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Lebensstilmanagement im frühen Stadium der Multiplen Sklerose

Entwicklung, Testung und Evaluation einer digitalen interaktiven und evidenzbasierten Lebensstilmanagementintervention zum Empowerment von Erstbetroffenen mit Multipler Sklerose

Dissertation

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I Synopse

Die vorliegende Dissertation ist das Ergebnis meiner Forschungsarbeit in der Multiple Sklerose (MS) Tagesklinik des Universitätsklinikums Hamburg-Eppendorf. Sie besteht aus drei veröffentlichten und zur kumulativen Dissertation angenommenen Publikationen sowie einer weiteren zur Publikation eingereichten Arbeit. Als Kern dieser Dissertation wurde zunächst eine interaktive und evidenzbasierte Lebensstilmanagementintervention („levidex“) für Erstbetroffene mit MS entwickelt und eine Machbarkeits- und Pilotstudie durchgeführt (1). Levidex vermittelt evidenzbasierte Patient:inneninformationen (EBPI) (2) sowie Hilfen zur Verhaltensänderung und soll als Ergänzung zur Standardversorgung von Erstbetroffenen mit MS eingesetzt werden. Das Ziel dieser Studie, an der erfahrene MS-Betroffene und MS-Expert:innen beteiligt waren, war die Entwicklung und Untersuchung der Machbarkeit dieser neuen digitalen Gesundheitsanwendung. Um herauszufinden, ob eine Stärkung der Patient:innenautonomie und die Beratung zur Lebensstilveränderung zu einer Reduktion der Krankheitsaktivität beitragen können, wurde anschließend eine deutschlandweite randomisiert kontrollierte Studie (RCT) geplant (3) und durchgeführt. Zudem wurden die Zusammenhänge zwischen Lebensstilfaktoren und klinischen Charakteristika der im Rahmen des RCTs eingeschlossenen frühen MS-Kohorte durch eine explorative Analyse der Basisdaten zum Zeitpunkt des Studieneinschlusses untersucht (4). In einer weiteren, zur Publikation eingereichten Arbeit, wurden beispielhaft die ernährungsbezogenen Inhalte von levidex auf Grundlage eines internationalen Rahmenkonzeptes zur Klassifikation von Verhaltensänderungstechniken (5) charakterisiert.

Im Folgenden werden zunächst das Krankheitsbild MS sowie die Datenlage zu den Möglichkeiten und Effekten des Lebensstilmanagements bei MS vorgestellt, gefolgt von den Zielen und Fragestellungen dieser Arbeit. Anschließend werden die Methoden der Dissertation aufgeführt. Nach einer Zusammenfassung der wesentlichen Ergebnisse erfolgt eine Diskussion der Ergebnisse unter Einbezug des theoretischen und wissenschaftlichen Hintergrunds. Darüber hinaus werden die methodischen Stärken und Schwächen dieser Arbeit beleuchtet. Abschließend werden Schlussfolgerungen gezogen und ein Ausblick für die klinische Praxis und weitere Forschung gegeben.

1 Theoretischer Hintergrund

1.1 Multiple Sklerose: Diagnose, Verlauf und Therapiemöglichkeiten

Multiple Sklerose (MS) ist eine chronische, entzündliche und degenerative Erkrankung des zentralen Nervensystems, welche in Deutschland mit über 200.000 betroffenen Personen zu den relativ häufigen seltenen Erkrankungen gehört und in der Regel im jungen Erwachsenenalter diagnostiziert wird (6). In den letzten Jahren konnte eine steigende Prävalenz der MS verzeichnet werden, welche teilweise neuen diagnostischen Kriterien (7), die eine frühere MS-Diagnose erlauben, zugeschrieben werden kann (8). Gleichzeitig scheint die Entzündungsaktivität im Frühstadium der MS geringer zu sein, was möglicherweise mit einer späteren Entwicklung von Beeinträchtigungen einhergeht (9). Bei circa 85% der MS-Betroffenen verläuft die Erkrankung zunächst in Schüben, im späteren Verlauf dann chronisch progredient (10). Zu den typischen Symptomen der Erkrankung zählen Ermüdbarkeit (Fatigue), Sensibilitäts- und Gangstörungen sowie Schmerzen und Spastiken (6). Eine verlässliche Prognoseeinschätzung gestaltet sich extrem schwierig, da der individuelle MS-Verlauf hoch variabel ist und von benignen Fällen bis hin zu schnell voranschreitender Behinderung reichen kann (11-13). Diagnostische Informationen im Zusammenhang mit der MS werden häufig als erheblich emotional belastend erlebt und können in einem frühen Stadium Enttäuschung und Misstrauen gegenüber dem medizinischen System hervorrufen (14, 15). Insbesondere zu Beginn der Erkrankung bedarf es daher einer intensiven und hochindividuellen Beratung, welche innerhalb der Standardversorgung in Deutschland nicht ausreichend abgedeckt wird.

Zur Therapie der MS, insbesondere der schubförmigen MS, wurden in den vergangenen Jahren zahlreiche Immuntherapeutika zugelassen, welche die Schubrate senken und den MS Verlauf modifizieren können (8). Der langfristige Nutzen für das Fortschreiten der Beeinträchtigung ist jedoch weiterhin unklar (16, 17). Während die Verschreibung von Immuntherapeutika mit erheblichen Gesundheitskosten verbunden ist (18), liegt die Adhärenz zur Immuntherapie zu Beginn der Therapie (innerhalb der ersten zwei Jahre) bei nur 30-50% (19). Außerdem beginnt nicht jede von MS betroffene Person direkt nach der Diagnose mit der Behandlung (20) und rund 30% der MS-Betroffenen nehmen gar keine

Immuntherapie in Anspruch (18). MS-Betroffene möchten eine aktive Rolle in der Therapieentscheidung einnehmen (21) und fragen sich häufig, was sie selbst zu einer optimalen Anpassung an die MS beitragen können. Neben der Immuntherapie stehen MS-Betroffenen auch Lebensstilmaßnahmen als Therapiemöglichkeit zur Verfügung, deren Potential in den folgenden Abschnitten dargestellt wird.

1.2 Lebensstilmanagement bei Multipler Sklerose

Lebensstilfaktoren oder modifizierbare Risikofaktoren, wie das Bewegungs- und Ernährungsverhalten, werden bei MS zunehmend als relevant angesehen (22). Mit dem Ziel ihre Gesundheit zu erhalten und zu verbessern, haben MS-Betroffene einen hohen Bedarf an lebensstilbezogenen Informationen (23). Zudem berichten MS-Betroffene, die sich selbst als erfolgreich im Umgang mit der MS bezeichnen, dass die Aufrechterhaltung eines gesunden Lebensstils ein Schlüsselfaktor für ein effektives Selbstmanagement sei und halten die Bereitstellung von lebensstilbezogenen Informationen für sehr wichtig (24). Systematische, geprüfte EBPI zu Lebensstilinterventionen liegen bisher nicht vor. Dabei ist beispielsweise der Zusammenhang zwischen psychischem Stress und Krankheitsaktivität bei MS metaanalytisch gut belegt (25). Während wahrgenommener Stress und Ungewissheit unter anderem in engem Zusammenhang mit weniger Anpassungsfähigkeit an die MS stehen, wirken sich soziale Unterstützung und positive psychologische Faktoren förderlich auf die Anpassungsfähigkeit von MS-Betroffenen aus (26). Durch eine Meta-Analyse zum Zusammenhang zwischen sogenannten „Mind-Body"-Therapien (z.B. Achtsamkeits-Meditation) und der Funktion des Immunsystems konnte zudem gezeigt werden, dass diese Therapieformen die Aktivität bestimmter pro-inflammatorischer Zytokine reduzieren und den Krankheitsverlauf somit positiv beeinflussen könnten (27). Körperliche Aktivität wirkt sich positiv auf die Balance (28), die mit MS assoziierte Fatigue (29) sowie die Stimmung und Lebensqualität aus (30). Eine weitere systematische Übersichtsarbeit ergab darüber hinaus, dass regelmäßiges Training zwei Mal pro Woche die Muskelkraft erhöht und die Fitness verbessert und möglicherweise auch zu Verbesserungen in der Mobilität führt (31). Körperliche Aktivität könnte sich zudem sowohl auf die Krankheitsaktivität als auch auf Surrogate der Gehirnintegrität auswirken (32). Auch bei psychologisch ausgerichteten Interventionen konnten diese Effekte beobachtet werden (33, 34). Ein Vitamin-D-Mangel ist ein gut belegter Risikofaktor für MS und Evidenz von geringer

bis mittlerer Qualität zeigt eine positive immunmodulatorische Wirkung der Vitamin-D-Supplementierung bei inadäquater Versorgung (35, 36). Obwohl es an kontrollierten Studien zum potenziellen Einfluss von Ernährungsfaktoren auf MS mangelt (37, 38), wird die Einhaltung von aktuellen Empfehlungen für eine gesunde Ernährung unter Berücksichtigung MS-spezifischer Aspekte empfohlen (39). Eine mediterrane Ernährungsform scheint aufgrund ihres Zusammenhangs mit vaskulären Komorbiditäten dabei besonders empfehlenswert für MS-Betroffene zu sein (37). Qualitativ hochwertige Daten zum Einfluss spezieller Ernährungsformen oder einzelner Nährstoffe auf das Fortschreiten der MS sind dennoch nicht verfügbar (22, 38).

Die erfolgreiche Veränderung von Lebensgewohnheiten und insbesondere die langfristige Aufrechterhaltung dieser Verhaltensänderung sind ein schwieriges Unterfangen (40). Gemäß dem COM-B (Capability-Opportunity-Motivation-Behaviour) Modell ist Verhalten das Ergebnis eines interagierenden Systems, welches die Fähigkeiten (z.B. Wissen, Fertigkeiten), Möglichkeiten (z.B. Zugang, Zeitressourcen) und Motivation eines Individuums umfasst (41). Das COM-B Modell ist darüber hinaus auch auf der Bevölkerungsebene anwendbar. Neben Verhaltensdeterminanten berücksichtigt das dem COM-B Modell übergeordnete Behaviour Change Wheel (BCW) auch soziale, gesundheitspolitische und gesellschaftliche Ebenen sowie Umweltfaktoren. Um tatsächlich eine Verhaltensänderung bei Personen zu erreichen, muss mindestens eine der Komponenten des COM-B Modells adressiert werden. Gleichzeitig ist die Zeit für eine persönliche Beratung und individuelle Gespräche bezüglich Behandlungsmöglichkeiten jenseits zugelassener Immuntherapeutika und Möglichkeiten der Lebensstiländerung im Rahmen von neurologischen Sprechstunden begrenzt. Angesichts des hohen lebensstilbezogenen Informationsbedarfs von MS-Betroffenen (23), sollten geeignete Methoden zur Veränderung von Verhaltensdeterminanten im Rahmen von Interventionen unter Einbezug aktueller Evidenz eingesetzt werden. Die Vermittlung von Informationen über gesundheitliche Folgen von Verhalten gestützt von verlässlichen Quellen gehört zudem zu den anerkannten Techniken der Verhaltensänderung (Behaviour Change Techniques, BCTs). Zur Vereinheitlichung der Terminologie dieser Techniken wurden insgesamt 93 BCTs im Rahmen einer BCT-Taxonomie definiert (5). MS-Betroffene

nutzen häufig Internetquellen und eHealth-Technologien zur Informationsbeschaffung (42). Ein Ansatz, um die Lücke zwischen der begrenzten Zeit in neurologischen Sprechstunden und dem lebensstilbezogenen Informationsbedarf von MS-Betroffenen zu schließen, könnte die Bereitstellung von EBPI über webbasierte Dienste sein. Während viele kleine Studien die positiven Auswirkungen von körperlicher Aktivität und psychologischen Interventionen bereits zeigen konnten (22), wurden digitale Interventionen bei MS bisher nur selten untersucht. Eine umfassende digitale Lebensstilintervention für MS-Betroffene, die zusätzlich auf BCTs basiert, wurde nach unserem Wissen noch nie eingesetzt und geprüft.

2 Ziele und Fragestellungen

Die bestehenden Versorgungsstrukturen können den komplexen Bedürfnissen von MS-Betroffenen nach umfassenden evidenzbasierten Gesundheitsinformationen und einer individualisierten Begleitung zur Lebensstilveränderung, insbesondere im frühen Stadium der Erkrankung, nicht gerecht werden. Darüber hinaus ist unklar, welche Komponenten und Techniken bei Verhaltensänderungsinterventionen am besten geeignet sind, um eine Veränderung von Lebensgewohnheiten (z.B. Optimierung von Bewegungs- und Ernährungsverhalten) zu erreichen (43, 44). Die Ziele dieser Dissertation sind daher:

1) Die Entwicklung und Testung der Machbarkeit und Akzeptanz einer digitalen, interaktiven und evidenzbasierten Lebensstilmanagementintervention („levidex“) auf Basis einer vorangegangenen Entwicklung in der Onkologie („Optimune“) (1). Die Intervention soll als umfassende Begleitung und Ergänzung zur Standardversorgung in der Orientierungsphase nach der MS-Diagnose dienen. In diesem Zusammenhang befasst sich die Arbeit mit folgenden Fragestellungen:

   - Ist die entwickelte Intervention praktikabel für MS-Betroffene? Wie werden z.B. die Länge, Navigation, Zusammensetzung von Texten und grafische Darstellung der Intervention von MS-Betroffenen und MS-Expert:innen wahrgenommen?

   - Wird die Intervention von MS-Betroffenen und MS-Expert:innen akzeptiert? Wie werden z.B. die Evidenzkommunikation, die Motivationsanreize und der mögliche Nutzen der Intervention von MS-Betroffenen und MS-Expert:innen wahrgenommen?

   - Kann die Intervention MS-Betroffene dazu anregen, Lebensstilveränderungen zu planen oder umzusetzen?

2) Die deskriptive Charakterisierung von levidex anhand von BCTs, dem BCW und dem Theoretical Domains Framework (TDF) am Beispiel der ernährungsbezogenen Gespräche. Diese zur Publikation eingereichte Arbeit beschäftigt sich mit folgenden Fragestellungen:

- Welche BCTs werden in den ernährungsbezogenen Inhalten eingesetzt, um eine Optimierung der Ernährungsgewohnheiten bei Erstbetroffenen mit MS zu erreichen?

- Welchen Komponenten des BCW und Domänen des TDF können die Verhaltensänderungsstrategien zugeordnet werden?

3) Die Planung und Durchführung der Evaluation von levidex durch ein deutschlandweites RCT mit begleitender Prozessevaluation sowie einer gesundheitsökonomischen Evaluation bei Erstbetroffenen mit MS (3). Folgende Fragestellungen werden durch diese Arbeit adressiert:

   - War das RCT in seiner geplanten Form durchführbar?

