from: https://www.who.int/publications/i/item/9789240033245

2. Zhu CW, Cosentino S, Ornstein K, Gu Y, Andrews H, Stern Y. Use and cost of hospitalization in dementia: longitudinal results from a community-based study. Int J Geriatr Psychiatry. 2015 Aug 29;30(8):833–41.

3. Mahoney R, Regan C, Katona C, Livingston G. Anxiety and Depression in Family Caregivers of People With Alzheimer Disease: The LASER-AD Study. The American Journal of Geriatric Psychiatry. 2005 Sep;13(9):795–801.

4. Xu XY, Kwan RYC, Leung AYM. Factors associated with the risk of cardiovascular disease in family caregivers of people with dementia: a systematic review. Journal of International Medical Research. 2020 Jan 22;48(1):030006051984547.

5. World Health Organization. Global strategy on human resources for health: Workforce 2030 [Internet]. 2016 [cited 2024 Mar 13]. Available from: https://apps.who.int/iris/bitstream/handle/10665/250368/9789241511131-eng.pdf

6. Gentili A, Failla G, Melnyk A, Puleo V, Tanna GL Di, Ricciardi W, et al. The cost-effectiveness of digital health interventions: A systematic review of the literature. Front Public Health. 2022 Aug 11;10.

7. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's & Dementia. 2015 Jun 31;11(6):718–26.

8. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet [Internet]. 2020 Aug 8 [cited 2024 Mar 27];396(10248):413–46. Available from: http://www.thelancet.com/article/S0140673620303676/fulltext

9. Veronese N, Soysal P, Demurtas J, Solmi M, Bruyère O, Christodoulou N, et al. Physical activity and exercise for the prevention and management of mild cognitive impairment and dementia: a collaborative international guideline. Eur Geriatr Med [Internet]. 2023 Oct 1 [cited 2024 Mar 27];14(5):925. Available from: /pmc/articles/PMC10587099/

10. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014 Aug;13(8):788–94.

11. World Health Organisation. Global action plan on the public health response to dementia [Internet]. 2017 [cited 2023 Jul 14]. Available from: https://www.who.int/publications/i/item/global-action-plan-on-the-public-health-response-to-dementia-2017---2025

12. World Health Organization. WHO guideline: recommendations on digital interventions for health system strengthening [Internet]. 2019 [cited 2024 Mar 13]. Available from: https://www.who.int/publications/i/item/9789241550505

13. Jacobson N, Kowatsch T, Marsch L, editors. Digital Therapeutics for Mental Health and Addiction. 1st ed. Elsevier, Academic Press; 2023.

14. Kowatsch T, Fleisch E. Digital Health Interventions. In: Connected Business. Cham: Springer International Publishing; 2021. p. 71–95.

15. Safavi K, Mathews SC, Bates DW, Dorsey ER, Cohen AB. Top-Funded Digital Health Companies And Their Impact On High-Burden, High-Cost Conditions. Health Aff. 2019 Jan;38(1):115–23.

16. Janesick VJ. Peer Debriefing. In: The Blackwell Encyclopedia of Sociology. Wiley; 2015.

17. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276–82.

18. Çinar N, Sahiner TAH. Effects of the online computerized cognitive training program BEYNEX on the cognitive tests of individuals with subjective cognitive impairment and Alzheimer's disease on rivastigmine therapy. Turk J Med Sci [Internet]. 2020 Jan 1 [cited 2024 Mar 26];50(1):231–8. Available from: https://journals.tubitak.gov.tr/medical/vol50/iss1/31

19. Sahiner TAH, Cınar N. TD-P-002: EFFECTS OF ONLINE COMPUTERIZED COGNITIVE TRAINING PROGRAM BEYNEX ON THE COGNITIVE TESTS OF INDIVIDUALS WITH SUBJECTIVE COGNITIVE IMPAIRMENT (SCI). Alzheimer's & Dementia [Internet]. 2018 Jul 1 [cited 2024 Mar 26];14(7S_Part_3):P186–P186. Available from: https://onlinelibrary.wiley.com/doi/full/10.1016/j.jalz.2018.06.2018

20. Bahar-Fuchs A, Barendse MEA, Bloom R, Ravona-Springer R, Heymann A, Dabush H, et al. Computerized Cognitive Training for Older Adults at Higher Dementia Risk due to Diabetes: Findings From a Randomized Controlled Trial. The Journals of Gerontology: Series A [Internet]. 2020 Mar 9 [cited 2024 Mar 26];75(4):747–54. Available from: https://dx.doi.org/10.1093/gerona/glz073

21. Bahar-Fuchs A, Webb S, Bartsch L, Clare L, Rebok G, Cherbuin N, et al. Tailored and Adaptive Computerized Cognitive Training in Older Adults at Risk for Dementia: A Randomized Controlled Trial. Journal of Alzheimer's Disease. 2017 Jan 1;60(3):889–911.

22. Embon-Magal S, Krasovsky T, Doron I, Asraf K, Haimov I, Gil E, et al. The effect of co-dependent (thinking in motion [TIM]) versus single-modality (CogniFit) interventions on cognition and gait among community-dwelling older adults with cognitive impairment: a randomized controlled study. BMC Geriatr [Internet]. 2022 Aug 31 [cited 2024 Mar 26];22(1):720. Available from: https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-022-03403-x

23. Gigle KL, Blomeke K, Shatil E, Weintraub S, Reber PJ. Preliminary evidence for the feasibility of athome online cognitive training with older adults. Gerontechnology. 2013;12(1):26–35.

24. Shatil E. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. Front Aging Neurosci. 2013 Mar 26;5(MAR):41237.

25. Edgar DL, Bargmann PL. Clinical Study of the Effectiveness of Constant Therapy in the Treatment of Clients With Dementia: Implications for Telepractice. Perspect ASHA Spec Interest Groups [Internet]. 2021 Jun 7 [cited 2024 Mar 26];6(3):691–703. Available from: https://pubs.asha.org/doi/10.1044/2021_PERSP-20-00123

26. Marin A, DeCaro R, Schiloski K, Elshaar A, Dwyer B, Vives-Rodriguez A, et al. Home-Based Electronic Cognitive Therapy in Patients With Alzheimer Disease: Feasibility Randomized Controlled Trial. JMIR Form Res [Internet]. 2022 Sep 12 [cited 2024 Mar 26];6(9):e34450. Available from: http://www.ncbi.nlm.nih.gov/pubmed/36094804

27. Salamanca-Sanabria A, Castro O, Alattas A, Teepe GW, Leidenberger K, Fleisch E, et al. Top-Funded Companies Offering Digital Health Interventions for the Prevention and Treatment of Depression: A Systematic Market Analysis (Preprint). JMIR Preprints. 2022;

28. Wimo A, Seeher K, Cataldi R, Cyhlarova E, Dielemann JL, Frisell O, et al. The worldwide costs of dementia in 2019. Alzheimer's & Dementia. 2023 Jul 8;19(7):2865–73.

29. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet. 2015 Jun;385(9984):2255–63.

30. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for persons with mild to moderate dementia of the Alzheimer's or vascular type: a review. Alzheimers Res Ther. 2013;5(4):35.

31. Clare L. Cognitive training and cognitive rehabilitation for people with early-stage dementia. Rev Clin Gerontol. 2003 Feb 29;13(01).

32. Galante E, Venturini G, Fiaccadori C. Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. G Ital Med Lav Ergon. 2007;29(3 Suppl B):B26-32.

33. Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and memory training in adults at risk of dementia: A Systematic Review. BMC Geriatr. 2011 Dec 25;11(1):55.

34. Neurotrack. Clinical Studies on Cognitive Screening and Intervention by Neurotrack [Internet]. [cited 2024 Mar 29]. Available from: https://neurotrack.com/science

35. NeuroNation. The science behind NeuroNation [Internet]. [cited 2024 Mar 29]. Available from: https://www.neuronation.com/science/en/science-behind-neuronation/

36. Five Lives. Behind the Science [Internet]. [cited 2024 Mar 29]. Available from: https://www.fivelives.health/science

37. Mindsteps. Concept [Internet]. [cited 2024 Mar 29]. Available from: https://www.mindsteps.ch/konzept/

38. Luci. Science [Internet]. [cited 2024 Mar 29]. Available from: https://lucilab.ca/en/science/

39. OptiChroniX. Fight Alzheimer, Lifestyle Medicines, Health Coach [Internet]. [cited 2024 Mar 29]. Available from: https://optichronix.com/science

40. Guo C, Ashrafian H, Ghafur S, Fontana G, Gardner C, Prime M. Challenges for the evaluation of digital health solutions—A call for innovative evidence generation approaches. NPJ Digit Med. 2020 Aug 27;3(1):110.

41. Bentley C, Cressman S, van der Hoek K, Arts K, Dancey J, Peacock S. Conducting clinical trials—costs, impacts, and the value of clinical trials networks: A scoping review. Clinical Trials. 2019 Apr 10;16(2):183–93.

42. Simons DJ, Boot WR, Charness N, Gathercole SE, Chabris CF, Hambrick DZ, et al. Do “Brain-Training” Programs Work? Psychological Science in the Public Interest. 2016 Oct 2;17(3):103–86.

43. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018 Sep;11:156–64.