   - Wurden das Studiendesign und die entwickelte Intervention von Erstbetroffenen mit MS akzeptiert?

   - Konnte die geplante Zielgruppe und Stichprobengröße für das RCT rekrutiert werden?

4) Die Untersuchung der Zusammenhänge zwischen Lebensstilfaktoren und klinischen Charakteristika bei Erstbetroffenen mit MS durch eine explorative Analyse der Basisdaten der Studienteilnehmenden zum Zeitpunkt des Studieneinschlusses (4). Diese Arbeit befasst sich neben der Beschreibung der demografischen und klinischen Charakteristika sowie dem Gesundheitsverhalten der Kohorte mit folgenden Fragestellungen:

   - Sind klinische Charakteristika (gemessen als Grad der Beeinträchtigung, Anzahl an T2-Läsionen und Lebensqualität) von Personen mit früher MS miteinander oder mit der Behandlung mit Immuntherapeutika assoziiert?

   - Sind demografische oder klinische Charakteristika (gemessen als Alter zum Diagnosezeitpunkt, Grad der Beeinträchtigung, Schubrate, Anzahl an T2-Läsionen und Lebensqualität) von Personen mit früher MS mit dem Gesundheitsverhalten oder dem Vorliegen von Komorbiditäten assoziiert?

- Ist das Gesundheitsverhalten von Personen mit früher MS miteinander oder mit dem Vorliegen von Komorbiditäten assoziiert?

- Sind klinische Charakteristika (gemessen als Grad der Beeinträchtigung, Schubrate, Anzahl an T2-Läsionen und Lebensqualität) von Personen mit früher MS mit dem Interesse an Möglichkeiten zur Optimierung des Gesundheitsverhaltens, der Absicht, das Gesundheitsverhalten zu verändern, oder mit Stadien der Verhaltensänderung assoziiert?

3 Methodik

Im vorliegenden Kapitel werden die Methoden zusammengefasst, die zur Untersuchung der Fragestellungen angewandt wurden. Im Rahmen dieser Forschungsarbeit wurde eine „Mixed-Methods-Studie“ geplant und durchgeführt, welche die ersten drei Phasen des Medical Research Council (MRC) Frameworks für die Entwicklung und Evaluation komplexer Interventionen (45) abdeckt (siehe Abbildung 1).

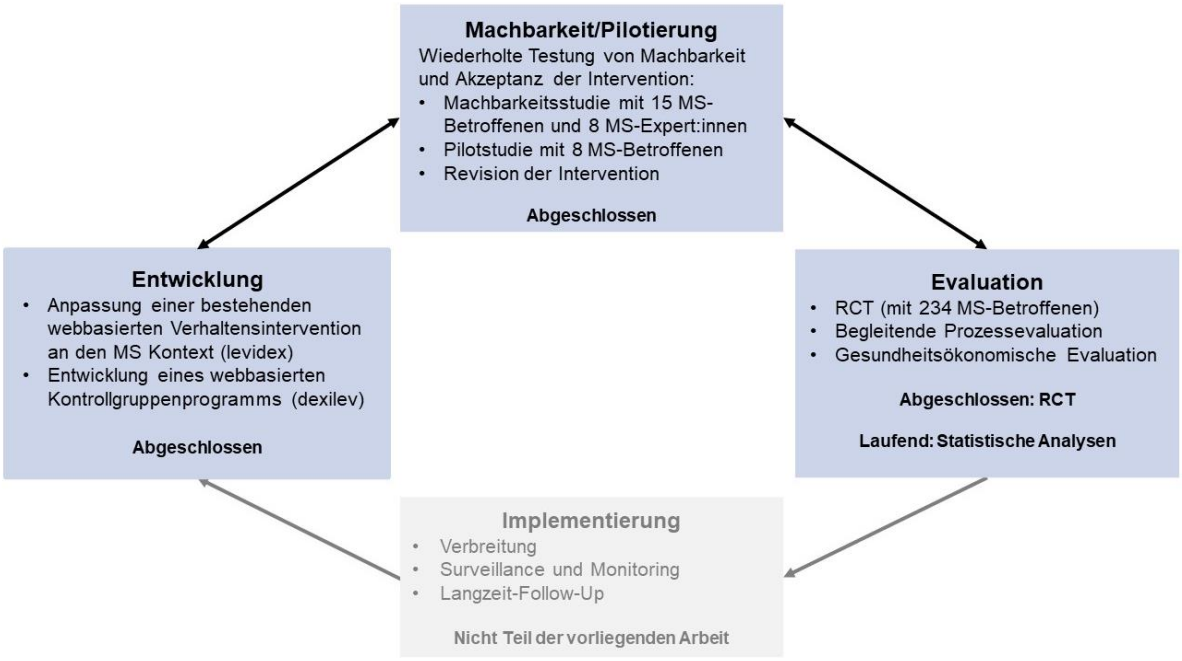

Abbildung 1: Schritte der „Mixed-Methods-Studie“ nach MRC Framework (45)

Daten zu Effekten der Intervention liegen erst nach Abschluss der statistischen Analysen zur Evaluation vor, weshalb die vierte Phase der Implementierung nicht Teil dieser Dissertation ist.

3.1 Entwicklung eines Interventions- und Kontrollgruppenprogramms

Eine komplexe digitale Gesundheitsanwendung zum Lebensstilmanagement (levidex) wurde angepasst und als individualisiertes Programm für Erstbetroffene mit MS konzipiert. Es handelt es sich dabei um eine MS-spezifische Anpassung von „Optimune", einer digitalen Gesundheitsanwendung, welche zur Förderung des Lebensstilmanagements bei Überlebenden von Brustkrebs entwickelt wurde. Die Wirksamkeit von Optimune wurde durch eine signifikant verbesserte Lebensqualität

sowie eine Steigerung von gesunden Ernährungsgewohnheiten bereits nachgewiesen (46, 47). Auf der Grundlage von Vorarbeiten zu EBPI (48-51) sowie den Vorschlägen eines multidisziplinären Studienteams (Psycholog:innen, Neurolog:innen, Ernährungs- und Gesundheitswissenschaftler:innen) wurden zunächst MS-spezifische Themen ermittelt. Diese Themen wurden der bestehenden digitalen Gesundheitsanwendung als wissenschaftliche Basis für die Einladung zur Verhaltensänderung hinzugefügt. Die implementierten EBPI stützen sich dabei insbesondere auf einen umfangreichen Health Technology Report, der den möglichen Einfluss modifizierbarer Risikofaktoren auf die Entwicklung von Beeinträchtigung und Behinderung im Zusammenhang mit MS untersucht (22).

Die Nutzung von levidex soll Erstbetroffene dazu motivieren, ihr Verhalten zu ändern (z.B. ihre körperliche Aktivität zu steigern oder ihr Ernährungsverhalten zu optimieren). Auf Basis der Softwareplattform broca® werden regelbasierte Algorithmen der künstlichen Intelligenz eingesetzt, um Informationen und therapeutische Übungen auf die individuellen Eigenschaften der Nutzenden abzustimmen. Mit Hilfe von "simulierten Dialogen", welche einen Gesprächsverlauf imitieren, fordert levidex die Nutzenden dabei kontinuierlich dazu auf, eine oder mehrere geeignete Antwortoptionen auszuwählen. Auf Grundlage der gewählten Antworten werden die nachfolgenden Inhalte dann auf die Bedürfnisse der nutzenden Person zugeschnitten. So können beispielsweise individuelle Trainingspläne erstellt werden, die auf den eigenen MS-Erkrankungsmerkmalen und körperlichen Fähigkeiten basieren oder zwischen einer Vielzahl an Rezepten gewählt werden, die auf bevorzugten Ernährungsgewohnheiten und aktuellen Kochkompetenzen beruhen. Durch die beabsichtigte Optimierung des Gesundheitsverhaltens soll levidex letztendlich die Lebensqualität von Erstbetroffenen mit MS verbessern und möglicherweise sogar die entzündliche Aktivität der MS verringern. Um diese Verhaltensänderung zu erreichen, umfasst levidex ein breites Spektrum an BCTs, insbesondere solche, die in der kognitiven Verhaltenstherapie (z.B. Zielsetzung und Handlungsplanung), der motivierenden Gesprächsführung sowie in Achtsamkeits- und Akzeptanzansätzen verwendet werden (52). Dabei folgt levidex dem Konzept der Patient:innenbefähigung (Empowerment) (53). Die integrierten BCTs sind darüber hinaus mit den

theoretischen Konstrukten des TDF (54) verknüpft, welches einen elaborierteren und integrativen Rahmen für das Verständnis von Gesundheitsverhalten bietet.

Nach der finalen Fertigstellung von levidex ist eine deskriptive Charakterisierung der Inhalte anhand der integrierten BCTs erfolgt. Eine vollständige Charakterisierung aller in levidex eingesetzten Verhaltensänderungsstrategien war aufgrund der großen Menge an Material im Rahmen dieser Dissertation nicht möglich. Da durch die Nutzung der Vorgängerversion von levidex (Optimune) bei Überlebenden von Brustkrebs bereits eine signifikante Verbesserung der gesunden Ernährungsgewohnheiten nachgewiesen werden konnte (47), werden durch die Nutzung von levidex auch bei Erstbetroffenen mit MS signifikante Verbesserungen des Ernährungsverhaltens angenommen. Des Weiteren hat das Thema Ernährung und insbesondere der mögliche Einfluss des Ernährungsverhaltens auf den Krankheitsverlauf eine hohe Relevanz bei MS-Betroffenen (50, 55). Aus diesen Gründen wurden die ernährungsbezogenen Inhalte von levidex zur Charakterisierung der Verhaltensänderungsstrategien ausgewählt. Eine BCT-Taxonomie mit 93 hierarchisch geclusterten Techniken (5) wurde zur Identifizierung und Kodierung der BCTs verwendet, die in den ernährungsbezogenen Komponenten von levidex eingesetzt werden. Diese Komponenten umfassen drei Gespräche zum Thema Ernährung, optionale ernährungsbezogene Kurznachrichten sowie einen optionalen Fragebogen zur Selbstkontrolle des Ernährungsverhaltens. Zur Kodierung der BCTs wurde das Textmaterial aus den Ernährungskomponenten verwendet. Die Kodierung und Analyse der Ergebnisse wurde mittels MAXQDA 2022, einer Software zur qualitativen Datenanalyse durchgeführt. Die BCTs wurden dabei von zwei Raterinnen kodiert, die zunächst an einer Online-Schulung zu der verwendeten BCT-Taxonomie (56) teilnahmen. Nach erfolgreichem Abschluss der Online-Schulung machten sich die Raterinnen zunächst durch das Durchlesen des Textmaterials mit dem Kodiermaterial vertraut. Anschließend kodierten beide Raterinnen unabhängig voneinander ein Gespräch zum Ernährungsverhalten. Unstimmigkeiten wurden anschließend diskutiert und die Kodierstrategien gemeinsam optimiert. Daraufhin wurden alle Ernährungskomponenten unabhängig voneinander von beiden Raterinnen kodiert. Im nächsten Schritt wurde das Ausmaß der prozentualen Kodierungsübereinstimmung (Inter-Rater-Reliabilität) mit MAXQDA 2022 ermittelt und die Unterschiede diskutiert, um die Kodierungsstrategien erneut zu optimieren.

Die optimierten Kodierungsstrategien wurden schriftlich festgehalten und anschließend als Leitlinie verwendet. Zusätzlich wurde der Kappa-Koeffizient (57) in MAXQDA 2022 berechnet, um die Inter-Rater-Reliabilität der kodierten BCTs zu ermitteln. Als Maß für die Stärke der Übereinstimmung der Kappa-Werte (58) wurde folgende Interpretation angenommen: <0,00=schlecht, 0,00-0,20=gering, 0,21-0,40=mittelmäßig, 0,41-0,60=mäßig, 0,61-0,80=substanziell und 0,81-1,00=nahezu perfekte Übereinstimmung. Die substanzielle Übereinstimmung (Kappa 0,61-0,80) wurde als Schwellenwert für ausreichende Inter-Rater-Reliabilität festgelegt und die unabhängige Kodierung wurde wiederholt, bis dieser Schwellenwert erreicht war. Nach dem Erreichen einer substanziellen Übereinstimmung wurden die Ergebnisse des finalen Kodierungsprozesses von den beiden Raterinnen diskutiert, um Unstimmigkeiten zu beseitigen und einen Konsens über die implementierten BCTs zu erzielen. Eine endgültige Einigung wurde durch die Diskussion mit einer dritten Raterin erzielt, welche über Erfahrungen in der Anwendung des BCW und des TDF verfügt. Um ein Verständnis für die in levidex implementierten Interventionsstrategien zu generieren, wurden die Komponenten des COM-B Modells für jede in den ernährungsbezogenen Inhalten kodierte BCT identifiziert. Darüber hinaus wurde jede BCT mit einer beispielhaften Textbeschreibung versehen. Anschließend wurden jeder kodierten BCT die Interventionsfunktionen zugeordnet. Hierfür wurden Orientierungshilfen von Michie und Kolleg:innen (59) verwendet. Im nächsten Schritt wurden die identifizierten Komponenten des COM-B Modells mit den Domänen (theoretischen Konstrukten) des TDF verknüpft.

Zur Evaluation von levidex wurde ein digitales Kontrollgruppenprogramm („dexilev“) in Form einer optimierten Standardversorgung entwickelt, für welches Informationsmaterialien der Deutschen Multiple Sklerose Gesellschaft (DMSG) genutzt wurden. Die verfügbaren Informationsmaterialien (z.B. Broschüren, Informationsblätter) wurden durch das im Rahmen der Anpassung von levidex involvierte multidisziplinäre Studienteam gesichtet. Anschließend wurden relevante Inhalte entsprechend der levidex Inhalte ausgewählt und in Form einer reinen Informationsplattform ohne Individualisierung zusammengestellt.

3.2 Machbarkeits- und Pilotstudie

Die Prüfung der Machbarkeit von levidex umfasste mehrere Aspekte, wie den Inhalt, die Praktikabilität (z.B. Anmeldung, Länge, Navigation), die Akzeptanz (z.B. praktische Anwendbarkeit, Motivationsanreiz) und den wahrgenommenen Nutzen der Intervention (1). Diese Kriterien wurden auf Grundlage von Leitlinien für Machbarkeits- und Pilotstudien (60, 61) in drei aufeinanderfolgenden Testphasen untersucht. Die drei Testphasen gliedern sich in eine Machbarkeitsstudie auf, an welcher zunächst MS-Betroffene und anschließend MS-Expert:innen beteiligt waren sowie eine Pilotstudie, an welcher erneut MS-Betroffene teilgenommen haben (siehe Abbildung 2).

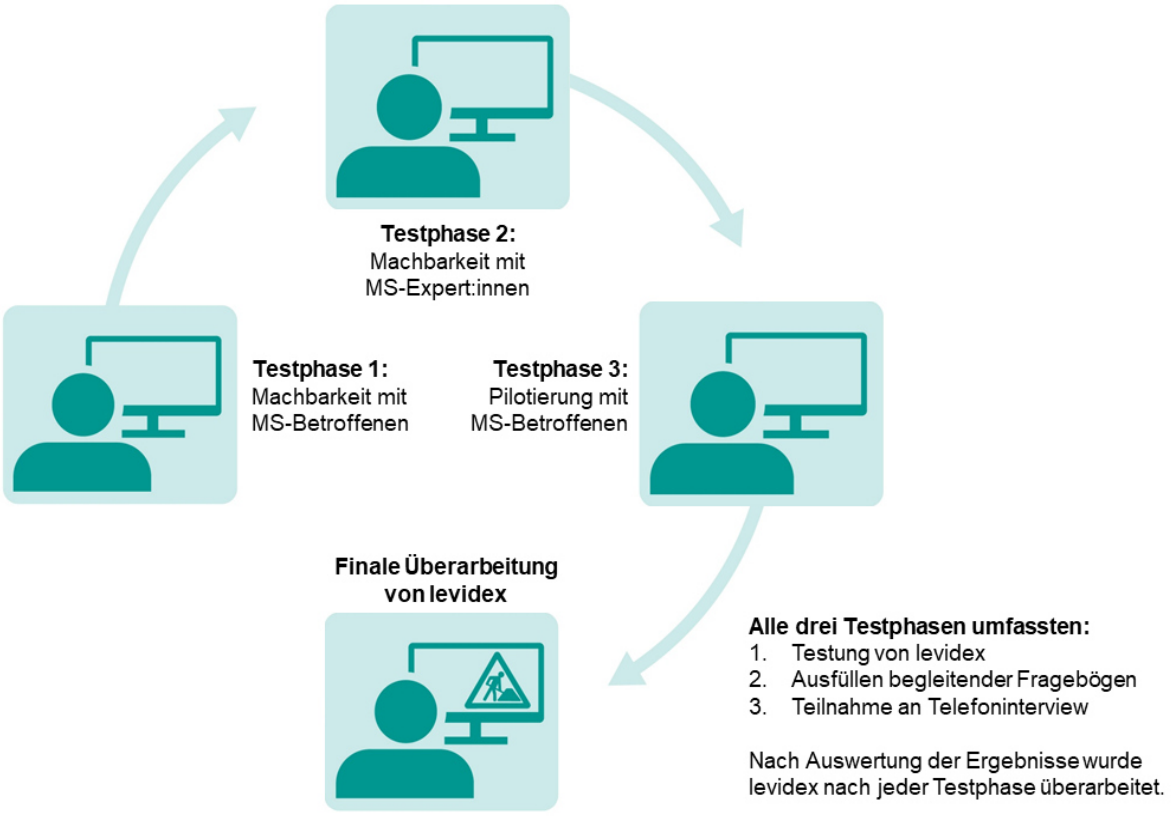

Abbildung 2: Machbarkeitsstudie (Phase 1 und 2) und Pilotstudie (Phase 3)

In einem frühen Entwicklungsstadium von levidex wurden einzelne Gespräche im Rahmen einer ersten Machbarkeitsstudie (Testphase 1) zunächst 15 erfahrenen MS-Betroffenen vorgestellt, um vorwiegend technische Aspekte zu testen. Anschließend wurde levidex auf Grundlage der Ergebnisse überarbeitet und in einer zweiten Machbarkeitsstudie (Testphase 2) von acht MS-Expert:innen aus unterschiedlichen

Disziplinen (fünf Neurologen, zwei Ernährungswissenschaftlerinnen und ein Sportwissenschaftler) getestet, worauf eine erneute Überarbeitung von levidex folgte. Im Zuge der zweiten Machbarkeitstestung wurden einzelne Gespräche entsprechend der Expertise der Teilnehmenden evaluiert. Abschließend wurde erstmalig die gesamte Abfolge der levidex Gespräche in einer längeren Pilotphase (Testphase 3) mit acht erfahrenen MS-Betroffenen getestet. Auf Basis des akquirierten Feedbacks wurde levidex final überarbeitet.

In allen drei Testphasen wurden quantitative und qualitative Methoden angewandt. Zum einen wurden selbst entwickelte Fragebögen genutzt, welche in vier Teile unterteilt wurden: (1) demografische Angaben der Teilnehmenden, (2) Benutzerfreundlichkeit und optischer Eindruck, (3) Qualität und Personalisierung der Inhalte sowie (4) Zufriedenheit und wahrgenommener Nutzen. Für die Erstellung der Fragebögen wurden Rahmenwerke von Kowatsch et al. (62) und Allison et al. (63) herangezogen. Die Fragen bestanden aus einer Mischung aus geschlossenen (meist sechsstufige Likert-Skalen) und offenen Fragen. Zudem wurde der selbstberichtete Grad der MS-bezogenen Behinderung durch die PDDS-Skala (Patient Determined Disease Steps) (64) bei MS-Betroffenen erhoben. Die Fragebögen wurden nach jeder Testphase eingesammelt und mit Hilfe deskriptiver Statistik ausgewertet. Antworten auf offene Fragen wurden gesichtet und kategorisiert. Zusätzlich wurden in jeder Testphase halbstrukturierte Telefoninterviews geführt, die auf den Ergebnissen der ausgefüllten Fragebögen basierten. Die Interviews wurden aufgezeichnet, transkribiert und thematisch ausgewertet (65).

3.3 Evaluation – „POWER@MS1“ Studie

Die digitale Gesundheitsanwendung levidex wurde vom 01.07.2019 bis zum 05.04.2023 in einem multizentrischen RCT („POWER@MS1“) evaluiert (3). Als Grundlage für die Planung der POWER@MS1 Studie und Erstellung des Studienprotokolls wurde die SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Checkliste (66) verwendet. Die Studie adressiert Erstbetroffene mit MS, die sich in ihrem ersten Jahr nach der Diagnose befinden. Die Rekrutierung und Betreuung von Studienteilnehmenden lief über insgesamt 20 deutschlandweit teilnehmende Studienzentren, welche aus Kliniken, Privatpraxen und akademischen Krankenhäusern mit einer MS-Spezialisierung bestehen. Die

Studienteilnehmenden wurden nach dem Zufallsprinzip 1:1 in eine Interventionsgruppe mit Zugang zu levidex zusätzlich zur Standardversorgung oder in eine Kontrollgruppe mit Zugang zu dexilev als optimierte Standardversorgung randomisiert. Darüber hinaus wurden eine begleitende Prozessevaluation zur Ermittlung von fördernden Faktoren und Barrieren der Implementierung sowie eine gesundheitsökonomische Evaluation durchgeführt. Die Daten wurden über einen Zeitraum von zwölf bis maximal 24 Monaten im Rahmen von bis zu sechs klinischen Visiten und ihnen vorausgehenden Untersuchungen in der Magnetresonanztomographie (MRT) erhoben. Der primäre Endpunkt ist die Zeit bis zu einem neuen Schub oder, als Surrogat für entzündliche Krankheitsaktivität, einer neuen Läsion. Das Auftreten neuer Schübe wurde dabei klinisch von den teilnehmenden Neurolog:innen beurteilt und neue Läsionen wurden nach einem MRT-Protokoll erfasst. Darüber hinaus wurden zahlreiche sekundäre Endpunkte, wie das Bewegungs- und Ernährungsverhalten, die Lebensqualität und Veränderungen im Empowerment erfasst. Eine Fallzahlplanung unter Einbezug zu erwartender Ereignisse (neue Läsion oder neuer Schub) sowie einer Annahme von etwa 20% Studienabbrüchen ergab vor Studienbeginn insgesamt 328 notwendige Randomisierungen (165 pro Gruppe). Basierend auf einem Datenexport vom 16.08.2021 mit Daten zu Ereignisraten (neue Läsion oder neuer Schub) von zu diesem Zeitpunkt 135 eingeschlossenen Erstbetroffenen mit MS erfolgte ein verblindetes Fallzahlplanungsreview. Das Ziel war, die Annahmen zu Ereignisraten und Dropouts zu überprüfen und die notwendige Stichprobengröße neu zu bestimmen. Dabei wurden zwei verschiedene Definitionen für einen Schub überprüft, da das Auftreten von Schüben klinisch nicht in allen Fällen eindeutig beurteilt werden kann. Bei der ersten Definition wurden nur „sichere“ Schübe gezählt, während bei der zweiten Definition zusätzlich Schübe mitgezählt wurden, die als „mögliche“ Schübe gewertet wurden. Nach Abschluss der Rekrutierung und Bereinigung der Basisdaten wurden diese am 19.09.2022 exportiert und studiengruppenübergreifend (verblindet) explorativ statistisch ausgewertet (siehe 3.4). Die unverblindeten POWER@MS1 Gesamtdaten wurden nach Abschluss der Studie sowie der Datenbereinigung am 24.08.2023 exportiert und werden aktuell statistisch ausgewertet, sodass erste Ergebnisse voraussichtlich im Herbst 2023 vorliegen.

3.4 Analyse der „POWER@MS1“ Basisdaten

Die Basisdaten der POWER@MS1 Kohorte wurden explorativ statistisch ausgewertet, um Zusammenhänge zwischen demografischen oder klinischen Charakteristika und dem Gesundheitsverhalten (z.B. Rauchen, körperliche Aktivität, Ernährungsverhalten) zu untersuchen. Die zugrundeliegenden Daten wurden mithilfe von Papierfragebögen und webbasierten Ernährungsfragebögen erhoben. Demografische und klinische Charakteristika (z.B. Komorbiditäten, Schübe, T2-Läsionen) sowie Größe, Gewicht und Rauchstatus wurden anhand standardisierter Fragebögen von den behandelnden Neurolog:innen erhoben. Die Dokumentation von T2-Läsionen erfolgte dabei auf Grundlage radiologischer MRT-Befunde. Zudem wurde der Grad der MS-bezogenen Behinderung durch die EDSS-Skala (Expanded Disability Status Scale) (67) gemessen. Alle weiteren Daten wurden anhand von selbstberichteten Patient:innenfragebögen erhoben. Dies umfasst die Lebensqualität gemessen mittels Hamburg Quality of Life in Multiple Sclerosis Scale (HAQUAMS) (68) sowie Angst- und Depressionssymptome gemessen durch die deutsche Version der Hospital Anxiety and Depression Scale (HADS-D) (69). Das Ernährungsverhalten wurde durch ein Screening-Instrument für gesunde Ernährung erfasst, welches den Verzehr von zehn Lebensmittelgruppen (z.B. Gemüse, Obst und fettreicher Fisch) misst, die mit einem präventiven Potenzial für chronische Erkrankungen in Verbindung gebracht werden (70). Basierend auf den Ernährungsrichtlinien der Deutschen Gesellschaft für Ernährung e.V. (DGE) und zusätzlicher Evidenz werden für alle Lebensmittelgruppen (n=10) 0 bis 1 Punkte entsprechend der jeweiligen Verzehrempfehlung (geringe, moderate oder hohe Aufnahme) vergeben, was in einem „Diet Score“ mit einer Reichweite von 0 bis 10 resultiert. Eine maximale Punktzahl von 10 bedeutet dabei, dass alle Verzehrempfehlungen perfekt eingehalten werden. Der Godin Leisure-Time Exercise Questionnaire (GLTEQ) (71) wurde verwendet, um die Häufigkeit der üblichen wöchentlichen körperlichen Aktivität von mindestens 15 Minuten in der Freizeit zu messen. Auf der Grundlage selbstberichteter Häufigkeiten für mäßige und anstrengende Aktivitäten wird dabei der GLTEQ Health Contribution Score (GLTEQ HCS) berechnet, um die Teilnehmenden als unzureichend, moderat oder ausreichend aktiv einzustufen. In Anlehnung an die Einteilung in Stadien der Verhaltensänderung nach Lippke et al. (72) wurde das Ernährungsverhalten (gemessen als Verzehr von Obst und Gemüse)

sowie regelmäßige körperliche Aktivität zudem mit einem weiteren Instrument erhoben, um die Teilnehmenden in "nicht-aktive" Verhaltensstadien (Absichtslosigkeit, Absichtsbildung, Vorbereitung) oder "aktive" Verhaltensstadien (Handlung, Aufrechterhaltung/Stabilisierung) einzuordnen. Eine Beschreibung weiterer Erhebungsinstrumente ist im POWER@MS1 Studienprotokoll zu finden (3).

Im Rahmen der explorativen statistischen Analyse der verblindeten POWER@MS1 Basisdaten erfolgte zunächst eine Beschreibung der Kohorte durch die Gesamtzahl (n) und relative Häufigkeit (%) für kategoriale Variablen sowie den Mittelwert und die Standardabweichung (SD) oder den Median und Interquartilsabstand (IQA) für kontinuierliche Variablen. Zudem wurden Grenzwerte für eine hohe Schwere der Erkrankung (z.B. ≥10 T2-Läsionen) und eine hohe Krankheitsaktivität (≥2 bisherige Schübe) bei früher MS definiert. Der Zusammenhang zwischen kontinuierlichen abhängigen Variablen und kontinuierlichen bzw. binären erklärenden Variablen wurde mit Hilfe von linearen Regressionsmodellen unter Angabe von Regressionskoeffizienten (β) mit 95% Konfidenzintervallen (CI) quantifiziert. Für die Anzahl an bisherigen Schüben und T2-Läsionen wurde eine negative binomiale Regression zur Berechnung der Assoziationen verwendet und Rate Ratios (RR) angegeben. Zur Untersuchung von Gruppenunterschieden bei kategorialen Variablen wurde der Pearson Chi-Quadrat-Test verwendet. Multiple lineare Regressionsmodelle wurden für Alter, Geschlecht, Body-Mass-Index (BMI), Rauch- und Bildungsstatus adjustiert und fehlende Werte wurden entfernt. Das am besten passende Modell wurde anhand des Akaike-Informationskriteriums (AIC) ermittelt. Zur Veranschaulichung dieser Ergebnisse wurde eine lineare Regression auf einer verschobenen log-transformierten Skala (log(x+1)) verwendet. Die Unterschiede wurden bei einem zweiseitigen $p \leq 0{,}05$ als signifikant angesehen. Die Daten wurden mit der statistischen Programmiersprache R 4.2.1 (73) ausgewertet.

4 Ergebnisse

Im Folgenden werden die wesentlichen Ergebnisse der drei akzeptierten Publikationen und der zur Publikation eingereichten Arbeit dargestellt. Zunächst wird das Interventionsprogramm (levidex) sowie das Kontrollgruppenprogramm (dexilev) vorgestellt. Anschließend folgen Ergebnisse der Machbarkeits- und Pilotstudie zu levidex sowie erste Ergebnisse zur Evaluation der Intervention und Kernergebnisse zu den Basisdaten der frühen MS Kohorte. Weiterführende Ergebnisse sind in den veröffentlichten Originalartikeln zu finden.

4.1 Interventions- und Kontrollgruppenprogramm

4.1.1 Interventionsprogramm „levidex“

Das Interventionsprogramm levidex wurde so konzipiert, dass die Nutzung über ein Jahr erfolgen soll. Jedes Gespräch dauert etwa 30 bis 45 Minuten, abhängig von der Lesegeschwindigkeit und dem individuellen Weg durch das Programm. Insgesamt besteht levidex aus 16 Gesprächen, deren Anordnung in Abbildung 3 dargestellt ist.

Abbildung 3: levidex Gesprächsübersicht (1)

Neue Gespräche werden in levidex nach einer Wartezeit nacheinander freigeschaltet, so dass Nutzer:innen die Möglichkeit haben, die Inhalte zu reflektieren und Aufgaben und Übungen zu erledigen, bevor sie ein neues Gespräch starten. Optionale Kurznachrichten (E-Mails und Textnachrichten) informieren die Nutzer:innen über neu verfügbare Gespräche. Ein Einführungsgespräch erklärt zunächst den Zweck von levidex und gibt den Nutzer:innen einen Überblick des zu erwartenden Zeitrahmens und der Inhalte der Intervention. Levidex versorgt Nutzer:innen anschließend mit allgemeinen MS-Informationen sowie mit Informationen zu Therapiemöglichkeiten und adressiert, dass eine Entscheidung über die Behandlung mit einer Immuntherapie getroffen werden muss. Es bietet dabei einen Überblick zur Wirksamkeit von Immuntherapien, einschließlich der Bewertung und Interpretation von Effekten, Daten zur absoluten und relativen Risikoreduktion sowie zu möglichen Nebenwirkungen. Als Alternative zu einer sehr frühen MS-Therapie verweist levidex auf die leitliniengestützte Möglichkeit des Abwartens über einen Zeitraum von ein bis zwei Jahren, begleitet von regelmäßigen neurologischen und kernspintomographischen Kontrolluntersuchungen (8). Dieser Ansatz ist darin begründet, dass der natürliche Krankheitsverlauf ohne Therapie über einen Zeitraum von bis zu ein oder zwei Jahren dazu beitragen kann, die MS-Aktivität besser zu beurteilen und dann möglicherweise besser für oder gegen eine Therapie entscheiden zu können. Schließlich ermutigt levidex die Nutzer:innen mehr Informationen zu sammeln, sich Zeit für die Entscheidung zu nehmen und sich nicht zu sehr unter Druck zu setzen. In den folgenden Gesprächen befasst sich levidex mit drei Hauptthemenbereichen: Psychisches Wohlbefinden und Schlafmanagement, Ernährungsgewohnheiten und körperliche Aktivität, gefolgt von vier Auffrischungs-Gesprächen (siehe Abbildung 3).

Insgesamt sind 177 Referenzen und neu entwickelte leicht verständliche Zusammenfassungen (Laien-Abstracts) in levidex integriert. Diese beinhalten vereinfachte Informationen zum Studiendesign, zu relevanten Ergebnissen sowie Limitationen der zitierten Studien. Um den Nutzenden eine kritische Bewertung der Evidenz zu ermöglichen, werden zusätzlich wissenschaftliche Methoden, verschiedene Studiendesigns und die ihnen innewohnenden Limitationen erläutert. Die Gespräche enthalten darüber hinaus Aufgaben, die außerhalb von levidex zu erledigen sind (z.B. Planung von Übungen oder Einkauf bestimmter Lebensmittel)

sowie Übungen zur Beschäftigung mit levidex (z.B. Achtsamkeitsmeditations-Audioübungen). Zusätzlich werden optionale Kurznachrichten verschickt, die lebensstilbezogene Informationen oder kurze therapeutische oder motivierende Vorschläge enthalten. Handouts im PDF-Format (Arbeitsblätter und Gesprächszusammenfassungen) und alle verfügbaren Audioaufnahmen können über einen Menüpunkt direkt abgerufen werden. Optionale Fragebögen zur Selbstkontrolle (z.B. tägliche Stimmungschecks, wöchentliche Bewertung der körperlichen Aktivität) mit individuellem Feedback und Bewertungen des selbstberichteten Verhaltens werden ebenfalls über einen Menüpunkt angeboten, um die Erfolge im Zeitverlauf zu visualisieren. Das Menü enthält außerdem eine Bedienungsanleitung sowie ein Glossar mit zusätzlichen Erklärungen zu 62 in levidex verwendeten Begriffen.

4.1.2 „levidex“ – Verhaltensänderungstechniken im Bereich Ernährung

Die Ergebnisse der deskriptiven Charakterisierung der ernährungsbezogenen levidex Inhalte anhand von BCTs, dem COM-B Modell und dem TDF adressieren folgende zwei Fragestellungen:

1. Welche BCTs werden in den ernährungsbezogenen Inhalten eingesetzt, um eine Optimierung der Ernährungsgewohnheiten bei Erstbetroffenen mit MS zu erreichen?
2. Welchen Komponenten des COM-B Modells und Domänen des TDF können die eingesetzten BCTs zugeordnet werden?

Die prozentuale Übereinstimmung der Raterinnen betrug im ersten Kodierungsprozesses nur 58,9% (Kappa-Koeffizient: 0,58), was auf eine mäßige Inter-Rater-Reliabilität hindeutet. Nach einer Optimierung der Kodierungsstrategien zur Erhöhung der Übereinstimmung führte der zweite Kodierungsprozess mit einer prozentualen Übereinstimmung von 79% (Kappa-Koeffizient: 0,78) zu einer substanziellen Inter-Rater-Reliabilität. Nach einem finalen Konsens wurden 28 von 93 BCTs aus der verwendeten BCT-Taxonomie mindestens einmal in den ernährungsbezogenen levidex Komponenten kodiert. In Summe wurden 202 BCT-Kodierungen in den Ernährungskomponenten vorgenommen. Die zehn am häufigsten verwendeten BCTs sind nach Frequenz ihres Vorkommens sowie nach Vorhandensein in den einzelnen Ernährungskomponenten in Tabelle 1 aufgelistet.

Tabelle 1: levidex & Ernährung – Die 10 häufigsten BCTs

BCT Nr. und Label*	G4	G7	G10	oSMF	oKN	Gesamt (%)
5.1 Informationen über gesundheitliche Folgen	✓	✓	✓		✓	32 (15,84)
4.1 Anleitung zur Ausführung eines Verhaltens	✓	✓	✓		✓	30 (14,85)
9.1 Expert:innenmeinung (vertrauenswürdige Quelle)	✓		✓			21 (10,40)
8.1 Üben und Wiederholen	✓	✓			✓	18 (8,91)
8.2 Verhalten ersetzen	✓	✓	✓		✓	13 (6,44)
12.1 Umgestaltung der physischen Umgebung	✓		✓		✓	8 (3,96)
6.1 Verhalten demonstrieren	✓		✓			7 (3,47)
8.7 Gestufte Aufgaben	✓	✓		✓		6 (2,97)
12.5 Hilfreiche Gegenstände nutzen	✓		✓		✓	6 (2,97)
13.2 Umdeutung	✓	✓			✓	6 (2,97)

BCT = Behaviour change technique; G4 = Gespräch 4, „Ernährung und Gesundheit: Bestandsaufnahme und erste Schritte zur Optimierung"; G7 = Gespräch 7, „Ernährungsrichtlinien: Welches Essen empfehlen die Experten?"; G10 = Gespräch 10, „Die Mediterrane Ernährung: Bestandteile und Umsetzung"; oSMF = optionaler Selbst-Monitoring Fragebogen; oKN = optionale Kurznachrichten.
*Deutsche Übersetzung der BCT Labels gemäß Göhner und Koleg:innen (74)

Es wurden außerdem verschiedene Kombinationen von BCTs festgestellt. Insgesamt wurden 21 BCTs in Kombination mit mindestens einer anderen BCT an derselben Stelle verwendet. Die häufigste Kombination betraf Informationen über gesundheitliche Folgen (5.1 Information about health consequences), welche in 19 Fällen gemeinsam mit vertrauenswürdigen Quellen (9.1 Credible source) bereitgestellt wurden. In den Ernährungskomponenten werden beobachtbare Beispiele (Demonstrationen) für die Ausführung eines angestrebten Ernährungsverhaltens (6.1 Demonstration of the behaviour, z.B. Bilder von fertig zubereiteten gesunden Gerichten) zudem in sieben Fällen mit einer Anleitung zur Ausführung des Ernährungsverhaltens (4.1 Instruction on how to perform behaviour, z.B. detaillierte Kochanweisungen) versehen.

Die identifizierten BCTs decken darüber hinaus ein breites Spektrum an Interventionsfunktionen ab und sind über alle Komponenten des COM-B Modells und alle Domänen des TDF verteilt. Dementsprechend wurde kein Schwerpunkt der ernährungsbezogenen Komponenten auf bestimmte Bereiche ermittelt. Zur Veranschaulichung der gleichmäßigen Verteilung enthält Tabelle 2 einen Auszug der COM-B Komponenten und TDF-Domänen, welche durch die einzelnen identifizierten BCTs adressiert wurden.

Tabelle 2: Anwendung des COM-B Modells und TDF zur Einordnung der BCTs

	Capability				Opportunity		Motivation							
	Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT*	S	K	MAD	BR	SI	EN	B Cap	B Con	S/P ID	O	I	G	EM	R
1.1				■							■	■		
1.2				■			■	■						
1.4				■							■	■		
1.9							■			■	■	■		
2.2		■						■						
2.3				■										
3.1					■				■					
4.1	■	■												
5.1		■						■					■	
5.6		■						■					■	
6.1	■	■	■	■										
6.2					■		■		■					
7.1			■	■		■								
8.1	■	■	■	■										
8.2	■			■										
8.4	■			■										
8.7	■			■										
9.1		■						■						
10.4					■		■							■
10.9							■			■				■
12.1						■								
12.3				■		■								
12.5						■								
13.2			■	■										
15.1							■			■				■
15.2							■			■			■	
15.4							■			■				■
16.2										■			■	

BCT = Behaviour change technique; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.
*Eine Aufschlüsselung des zu jeder BCT-Nummerierung gehörigen BCT-Labels ist im Anhang dieser Arbeit zu finden.

Die Interventionsfunktionen und Textbeispiele zu jeder BCT sind aufgrund ihres Umfangs im Anhang dieser Dissertation zu finden (s. Kapitel VII „Weitere Arbeit (zur Publikation eingereicht)“).

4.1.3 Kontrollgruppenprogramm „dexilev“

Das Kontrollgruppenprogramm dexilev besteht aus insgesamt 13 Modulen, die analog zu levidex ebenfalls über einen Zeitraum von einem Jahr genutzt werden können und nach einer Wartezeit nacheinander freigeschaltet werden. Die dexilev Module sind nicht interaktiv und dienen der reinen Vermittlung von im Rahmen der Standardversorgung verfügbaren Informationen, weshalb der Begriff „Gespräch“ hier nicht zutrifft. Die Anordnung der Module ist in Abbildung 4 dargestellt.

Modul 1: Symptome, Ursachen, Diagnose, Verlauf der MS	**Allgemeine Informationen und Multiple Sklerose**
Modul 2: Therapiemöglichkeiten und Lebensstil	
Modul 3: Lebensqualität	**Psychisches Wohlbefinden**
Modul 4: Fatigue und Depression	
Modul 5: Krankheitsverarbeitung – Coping	
Modul 6: Leben im Gleichgewicht – Stress und MS	
Modul 7: Innere Ruhe finden	
Modul 8: Empowerment	
Modul 9: Sport und MS	**Körperliche Aktivität**
Modul 10: Gerätetraining	
Modul 11: Outdoor-Sport	
Modul 12: Gesunde Ernährung bei MS	**Ernährung**
Modul 13: Ernährung – Körpergewicht und Diätformen	

Abbildung 4: dexilev Modulübersicht

Die Informationen werden in thematisch geordneten Blöcken und ohne Individualisierung zur Verfügung gestellt. Nach einer Einführung in die Epidemiologie der MS folgen Informationen zu Therapie- und Lebensstilmöglichkeiten. Daraufhin werden Informationen zum psychischen Wohlbefinden, zur körperlichen Aktivität und zu gesunder Ernährung bei MS vermittelt. Optionale Textnachrichten informieren dexilev Nutzer:innen über neu verfügbare Module. Außer den Modulen beinhaltet dexilev keine weiteren Funktionen oder Zusatzmaterialien.

4.2 Machbarkeits- und Pilotstudie

Im Folgenden werden die Ergebnisse der Machbarkeits- und Pilotstudie zu levidex dargestellt, welche das Ziel hatten folgende Fragestellungen zu beantworten:

1. Ist die entwickelte Intervention praktikabel für MS-Betroffene?
2. Wird die Intervention von MS-Betroffenen und MS-Expert:innen akzeptiert?
3. Kann die Intervention MS-Betroffene dazu anregen, Lebensstilveränderungen zu planen oder umzusetzen?

Die demografischen und klinischen Charakteristika der insgesamt 23 teilnehmenden MS-Betroffenen (15 in der Machbarkeitsstudie und acht in der Pilotstudie) sind in Tabelle 3 aufgeführt.

Tabelle 3: Charakteristika der teilnehmenden MS-Betroffenen (1)

	Machbarkeitsstudie (n=15)	**Pilotstudie (n=8)**
Alter in Jahren, Median (Spannweite)	53 (26-60)	47 (23-54)
Weiblich, n	11	4
Männlich, n	4	4
Bildungsstatus		
Realschulabschluss/Mittlere Reife, n	6	1
(Fach-) Hochschulreife, n	5	4
Hochschulabschluss, n	4	3
Krankheitsdauer in Jahren, Median (Spannweite)	7 (1-19)	9 (2-25)
PDDS, Median (Spannweite)	1 (0-7)	3 (1-4)
0 - Normal, n	3	-
1 - Leichte Beeinträchtigung, n	5	3
2 - Mäßige Beeinträchtigung, n	2	-
3 - Gangstörung, n	3	4
4 - Leichte Gehhilfe, n	-	1
5 - Ständige Gehhilfe, n	-	-
6 - Beidseitige Unterstützung, n	-	-
7 - Rollstuhl/Elektroroller, n	2	-
8 - Bettlägerig, n	-	-
Verlaufsform der MS		
RRMS, n	10	5
SPMS, n	4	1
PPMS, n	1	2

PDDS = Patient Determined Disease Steps (Selbsteinschätzung des Grades der Beeinträchtigung); RRMS = schubförmig remittierende MS; SPMS = sekundär progrediente MS; PPMS = primär progrediente MS

Die MS-Betroffenen waren in beiden Testphasen überwiegend weiblich und mittleren Alters. Die Mehrheit hatte eine schubförmig remittierende MS mit leichten Beeinträchtigungen und lebte seit mehr als fünf Jahren mit der MS. Die an der Machbarkeitsstudie teilnehmenden MS-Expert:innen (n=8), bestehend aus fünf

Neurologen, zwei Ernährungswissenschaftlerinnen und einem Sportwissenschaftler, waren im mittleren Alter (Median=54, Spannweite=32-54) und sechs von ihnen waren männlich. Alle weiteren Ergebnisse der drei Testphasen werden aufgrund ihres Umfangs und ihrer inhaltlichen Überschneidungen zusammen dargestellt. Dabei wird auf die Benutzerfreundlichkeit und den optischen Eindruck, die wahrgenommene Qualität und Personalisierung der Inhalte sowie auf die Zufriedenheit und den wahrgenommenen Nutzen von levidex innerhalb der drei Testphasen eingegangen.

Benutzerfreundlichkeit und optischer Eindruck

Die Machbarkeitsstudie mit MS-Betroffenen hat durchweg gezeigt, dass die technische Anwendung von levidex machbar ist. Außerdem schätzten die Teilnehmenden das Layout sowie die einfache Navigation (13 von 15). Auch die Mehrheit der MS-Expert:innen (7 von 8) empfand levidex als visuell ansprechend. Nur ein MS-Experte (Neurologe) empfand die Visualisierung als eher eintönig und sehr textlastig, weshalb er empfahl, Videos und mehr Bilder für mehr grafische Abwechslung einzubauen. Die Anordnung der Gespräche wurde von fast allen MS-Expert:innen (7 von 8) als plausibel empfunden. Um die Benutzerfreundlichkeit von levidex zu verbessern, wurde eine Druckversion der Bedienungsanleitung erstellt, die künftigen Teilnehmenden zusammen mit den Anmeldedaten zugesandt werden sollte. Die Pilotstudie mit MS-Betroffenen zeigte ein gutes Maß an Akzeptanz und Praktikabilität. Die Hälfte der Teilnehmenden (4 von 8) hielt die Dauer der Gespräche für zu lang. Sie schätzten jedoch, dass Pausen jederzeit möglich waren. Ähnlich wie bei einem echten menschlichen Gespräch, werden die Inhalte in simulierten Dialogen vermittelt, die nur einmalig aufgerufen werden können. Hier hatten einige Teilnehmende Probleme mit der begrenzten Wiederholbarkeit der Gespräche. Ein Teilnehmer bemängelte die fehlende Möglichkeit, die bereits durchgearbeiteten Inhalte noch einmal zu lesen. Ein anderer Teilnehmer beklagte sogar eine Einschränkung der Informationsfreiheit. Aufgrund dieses Feedbacks wurden für jedes Gespräch kurze, jederzeit verfügbare Handouts mit Kernaussagen zusammengestellt und im Menü hinterlegt. Darüber hinaus werden die vermittelten Informationen in den letzten vier Auffrischungsgesprächen wiederholt. Ein Hinweis auf die begrenzte Wiederholbarkeit der Gespräche wurde zusätzlich in die Bedienungsanleitung aufgenommen, um falsche Erwartungen zu vermeiden.

Qualität und Personalisierung der Inhalte

Die Mehrheit der MS-Betroffenen in der Machbarkeitsstudie stimmte zu, dass die in levidex bereitgestellten Inhalte verständlich waren (14 von 15). Auch der Großteil der MS-Expert:innen (6 von 8) bestätigte die Verständlichkeit von levidex für MS-Betroffene. Ein MS-Experte (Sportwissenschaftler) empfand den Inhalt der Gespräche zur körperlichen Aktivität als angemessen, aber überladen. Auch das Einführungsgespräch wurde von den MS-Expert:innen im Allgemeinen als zu lang und komplex empfunden. Während einige MS-Betroffene (Machbarkeitsstudie: 5 von 15, Pilotstudie: 1 von 8) die optionalen Textnachrichten als lästig empfanden, wurde diese Funktion von allen anderen MS-Betroffenen geschätzt. Alle MS-Betroffenen der Machbarkeitsstudie und sechs von acht MS-Expert:innen bewerteten levidex als sehr vertrauenswürdig. Die Referenzen, einschließlich der in einfacher Sprache verfassten Zusammenfassungen, wurden zudem von fast allen MS-Betroffenen, die sie nutzten, als hilfreich angesehen (12 von 15). Die Zusatzmaterialien (z.B. Audioübungen, Handouts) und das Glossar wurden von allen MS-Betroffenen, die diese nutzten, ebenfalls als hilfreich eingeschätzt (Machbarkeitsstudie: 12 von 15, Pilotstudie: 5 von 8). Auch von den MS-Expert:innen wurden die Zusammenfassungen sowie das Glossar sehr geschätzt. Darüber hinaus schätzten zwei MS-Expert:innen (eine Ernährungswissenschaftlerin und ein Neurologe) die Evidenzkommunikation zu MS und Ernährung sowie zum Lebensstil im Allgemeinen, da sie sich der komplexen Evidenzlage in diesem Bereich bewusst waren. Einige MS-Betroffene (Machbarkeit: 4 von 15, Pilotierung: 4 von 8) merkten an, dass der simulierte Dialog nur eingeschränkte Antwortmöglichkeiten bot und schlugen vor, weitere neutrale Antwortmöglichkeiten aufzunehmen. Auch einige der teilnehmenden Neurologen wiesen darauf hin, dass die Antwortmöglichkeiten in den simulierten Dialogen ihrer Meinung nach zu begrenzt waren, weshalb sie diese als vorgegeben und teilweise aus dem Zusammenhang gerissen empfanden. Einige der Neurologen waren zudem bezüglich einer zu kritischen Betrachtung von Immuntherapien im Einführungsgespräch besorgt. Da die Entscheidungsfindung bezüglich Immuntherapien nicht im Fokus von levidex steht, wurde dieser Teil entfernt. Nach der Überarbeitung ermutigt levidex Nutzer:innen nun nur noch zur Entscheidungsfindung bei Immuntherapien und verweist sie bei weiteren immuntherapierelevanten Fragen an die behandelnden Neurolog:innen. Darüber

hinaus wurde das erste Gespräch aufgrund seiner Länge in zwei Teile aufgeteilt. Zusätzlich wurden in den Gesprächen mehr Pausenmöglichkeiten sowie ein Fortschrittsbalken implementiert, um die verbleibende Gesprächsdauer zu visualisieren.

Zufriedenheit und wahrgenommener Nutzen

Unter Verwendung eines Schulnotenformats, das von 1 (sehr gut) bis 6 (ungenügend) reicht, wurde levidex in der Machbarkeitsstudie als gut (Note 2) eingestuft, obwohl einige MS-Betroffene (4 von 15) und MS-Expert:innen (3 von 8) levidex nur als befriedigend (Note 3) wahrnahmen. In der Pilotstudie wurde levidex von 6 von 8 Teilnehmenden als gut (Note 2) bewertet. Während der Großteil der MS-Betroffenen levidex als relevant oder sehr relevant für neu diagnostizierte MS-Betroffene empfand (Machbarkeitsstudie: 10 von 15, Pilotstudie: alle Teilnehmenden), fühlten sich einige bereits mit den Inhalten vertraut und empfanden levidex daher als weniger relevant für sich selbst (Machbarkeitsstudie: 5 von 15, Pilotstudie: 5 von 8). Die Mehrheit der MS-Expert:innen (6 von 8) bewertete levidex als sehr relevant für MS-Betroffene. Während einige MS-Betroffene der Meinung waren, dass levidex besonders für neu diagnostizierte Personen geeignet sei, wiesen andere darauf hin, dass die Menge an Informationen für diese Zielgruppe zu viel sein könnte. Schließlich gab die Mehrheit aller MS-Betroffenen (20 von insgesamt 23) an, dass sie levidex wahrscheinlich oder sogar sehr wahrscheinlich Freund:innen oder Kolleg:innen empfehlen würden, die Hilfe bei der Bewältigung der Erkrankung benötigen könnten. Fünf MS-Betroffene aus der Pilotstudie berichteten, dass sie ihren Lebensstil durch die Nutzung von levidex geändert haben. Die MS-Expert:innen wurden gebeten, das Motivationspotenzial für eine langfristige Nutzung von levidex zu bewerten. Die diesbezüglichen Rückmeldungen waren gemischt. Obwohl fast alle (7 von 8) levidex als eher motivierend bis sehr motivierend einstuften, betonten sie, dass die Motivation sehr individuell sei und nicht alle MS-Betroffenen zugänglich für eine Verhaltensänderung allein aufgrund der Nutzung einer digitalen Gesundheitsanwendung seien. Einige MS-Expert:innen befürchteten, dass levidex im Hinblick auf parallele Verhaltensänderungen in vielen verschiedenen Bereichen zu anspruchsvoll sein könnte. Um die angestrebte Verhaltensänderung erreichbarer zu machen, empfahlen drei MS-Expert:innen eine spezifischere Zielsetzung, die auf positiven Formulierungen und praktischen Beispielen beruht. Aus diesem Grund

wurden die optionalen Textnachrichten um häufigere und gezieltere Impulse, insbesondere im Bereich Ernährung ergänzt.

4.3 Randomisiert kontrollierte Studie „POWER@MS1“

Im Folgenden werden primär drei Fragestellungen zum POWER@MS1 RCT adressiert:

1. War das RCT in seiner geplanten Form durchführbar?
2. Wurden das geplante Studiendesign und die entwickelte Intervention von Erstbetroffenen mit MS akzeptiert?
3. Konnte die geplante Zielgruppe und Stichprobengröße für das RCT rekrutiert werden?

Nach einem Amendment der Ein- und Ausschlusskriterien konnte das POWER@MS1 RCT wie in der Studienregistrierung (ClinicalTrials.gov: NCT03968172) und im Studienprotokoll festgelegt (3) durchgeführt werden. Da der Anteil an immuntherapierten Erstbetroffenen mit MS in den externen Studienzentren jedoch höher lag als erwartet und die Rekrutierung bedingt durch COVID-19 nur schleppend voranging, wurde das POWER@MS1 RCT für bereits immuntherapierte Erstbetroffene geöffnet. Die Randomisierung und Auswertung der Studienergebnisse erfolgten daher stratifiziert in Vortherapierte und Therapienaive. Ein verblindetes Fallzahlplanungsreview ergab aufgrund hoher Eventraten (MRT-Aktivität und Schübe) darüber hinaus eine geringere Anzahl notwendiger Studieneinschlüsse. Die Kalkulation von Ereignisraten zu neuen Läsionen und sicheren neuen Schüben (am 16.08.2021 insgesamt 46 sichere primäre Endpunktereignisse) sowie eine angenommene Dropoutrate von 20% ergab eine Fallzahl von 250 Patient:innen (125 pro Gruppe), die randomisiert werden müssten. Unter Einbezug von möglichen Schüben (am 16.08.2021 insgesamt 51 primäre Endpunktereignisse) müssten nur 216 Patient:innen (108 pro Gruppe) statt 328 randomisiert werden. Auf dieser Basis wurde die Studienregistrierung aktualisiert. Während des Screening-Prozesses im Zuge der Rekrutierung wurden 351 Erstbetroffene mit MS auf ihre Eignung hin überprüft und 117 davon ausgeschlossen (Screening-Daten sind nur von sieben Studienzentren verfügbar). Unter den ausgeschlossenen Personen erfüllten 66 nicht die Einschlusskriterien (z.B. aufgrund einer Immuntherapiebehandlung), 18 lehnten die Teilnahme ab (z.B. aufgrund von Zeitmangel oder fehlendem Interesse) und 33

wurden aus anderen Gründen ausgeschlossen (z.B. aufgrund der Entfernung zum Studienzentrum). Insgesamt konnten bis zum Abschluss der Rekrutierung (31.03.2022) 234 Erstbetroffene mit MS aus insgesamt 20 deutschlandweiten Studienzentren erfolgreich eingeschlossen und randomisiert werden (siehe Abbildung 5).

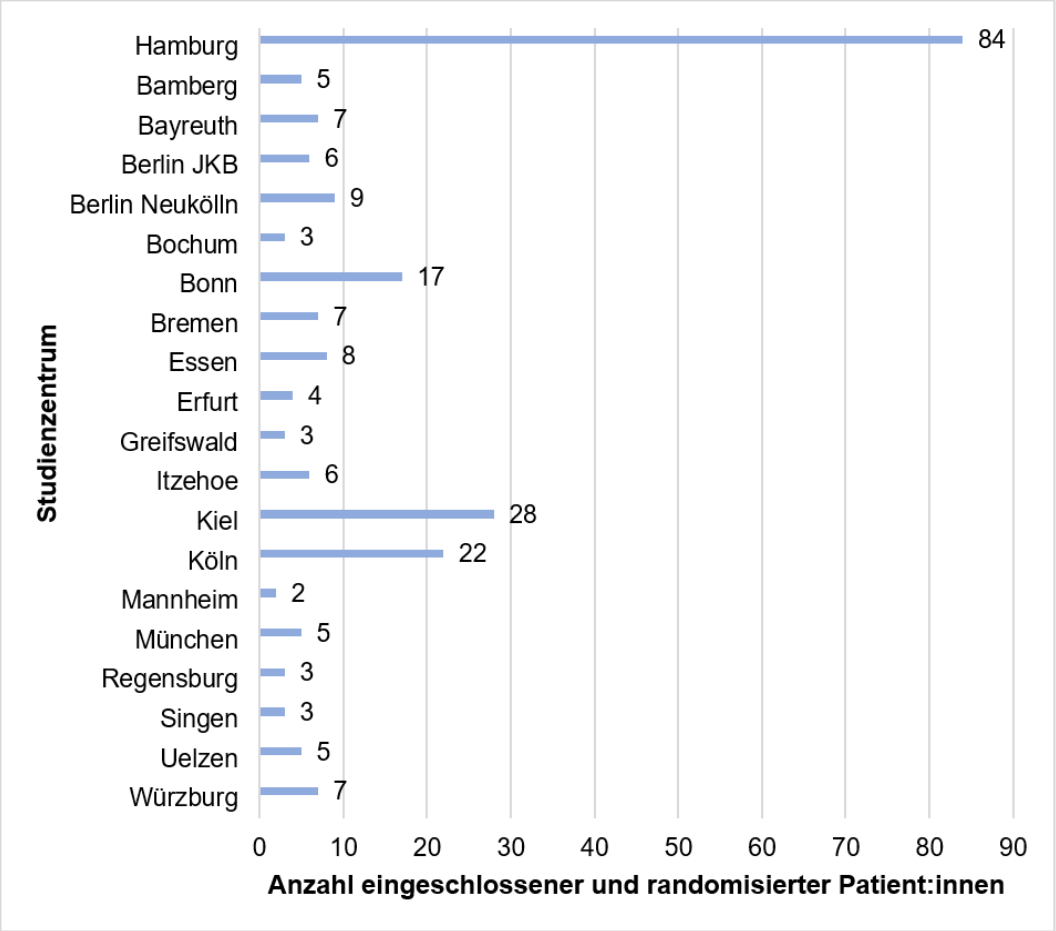

Abbildung 5: POWER@MS1 Studienteilnehmende nach Studienzentrum

Die frühe MS-Kohorte besteht aus 78 Teilnehmenden, die vor, und 156 Teilnehmenden, die nach der Änderung der Einschlusskriterien im März 2021 randomisiert wurden. Die meisten Teilnehmenden wurden mit etwa 36% im federführenden Studienzentrum in Hamburg eingeschlossen, gefolgt von einem Zentrum in Kiel mit etwa 12%, in Köln mit 9% und in Bonn mit 7% der Studieneinschlüsse. Während der Großteil der Teilnehmenden (91%, n=212) die geplante Zielgruppe repräsentiert (3), lag bei etwa 9% (n=22) der Teilnehmenden zum Studieneinschluss eine Protokollverletzung vor. Darunter fallen bis zu fünf Monate vor Studieneinschluss durchgeführte MRTs (n=11), fehlende MS-typische

Liquorbefunde mit Nachweis oligoklonaler Banden (n=5), Kortisontherapien innerhalb von vier Wochen vor Studieneinschluss (n=3), der MS-Diagnosezeitpunkt 14 Monate vor Studieneinschluss (n=2) sowie das Vorliegen nur einer MS-typischen T2-Läsion (n=1).

Die Anzahl an Studienabbrüchen bis zum Studienende liegt mit 15 Personen bei unter 7%. Zusätzlich kommen sieben Personen hinzu, die im Verlauf der Studie nicht mehr erreicht werden konnten (lost to follow-up). Insgesamt haben somit 91% (n=212) der Teilnehmenden die POWER@MS1 Studie abgeschlossen. Aufgrund der geringen Anzahl von Studienabbrüchen und Personen, die nicht mehr nachbeobachtet werden konnten, ist eine gute Akzeptanz der Studie anzunehmen. Auch vorläufige Nutzungsdaten zu levidex bestätigen eine gute Akzeptanz der Intervention. Die Daten der begleitenden Prozessevaluation werden im Herbst 2023 weitere Informationen zur Akzeptanz der Studie sowie der Intervention liefern.

4.4 Analyse der „POWER@MS1“ Basisdaten

Im Folgenden werden die Basisdaten der Studienteilnehmenden (n=234) zum Zeitpunkt des Studieneinschlusses (Baseline) sowie die Kernergebnisse einer weiterführenden explorativen Analyse dieser Daten präsentiert, welche das Ziel hatten, folgende Fragestellungen zu beantworten:

1. Sind klinische Charakteristika von Personen mit früher MS miteinander oder mit der Behandlung mit Immuntherapeutika assoziiert?

2. Sind demografische oder klinische Charakteristika von Personen mit früher MS mit dem Gesundheitsverhalten oder dem Vorliegen von Komorbiditäten assoziiert?

3. Ist das Gesundheitsverhalten von Personen mit früher MS miteinander oder mit dem Vorliegen von Komorbiditäten assoziiert?

4. Sind klinische Charakteristika von Personen mit früher MS mit dem Interesse an Möglichkeiten zur Optimierung des Gesundheitsverhaltens, der Absicht, das Gesundheitsverhalten zu verändern, oder mit Stadien der Verhaltensänderung assoziiert?

Demografische und klinische Charakteristika der Studienpopulation zum Zeitpunkt der Baseline-Datenerhebung sind in Tabelle 4 aufgeführt.

Tabelle 4: Demografische und klinische Charakteristika der Studienteilnehmenden an Baseline

	Baseline (n = 234)
Alter in Jahren, Mittelwert (SD)	36,1 (9,9)
Weiblich, n (%)	184 (78,6)
Schulbildung, n (%)[a]	
< 12 Jahre	74 (32,9)
≥ 12 Jahre	151 (67,1)
Berufstätige, n (%)[b]	213 (91,4)
Keine oder eher wenig sitzende Tätigkeiten[b]	52 (24,6)
Eher mehr oder viel sitzende Tätigkeiten[b]	159 (75,4)
Erkrankungsdauer in Monaten, Mittelwert (SD)	4,4 (4,0)
EDSS, Median (IQA)	1 (0-2)
Anzahl bisheriger Schübe, Median (IQA)	1 (1-2)
Anzahl bisheriger T2-Läsionen, Median (IQA)	10 (5-14)
Anzahl immuntherapierter Personen, n (%)	70 (29,9)
Vorliegen von Komorbiditäten, n (%)[b]	135 (57,9)
Body-Mass-Index, Mittelwert (SD)[b]	25,2 (5,6)
Untergewicht (< 18.5 kg/m^2), n (%)	7 (3,0)
Normalgewicht (18.5-24.9 kg/m^2), n (%)	128 (55,4)
Übergewicht (25.0-29.9 kg/m^2), n (%)	61 (26,4)
Adipositas (≥ 30.0 kg/m^2), n (%)	35 (15,2)
HAQUAMS Gesamtscore, Mittelwert (SD)	1,7 (0,5)
HADS-D Angst, Mittelwert (SD)	6,7 (3,7)
Moderate bis schwere Angstsymptome (8-17), n (%)	78 (33,3)
Schwere Angstsymptome (11-17), n (%)	35 (15,0)
HADS-D Depression, Mittelwert (SD)	3,4 (3,3)
Moderate bis schwere Depressionssymptome (8-16), n (%)	25 (10,7)
Schwere Depressionssymptome (11-16), n (%)	12 (5,1)

EDSS = Expanded Disability Status Scale; HADS-D = Hospital Anxiety and Depression Scale (deutsche Version); HAQUAMS = Hamburg Quality of Life in Multiple Sclerosis Scale; IQA = Interquartilsabstand; SD = Standardabweichung.
[a] Fehlende Werte, n = 9.
[b] Fehlende Werte, n = 1-3.

Der Großteil der Studienteilnehmenden ist mit fast 79% weiblich und das durchschnittliche Alter der Teilnehmenden lag an Baseline bei 36 Jahren. Der Bildungsstatus ist mit 67% der Teilnehmenden mit mindestens zwölf Jahren Schulbildung als hoch einzustufen. Über 90% waren zum Zeitpunkt der Baseline-Erhebung berufstätig. Die Teilnehmenden waren im Mittel seit 4 Monaten an MS erkrankt und dabei mit einem EDSS Score von 1 (Median) gering körperlich beeinträchtigt. Die Teilnehmenden hatten bisher einen Schub (Median) und zehn T2-Läsionen (Median, kranial und spinal). Der Anteil der zum Zeitpunkt des Studieneinschlusses immuntherapierten Teilnehmenden lag bei knapp 30% und bei mehr als der Hälfte der Teilnehmenden lagen Komorbiditäten vor. Insgesamt waren 42% der MS-Betroffenen übergewichtig oder adipös (BMI ≥25kg/m^2). Die Lebensqualität ist mit einem durchschnittlichen HAQUAMS Gesamtscore von 1,7 zur Baseline-Erhebung hoch. Der Großteil der Studienteilnehmenden war durch Angst- und Depressionssymptome zudem nur gering psychisch belastet (gemessen durch das Screening-Instrument HADS-D). Moderate bis schwere Angstsymptome (Score: 8-17) lagen an Baseline dennoch bei etwa einem Drittel der Teilnehmenden (n=78) und moderate bis schwere Depressionssymptome (Score: 11-16) bei etwa 10% der Teilnehmenden (n=25) vor. Davon waren 15% (n=35) durch schwere Angstsymptome und etwa 5% (n=12) durch schwere Depressionssymptome hoch psychisch belastet.

Kerndaten zum Gesundheitsverhalten der Studienpopulation zum Zeitpunkt der Baseline-Datenerhebung sind in Tabelle 5 aufgeführt.

Tabelle 5: Gesundheitsverhalten der Studienteilnehmenden an Baseline

	Baseline (n = 234)
Raucher:innen, n (%)[a]	45 (19,2)
Dauer in Jahren, Mittelwert (SD)[b]	18,1 (10)
Diet Score*, Mittelwert (SD)	5,1 (1,4)
GLTEQ HCS, Mittelwert (SD)	24,6 (19,1)
Unzureichend aktiv (unter 14), n (%)	40 (18)
Moderat aktiv (14-23), n (%)	42 (17,5)
Ausreichend aktiv (24 und höher)	146 (64,0)
Interesse an Möglichkeiten der Lebensstilveränderung, Mittelwert (SD)°[a]	8,8 (1,6)

Absicht das Bewegungsverhalten zu verändern, n (%)	7,0 (2,9)
Absicht das Ernährungsverhalten zu verändern, n (%)	7,3 (2,5)
Absicht das Schlafverhalten zu verändern	6,0 (3,1)
Absicht das Stressmanagement zu optimieren	8,6 (2,1)

GLTEQ HCS = Godin Leisure-Time Exercise Questionnaire health contribution score (Differenzierung gewöhnlich ausgeübter Freizeitaktivitäten nach Intensität); SD = Standardabweichung.
[a] Fehlende Werte, n = 1-3.
[b] Fehlende Werte, n = 8.
* Punktwert für gesunde Ernährung von 0 (keine Aufnahme wichtiger Lebensmittelgruppen) bis 10 (maximale Aufnahme wichtiger Lebensmittelgruppen)
°Likert-Skala von 0 ("stimme überhaupt nicht zu") bis 10 ("stimme voll zu").

Der Anteil an Raucher:innen lag an Baseline bei fast 20%. Mit einem mittleren Diet Score von 5,1 hielten sich die Teilnehmenden im Durchschnitt nur mäßig an Verzehrsempfehlungen für wichtige Lebensmittelgruppen (z. B. Gemüse, Obst und fettreicher Fisch). Hinsichtlich der körperlichen Aktivität wurden 64% der frühen MS-Kohorte als im Rahmen von Freizeitaktivitäten ausreichend aktiv eingestuft, während mehr als ein Drittel nur moderat oder unzureichend aktiv war. Mit einem Mittelwert von 8,8 (auf einer Skala von 0 bis 10, wobei 10 für volle Zustimmung steht) war das Interesse an Möglichkeiten der Lebensstilveränderung groß. Hinsichtlich der Absicht, ein bestimmtes Gesundheitsverhalten zu verändern, wurde die Optimierung des Stressmanagements als am relevantesten angesehen (Mittelwert: 8,6), gefolgt von dem Ernährungsverhalten (Mittelwert: 7,3) und dem Bewegungsverhalten (Mittelwert: 7,0).

Im folgenden Abschnitt werden die Kernergebnisse der weiterführenden explorativen Analyse der Basisdaten beschrieben. Eine stärkere körperliche Beeinträchtigung (gemessen als höhere EDSS-Werte) bei früher MS war mit einem höheren Alter bei Diagnosestellung (β=2,4; 95%-CI:[1,16,3,64],p<0,001), einer höheren Schubrate (RR=1,13; 95%-CI:[1. 01,1.25],p=0.02), einer höheren T2-Läsionslast (RR=1.2; 95%-CI:[1.08,1.32],p<0.001) sowie einer geringeren Lebensqualität (β=0.185; 95%-CI:[0.12,0.25],p<0.001) assoziiert. Die Behandlung mit Immuntherapeutika war nicht mit klinischen Charakteristika der frühen MS-Kohorte verbunden. Ein niedrigerer Bildungsstand der Studienteilnehmenden war mit aktuellem Rauchen (χ2=25; p<0,001), einem ungesünderen Ernährungsverhalten (β=0.89; 95%-CI:[0.47,1.31],p<0.001), einem höheren BMI (β=-1.82; 95%-CI: [-3.37,-0.27],p=0.02) sowie einem unzureichenden Bewegungsverhalten im Rahmen von Freizeitaktivitäten (β=10.02; 95%-CI: [3.97,16.06],p<0.001) assoziiert. Darüber

hinaus war aktuelles Rauchen mit einem ungesünderen Ernährungsverhalten (β=-1,26; 95%-CI:[-1,75,-0,78],p<0,001) und einer höheren T2-Läsionslast (RR=0,76; 95%-CI:[0,59,0,97],p=0,033) assoziiert. Mit einer mittleren erwarteten Anzahl von 15,53 (95%-CI:[12,4,19,47]) T2-Läsionen bei Raucher:innen und 11,8 (95%-CI:[10,54,13,2]) T2-Läsionen bei Nichtraucher:innen, hatten Nichtraucher:innen in dieser frühen MS-Kohorte zum Zeitpunkt des Studieneinschlusses etwa 24% weniger T2-Läsionen als Raucher:innen. Das Gesundheitsverhalten der frühen MS-Kohorte war jedoch nicht mit dem Vorliegen von Komorbiditäten verbunden. Zudem waren klinische Charakteristika der frühen MS-Kohorte nicht mit dem generellen Interesse an Möglichkeiten der Lebensstilveränderung verbunden. Eine stärkere Absicht zur Optimierung des Stressmanagements unter den teilnehmenden Erstbetroffenen mit MS konnte jedoch durch eine höhere T2-Läsionslast (β=0,029; 95%-CI:[0,006,0,05],p=0,015), eine stärkere körperliche Beeinträchtigung (β=0,388; 95%-CI:[0,12,0,65],p=0,004) und eine geringere Lebensqualität (β=0,982; 95%-CI:[0,47,1,49],p<0,001) erklärt werden. Auch eine stärkere Absicht das Bewegungsverhalten zu verändern konnte durch eine stärkere körperliche Beeinträchtigung (β=0,39; 95%-CI:[0,01,0,77],p=0,043) und eine geringere Lebensqualität (β=0,745; 95%-CI:[0,01,1,47],p=0,046) unter den teilnehmenden Erstbetroffenen mit MS erklärt werden. Darüber hinaus deutete eine geringere Lebensqualität auf eine stärkere Absicht hin, das Schlafverhalten zu verändern (β=1,82; 95%-CI:[1,08,2,56],p<0,001). Es gab jedoch keinen Zusammenhang zwischen klinischen Charakteristika der frühen MS-Kohorte und Stadien der Verhaltensänderung.

5 Diskussion

Die Ergebnisse der im Rahmen dieser Dissertation aufgeführten Machbarkeits- und Pilotstudie haben die Überarbeitung und Finalisierung einer neuen digitalen Gesundheitsanwendung (levidex) für Erstbetroffene mit MS ermöglicht. Während allen drei Testphasen wurden relevante Erkenntnisse für Änderungen gesammelt und die ursprüngliche Version von levidex entsprechend angepasst. Levidex wurde als umfassend und komplex eingestuft, aber gleichzeitig von den teilnehmenden MS-Betroffenen und MS-Expert:innen akzeptiert und als machbar eingestuft. Insbesondere das Vertrauen in levidex und die wahrgenommene Relevanz für Erstbetroffene mit MS waren hoch. Trotz der Bedenken einiger MS-Expert:innen hinsichtlich der Komplexität, empfanden MS-Betroffene levidex als verständlich und schätzten insbesondere das Glossar, die zusammenfassenden Handouts und die Audioübungen. Die MS-Expert:innen schätzten die Evidenzkommunikation durch EBPI in levidex, welche ihrer Ansicht nach die Glaubwürdigkeit der Intervention erhöht. Eine umfassende und verständliche Darstellung wissenschaftlicher Evidenz und Informationen mit praktischer Relevanz sind im Sinne der Patient:innenzentrierung essenziell (75). Dabei sollen EBPI auf Grundlage der individuellen Gesundheitskompetenz und -bedürfnisse in verschiedenen Komplexitätsstufen zugänglich gemacht werden (76). In levidex werden daher laienverständliche Zusammenfassungen mit vereinfachten Informationen zum Studiendesign, den relevanten Ergebnissen sowie den Limitationen für alle Referenzen zur Verfügung gestellt. Zusätzlich wird auf die Originalreferenz der zitierten Studien verwiesen, um Nutzer:innen eine weiterführende autonome Informationssuche zu ermöglichen. Mithilfe zusätzlicher Erläuterungen zu wissenschaftlichen Methoden, verschiedenen Studiendesigns und ihnen innewohnenden Limitationen wird durch die Nutzung von levidex zudem eine kritische Bewertung der Evidenz gefördert.

Durch die Charakterisierung der im Bereich Ernährung angestrebten Verhaltensänderung wurde ein breites Spektrum eingesetzter BCTs identifiziert. Mit zunehmender Anzahl von BCTs, die in Interventionen verwendet werden, wurden größere Effekte auf das Verhalten beobachtet (77). Eine Klassifizierung der exakten Anzahl und Kombination von BCTs, die bei Interventionen zur Verhaltensänderung

als wirksam eingestuft werden können, konnte jedoch noch nicht definiert werden (44). In einer Übersichtsarbeit zu Ernährungsinterventionen für Menschen mit neurologischen Erkrankungen (einschließlich MS) konnte gezeigt werden, dass die BCTs „4.1 Anleitung zur Ausführung eines Verhaltens“, „9.1 Expert:innenmeinung (vertrauenswürdige Quelle)“ und „8.1 Üben und Wiederholen“ dort am häufigsten verwendeten werden (78). Obwohl sich dieses Ergebnis mit den am häufigsten in levidex eingesetzten BCTs deckt, bleibt aufgrund der Heterogenität bezüglich der Ergebnisse anderer Studien (79, 80) weiterhin unklar, welche BCTs für Ernährungsinterventionen am wirksamsten sind. In Kombination mit dem POWER@MS1 RCT besteht dennoch die Chance, weitere Erkenntnisse zu wirksamen BCTs im Kontext von Ernährungsinterventionen für MS-Betroffene zu gewinnen. Die POWER@MS1 Ergebnisse können durch die Charakterisierung der BCTs zukünftig möglicherweise mit den Wirkmechanismen von levidex abgeglichen werden, um die Beziehung zwischen den implementierten BCTs und ihrer Wirksamkeit hinsichtlich der anvisierten Änderung des Ernährungsverhaltens zu spezifizieren. Möglicherweise könnte dies durch weitere Evidenzsynthesen zur Identifizierung eines Kernsatzes von BCTs im Ernährungskontext beitragen. Im Falle signifikanter Effekte in anderen Lebensstilbereichen (z.B. körperliche Aktivität, psychisches Wohlbefinden) sollte eine Charakterisierung der eingesetzten BCTs in weiteren levidex-Inhalten vorgenommen werden.

Obwohl die Ergebnisse der Machbarkeits- und Pilotstudie die Idee unterstützen, dass levidex MS-Betroffene dazu motivieren kann, ihren Lebensstil zu ändern, ist die Änderung von Lebensgewohnheiten herausfordernd. Es bleibt daher unklar, ob eine digitale Gesundheitsanwendung ausreicht, um eine langfristige Verhaltensänderung zu ermöglichen. Eine aktuelle Metaanalyse internetbasierter Interventionen zur Förderung psychischer Gesundheit konnte jedoch zeigen, dass der zusätzliche Nutzen persönlich angeleiteter Interventionen gering sein könnte (81). Im Vergleich zu kostenintensiven und zeitaufwändigen persönlich vermittelten Interventionen, könnte levidex eine kosteneffiziente und unterstützende Ergänzung der Standardversorgung darstellen, die auch im ländlichen Raum leicht umgesetzt werden kann. Das POWER@MS1 RCT ist außerdem die erste Studie, in der die Auswirkungen einer Lebensstilmanagementintervention in Kombination mit EBPI auf die Entzündungsaktivität bei MS untersucht werden. Das vorwiegend weibliche

Geschlecht der Studienteilnehmenden im POWER@MS1 RCT deckt sich mit aktuellen Daten zur Prävalenz der MS (6). Das Alter der Teilnehmenden liegt mit ca. 36 Jahren für eine Kohorte von Erstbetroffenen jedoch im oberen Segment, da die MS in der Regel zwischen dem 20. und dem 40. Lebensjahr beginnt. Der Anteil an Raucher:innen ist mit fast 20% etwas niedriger als in der deutschen Allgemeinbevölkerung, in welcher der Anteil bei etwa 28% liegt (82) und niedriger als in einer vergleichbaren deutschen MS-Kohorte mit etwa 32% Raucher:innen (83). Angesichts der Evidenz für negative Auswirkungen des Rauchens auf den MS Verlauf, wie schnellere Progression (22) und langfristig schlechtere kognitive Leistungsfähigkeit (84) sowie für eine höhere Moralität (85), ist der Anteil an Raucher:innen unter den teilnehmenden MS-Betroffenen dennoch als hoch einzustufen. Außerdem war das Rauchen mit einem ungesünderen Ernährungsverhalten verbunden und das gleichzeitige Auftreten dieser modifizierbaren Risikofaktoren könnte zu einer Kumulierung negativer Auswirkungen führen (86). Die Raucherentwöhnung könnte im Frühstadium der MS besonders wichtig sein, da die Raucher:innen in dieser frühen MS-Kohorte bereits eine höhere Schwere der Erkrankung (gemessen als T2-Läsionslast) aufwiesen. Die Prävalenz von Übergewicht und Adipositas verdeutlicht aufgrund von kardiovaskulären Risikofaktoren und einer damit assoziierten erhöhten MS-Krankheitsaktivität und Progression (87) zudem die Notwendigkeit einer Optimierung der Ernährungs- und Bewegungsgewohnheiten in dieser frühen MS-Kohorte. Obwohl die selbstberichtete psychische Belastung durch Angst- und Depressionssymptome bei dem Großteil der Teilnehmenden zum Zeitpunkt des Studieneinschlusses nur gering war, ist ein relevanter Anteil der Erstbetroffenen mit MS insbesondere durch Angstsymptome hoch psychisch belastet. Dabei stimmt die Häufigkeit von Depressionssymptomen mit den für eine große deutsche frühe MS-Kohorte berichteten Daten überein (88) und auch das Vorliegen von Angstsymptomen entspricht den Ergebnissen einer Meta-Analyse zu emotionalen Outcomes bei früher MS (89). Eine Optimierung des Stressmanagements wurde in dieser frühen MS-Kohorte zudem als hoch relevant angesehen. Dies ist möglicherweise auf die häufig als erheblich emotional belastend erlebte Diagnose der MS zurückzuführen (14, 15) und unterstreicht die Relevanz von Unterstützung bei der Entwicklung eines individualisierten Bewältigungskonzeptes in der Zeit nach einer MS-Diagnose.

5.1 Methodische Stärken und Limitationen

Die Ergebnisse der vorliegenden Dissertation müssen im Kontext der methodischen Stärken und Limitationen diskutiert werden. Eine Stärke dieser Arbeit ist die aktive Beteiligung von MS-Betroffenen und MS-Expert:innen an der Entwicklung von levidex, um den komplexen Bedürfnissen von Erstbetroffenen mit MS möglichst gerecht zu werden. Die Ergebnisse der Machbarkeits- und Pilotstudie sind durch die geringe Stichprobengröße in allen drei Testphasen begrenzt belastbar. Die Stichprobe bestand zudem aus erfahrenen MS-Betroffenen, bei welchen die Diagnose vor mehr als fünf Jahren gestellt wurde, während levidex sich an Erstbetroffene mit MS richtet. Erfahrenere und bereits informierte MS-Betroffene können jedoch möglicherweise besser einschätzen, was sie unmittelbar nach der MS-Diagnose gebraucht hätten und welche Inhalte für sie relevant gewesen wären, da ein relevanter Anteil der mit MS diagnostizierten Personen nach Erhalt der Diagnose erheblich emotional belastet sein kann (14). Aufgrund der vorgesehenen Nutzungsdauer von einem Jahr konnte levidex außerdem nicht in seinem vollen Umfang und mit der sequentiellen Aktivierung der Gespräche getestet werden. Die im Zuge der Machbarkeits- und Pilotstudie geäußerten Bedenken werden im Rahmen der Prozessevaluation des POWER@MS1 RCTs aufgegriffen, um hier eine größere Datenbasis zu schaffen und gegebenenfalls eine Weiterentwicklung von levidex zu ermöglichen. Die Ergebnisse der Machbarkeits- und Pilotstudie deuten dennoch darauf hin, dass levidex für alle MS-Stadien hilfreich sein könnte. Darauf aufbauend konnte durch eine Kohortenstudie mit 43 MS-Betroffenen in einem fortgeschrittenen Stadium der Erkrankung eine hohe Akzeptanz einer angepassten Version von levidex gezeigt werden, die speziell auf die Bedürfnisse späterer MS-Stadien zugeschnitten wurde (90). Darüber hinaus gab es nach der Nutzung von levidex einen Trend in Richtung optimierter Ernährungs- und Bewegungsgewohnheiten, welcher vermutlich aufgrund der geringen Stichprobengröße jedoch nicht statistisch signifikant war.

Obwohl levidex eine starke Individualisierung ermöglicht und gleichzeitig vollständig softwarebasiert ist, sind die Möglichkeiten zur Individualisierung im Rahmen digitaler Interventionen, die als simulierter Gesprächsverlauf konzipiert sind, in ihren vorprogrammierten Antwortmöglichkeiten begrenzt. Eine weitere Limitation von levidex könnte das Fehlen einer persönlichen Beratung sein, welche das Ausmaß

und die Nachhaltigkeit von Veränderungen der Lebensgewohnheiten möglicherweise einschränken könnte. Gleichzeitig ist levidex durch die Vermittlung von lebensstilbezogenen EBPI und den Einsatz von zahlreichen Verhaltensänderungsstrategien einzigartig. Bemerkenswert ist zudem, dass alle Interventionsfunktionen, alle COM-B-Komponenten und alle TDF-Domänen in den ernährungsbezogenen Inhalten von levidex abgedeckt wurden. Es gab nur wenig verhaltensändernde Stimuli, die nicht eindeutig einer BCT zuzuordnen waren.

Da das POWER@MS1 RCT auf Basis der verfügbaren finanziellen Ressourcen als pragmatische Studie konzipiert wurde, wurden patient:innenberichtete Instrumente als sekundäre Endpunkte ausgewählt. Nichtsdestotrotz wird der primäre Endpunkt durch objektive und sensitive Messverfahren erhoben (Auftreten neuer Läsionen anhand MRT-Untersuchung; neue Schübe durch klinische Bewertung verblindeter Neurolog:innen). Es ist somit das erste RCT, in dem die Auswirkungen einer digitalen Gesundheitsanwendung zum Lebensstilmanagement in Kombination mit EBPI auf die entzündliche Krankheitsaktivität bei MS untersucht werden.

5.2 Schlussfolgerungen und Ausblick

MS-Betroffene suchen nach Möglichkeiten, selbst etwas für ihre Gesundheit zu tun und gleichzeitig verbessert sich die Evidenz, dass Lebensstilfaktoren den Verlauf der Erkrankung beeinflussen können (22). Die digitale Gesundheitsanwendung levidex bietet die Möglichkeit, lebensstilbezogene Aspekte, die sich potenziell auf die Gesundheit auswirken, anzupassen. Zusammenfassend hat levidex das Potenzial, die Lücke zwischen der begrenzten Zeit in neurologischen Sprechstunden und dem lebensstilbezogenen Informationsbedarf von MS-Betroffenen zu schließen. Darüber hinaus kann es MS-Betroffenen ermöglichen, sich frühzeitig durch eine Optimierung ihrer Lebensgewohnheiten auf die MS einzustellen. Aufgrund der erfolgreichen Rekrutierung und geringen Studienabbruchsrate sind belastbare Ergebnisse des POWER@MS1 RCTs realistisch. Nach Abschluss der Datenerhebung im April 2023 liegen die Ergebnisse voraussichtlich im Herbst 2023 vor. Bestenfalls zeigen die Ergebnisse des RCTs, dass eine digitale Gesundheitsanwendung zum Lebensstilmanagement bei Erstbetroffenen mit MS zu einer Reduktion der Krankheitsaktivität sowie einer Verbesserung der Lebensqualität und des Lebensstils (z.B. Optimierung von Ernährungsgewohnheiten) führt. Im Falle eines

Wirksamkeitsnachweises könnte das Lebensstilmanagement als mutmaßlich krankheitsverändernd eingestuft werden. Dies kann sich auf die MS-Leitlinien auswirken. In Anbetracht der unzureichenden Studienlage zu mHealth-Anwendungen (z.B. Apps) im Kontext des Selbstmanagements von MS-Betroffenen (91, 92) stellt die Evaluation der verhaltenstherapeutisch orientierten digitalen Gesundheitsanwendung levidex einen relevanten Beitrag zur Verbesserung der Evidenzbasis dar.

II Abkürzungsverzeichnis

BCT	Behaviour Change Technique (Technik der Verhaltensänderung)
BCW	Behaviour Change Wheel
BMI	Body-Mass-Index
CI	Konfidenzintervall
COM-B	Capability-Opportunity-Motivation-Behaviour
COVID-19	Coronavirus-Krankheit-2019
DMSG	Deutsche Multiple Sklerose Gesellschaft
EBPI	evidenzbasierte Patient:inneninformationen
EDSS	Expanded Disability Status Scale (Grad der Behinderung bei MS)
HADS-D	Hospital Anxiety and Depression Scale (deutsche Version)
HAQUAMS	Hamburg Quality of Life in Multiple Sclerosis Scale
IQA	Interquartilsabstand
MRT	Magnetresonanztomographie
MS	Multiple Sklerose
n	Größe der Stichprobe
PAM	Patient Activation Measure
PDDS	Patient Determined Disease Steps (Grad der selbstberichteten Behinderung bei MS)
PPMS	primär progrediente MS
RCT	randomised controlled trial (randomisiert kontrollierte Studie)
RRMS	schubförmig remittierende MS
SD	Standardabweichung
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SPMS	sekundär progrediente MS
TDF	Theoretical Domains Framework

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IV Publikation 1

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‘That would have been the perfect thing after diagnosis’: development of a digital lifestyle management application in multiple sclerosis

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Abstract

Background: A multiple sclerosis (MS) diagnosis urges decision-making on immunotherapies, while persons with MS (PwMS) need to develop a coping concept in parallel. At this stage, PwMS ask how they themselves may contribute to controlling the disease. Evidence suggests that maintaining a healthy lifestyle (e.g. physical activity and stress management) is a key factor for healthy aging and preserving activity, while data on MS are complex.

Objectives: Following the Medical Research Council framework, this study aimed to develop and investigate the feasibility of a new digital health application that conveys evidence-based patient information about lifestyle factors in MS and engages PwMS in relevant behaviour change techniques.

Methods: Based on a digital health application promoting lifestyle management in breast cancer survivors, an MS-specific adaptation (‘levidex’) was developed. Feasibility was tested with 15 PwMS and eight MS experts. Subsequently, a six-week pilot study with eight PwMS was conducted. All participants provided feedback on practicability and acceptability via a questionnaire and took part in a semi-structured telephone interview. Levidex was revised after each test phase.

Results: The final levidex tool includes 16 modules, 177 references and several other functions. Feasibility results showed that PwMS and MS experts perceived levidex as understandable (14 out of 15; 6 out of 8), trustworthy (15 out of 15; 8 out of 8), and relevant (10 out of 15; 8 out of 8). Interviews revealed potential for improvement regarding the length and complexity of some content. Piloting of the revised version confirmed good feasibility and high acceptance. Most participants felt inspired to initiate (7 out of 8) or had already implemented (5 out of 8) lifestyle changes after working with levidex.

Conclusion: Results suggest that levidex is feasible and well-accepted by PwMS and MS experts. It might be a useful tool to support PwMS in adapting to their diagnosis and initiating health-promoting lifestyle changes.

Keywords: eHealth, evidence-based medicine, feasibility testing, piloting, digital health application, lifestyle intervention, multiple sclerosis

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Introduction

The incidence of multiple sclerosis (MS) is increasing worldwide, while the inflammatory activity in the early course seems lower, possibly leading to later disability development.[1] Modified diagnostic criteria may contribute to this observation.[2] After

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diagnosis, persons with MS (PwMS) are shocked and often even traumatised[3] but at the same time urged to make a decision on immunotherapies. Based on their need for time to develop a coping concept and also based on complex evidence of effects and side effects of immunotherapies, not everyone embarks on treatment directly after diagnosis,[4] although immediate action is recommended. However, PwMS often ask what they themselves might contribute to optimal adaptation. Lifestyle factors or modifiable risk factors are increasingly considered relevant in MS.[5] Exercise training might have an impact on disease activity as well as on surrogates of brain integrity,[6] and the same holds true for psychological interventions.[7,8] Finally, although there is a lack of controlled studies on the potential influence of dietary factors on MS,[9] adhering to guidelines for a healthy diet while taking MS-specific aspects into account[10] is highly recommended.

PwMS who identify themselves as successfully managing MS often report that maintaining a healthy lifestyle appears to be a key factor for effective self-management,[11] and they regard the provision of lifestyle-related information as very important. However, time for personal advice and individual consultation regarding alternative treatment options and lifestyle changes is limited during typical patient-neurologist encounters. PwMS frequently use Internet sources and eHealth technologies to gather information.[12] One approach to closing the gap between limited time in neurologist encounters and lifestyle-related information needs of PwMS may be the provision of evidence-based patient information (EBPI)[13] via web-based services. While many small and short-term studies have shown beneficial effects of exercise and psychological interventions,[5] Internet interventions have rarely been studied in MS. However, we were recently able to show that digital health applications can ameliorate depression[14] and fatigue[15] in PwMS. A comprehensive web-based lifestyle intervention for PwMS based on behaviour change techniques (BCTs) has not yet been investigated, to our knowledge.

The goal of this study involving PwMS and MS experts was to develop and investigate the feasibility of a new, interactive digital lifestyle management application (termed 'levidex') that conveys EBPI and is intended to be used as an add-on to standard care among persons with early-stage MS.

Methods

The development and testing of levidex, including the subsequent evaluation in a randomised controlled trial (RCT),[16] is part of a 'multiphase mixed-methods study' covering the first three phases of the Medical Research Council (MRC) framework for the development and evaluation of complex interventions.[17] This paper focuses on the first two phases: development and piloting of the complex intervention involving PwMS and MS experts.

Intervention development

The complex intervention levidex is an MS-specific adaptation of 'optimune', a digital health application developed to promote lifestyle management in breast cancer survivors with proven efficacy in an RCT.[18,19] Both optimune and levidex were developed and are owned and operated by GAIA, a small-to-medium enterprise that specialises in the development and evaluation of digital health applications. Based on preliminary patient-education work[14,15,20,21] and the knowledge and suggestions of the multidisciplinary study team – consisting of neurologists, psychologists, health scientists and nutritionists – MS-specific topics to add to the existing programme were identified. Like other GAIA digital health applications, optimune and levidex were developed with the proprietary software platform broca®, which uses rule-based artificial intelligence algorithms to tailor information and therapeutic exercises to individual user characteristics. Broca-based digital interventions have been examined in more than 15 RCTs.[14,15,20,22,23] Using 'simulated dialogues' that mimic a conversational flow, broca-based digital health applications aim to engage users in therapeutic topics and exercises and continuously invite them to select one or several suitable response options. Based on individual responses, subsequent content is then tailored to match individual users' needs and preferences. For instance, PwMS can create individual exercise plans based on their own MS disease characteristics and physical ability, or choose between a variety of recipes based on preferred diets and current cooking skills. Like all broca-based programmes, levidex incorporates a broad range of BCTs, particularly those used in cognitive behavioural therapy (CBT), motivational interviewing, and mindfulness and acceptance approaches.[24] It follows the concept of patient empowerment,[25] and several CBT techniques (e.g. behavioural activation,

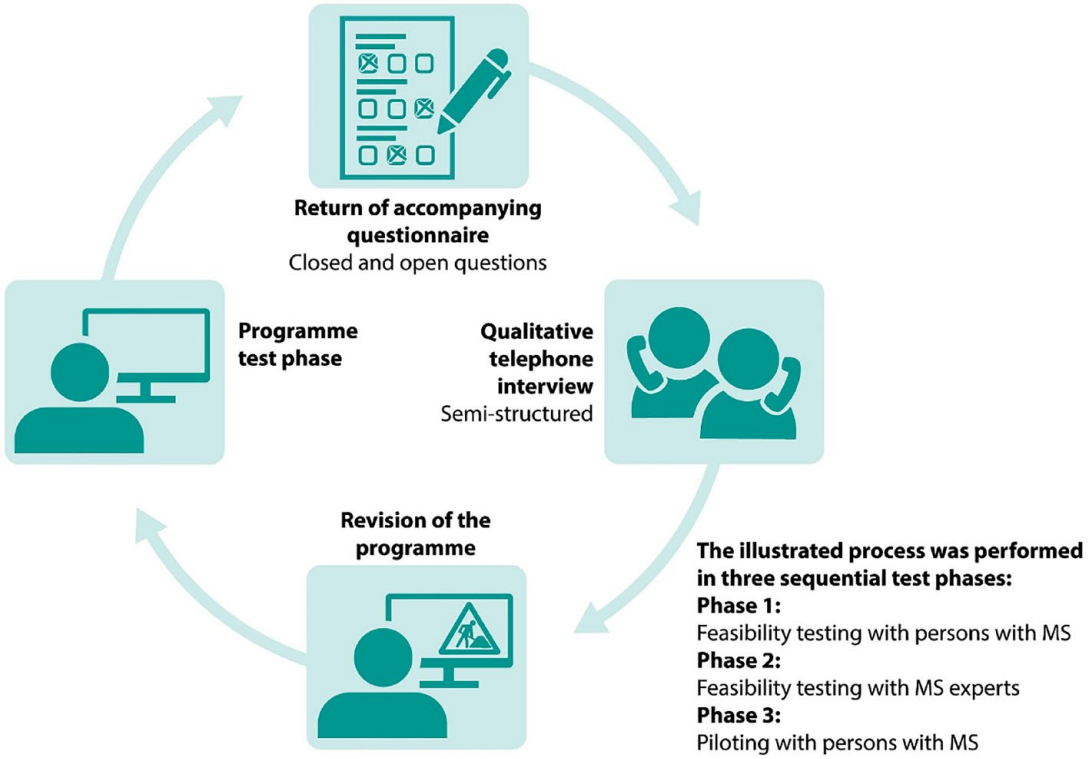

Figure 1. Feasibility testing and piloting.

goal-setting, and action-planning) form the main foundation of the intervention.[16] Moreover, incorporated BCTs are linked to the domains (theoretical constructs) provided in the Theoretical Domains Framework[26] and target physical activity, dietary behaviour, psychological well-being, and stress management in MS. Based on its theory-driven approach, levidex is expected to motivate participants to change their behaviour (e.g. increase their physical activity or optimise their dietary behaviour), improve their quality of life and possibly reduce inflammatory disease activity in MS. This approach was combined with EBPI.[13] The implemented information was specifically based on an extensive health technology report examining the possible influence of modifiable risk factors on the development of MS disability[5] as well as 177 references to scientific papers. Complete citation as well as a plain language summaries with simplified information, focusing on study design and relevant findings together with the limitations, are provided in levidex. In a scientific methods section, different study designs and their inherent limitations were also explained, aiming to enable a critical appraisal of the evidence by the users.

Feasibility testing and piloting

In accordance with the MRC framework, feasibility and progression criteria relating to the content and delivery of levidex as well as its practicability (e.g. login, length, and navigation), acceptability (e.g. practical applicability and motivation incentive) and perceived demand were explored in three sequential test phases that combined quantitative and qualitative methods based on guidelines for feasibility and pilot studies.[27,28] The extended Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist[27] for the reporting of this study is provided as Supplemental File. An overview of the methodological steps of the test phases is provided in Figure 1.

Due to the large amount of material provided in levidex, application of teach-back and think-aloud was not feasible. For this reason, questionnaires were used. Corresponding to the frameworks provided by Kowatsch *et al.*[29] and Allison *et al.*,[30] the questionnaires were divided into four parts: (1) participant demographics, (2) ease of use and appearance, (3) content quality and personalisation, and (4) satisfaction and perceived benefit. Patient Determined Disease Steps

(PDDS) scale[31] was used as a patient-reported outcome measure of disability in MS. Self-developed question items consisted of a mix of closed (mostly 6-point Likert-type scales) and open questions. Questionnaires were collected after each programme test phase. Responses to closed questions were analysed using descriptive statistics. Continuous variables were described using median and range, and categorical variables were expressed as counts. Responses to open questions were reviewed and categorised. Subsequently, semi-structured telephone interviews were conducted in each phase, based on the results of the filled-in questionnaires. The interviews were recorded, transcribed and analysed thematically.[32] Based on feedback discussions of the teams affiliated with UKE and GAIA, each test phase was completed with a revision of levidex based on the feedback evaluation.

Persons with relapsing-remitting MS (RRMS) were recruited for all development stages by GAIA's collaborating partners, from the German MS Society (DMSG) and from UKE's MS day clinic. Participants provided written informed consent and needed to be aged between 18 and 65 years and have Internet access. Feasibility participants were recruited in August 2018. In the feasibility study, participants were provided with login details for single modules (without specific allocation) of levidex for two weeks. In February 2019, a sample of eight PwMS with six weeks of access was intended for piloting, to ensure that all 16 modules were tested, two addressing each subject area. All piloting participants were asked to go through the introductory part and the booster modules. In both test phases, the sequential activation of modules was inactivated and full access was provided directly after login. The accompanying questionnaire and the qualitative telephone interview for the feasibility study focused on technical aspects of levidex.

After patient feedback in the feasibility phase, in October 2018, MS experts from different disciplines (neurologists, nutritionists, or sports scientists with an MS specialisation) from all over Germany were invited to give feedback on the revised levidex programme. After obtaining written informed consent, MS experts were provided with access to levidex for 2 weeks. They were asked to evaluate specific modules related to their expertise. Feasibility testing with MS experts focused on feedback regarding acceptability, content quality, and the motivational potential of levidex.

Results

Final levidex programme

An overview of the finalised version of levidex consisting of 16 modules is provided in Figure 2.

An introductory module explains the purpose of levidex and provides users with an overview of the anticipated timeframe and content. Levidex informs PwMS that an immunotherapy treatment decision needs to be made. More precisely, it provides overview information on the effectiveness of immunotherapies, including the evaluation and interpretation of effects, as well as absolute and relative risk reduction data and possible side effects. As an alternative to very early MS therapy, levidex points to the possibility of a watch-and-wait approach over a space of one to two years, accompanied by regular neurological and magnetic resonance imaging check-ups,[33] since the natural disease course without therapy for a period up to one or two years can help to better assess MS activity and then possibly better motivate for or against therapy. It should be noted that levidex does not intend to replace or prevent immunotherapies, but is designed as an add-on to standard care. Finally, the programme encourages participants to gather more information, take time to decide, and not put too much pressure on themselves. In the following, levidex addresses three main subject areas: psychological well-being and sleep management, dietary habits and physical activity, followed by four booster sessions (see Table 1).

In total, 177 references and plain language summaries are integrated in levidex. An example for each area with sources of varying quality (meta-analysis, cohort study, RCT) is given in Supplemental File 1. Levidex was designed to be accessed over one year. Each module takes about 30–45 minutes to complete, depending on reading speed, individual paths through the programme and decisions to listen to or skip optional audio exercises. The modules include tasks to be completed outside of levidex (e.g