44. Zeiler M, Chmelirsch C, Dietzel N, Kolominsky-Rabas PL. Wissenschaftliche Evidenz und Nutzerqualität von Mobile-Health-Anwendungen für Menschen mit kognitiven Beeinträchtigungen und deren Angehörige. Z Evid Fortbild Qual Gesundhwes. 2023 Apr;177:10–7.

45. Digital Medicine Society (DiMe). Defining Digital Medicine [Internet]. [cited 2024 Mar 13]. Available from: https://dimesociety.org/about-us/defining-digital-medicine/

46. Steinberg D, Horwitz G, Zohar D. Building a business model in digital medicine. Nat Biotechnol. 2015 Sep 1;33(9):910–20.

List of supplemental materials

S1 Table. Search categories and keywords for the Pitchbook search.

S2 Table. Search categories and keywords for the Crunchbase search.

Figure 1:

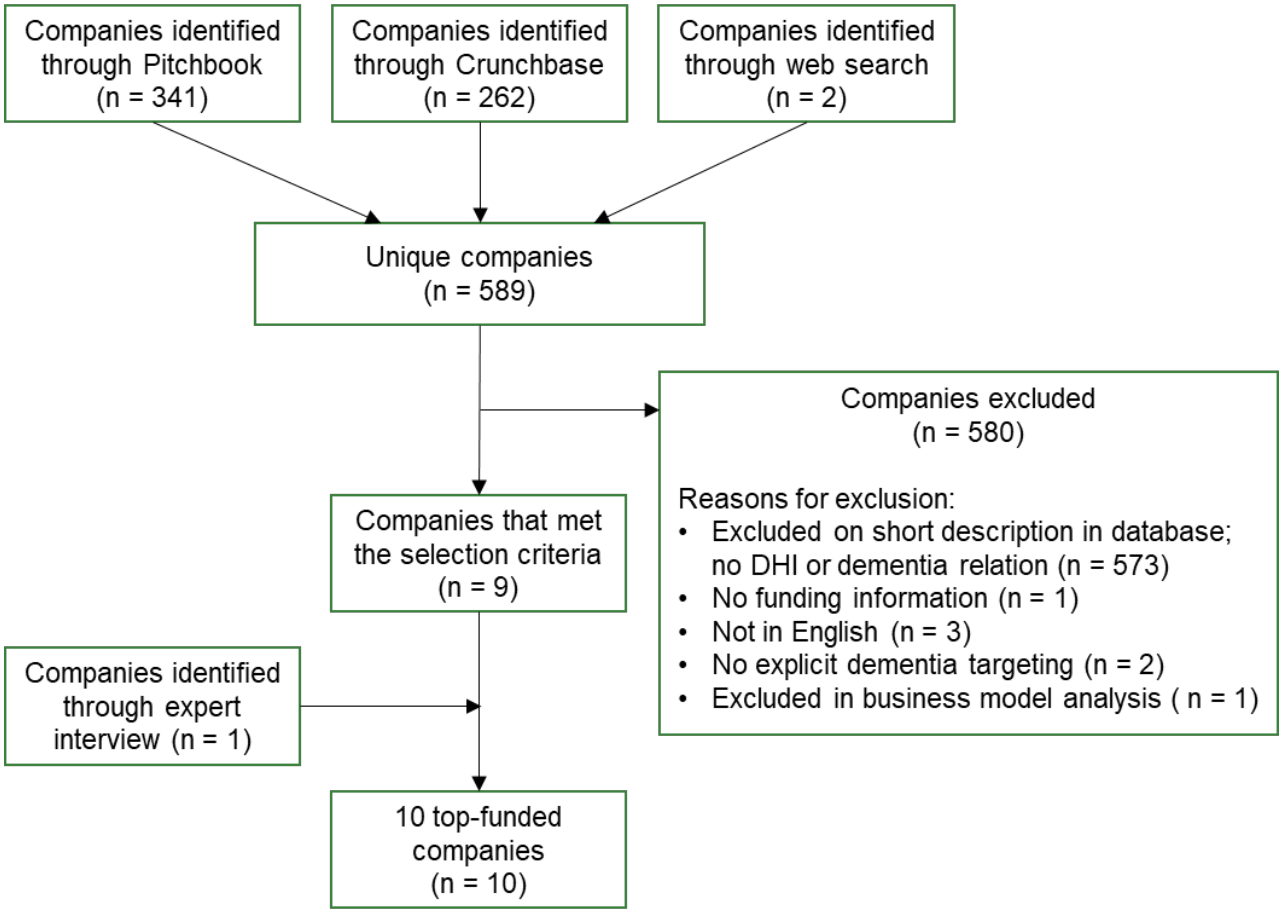

Figure 2: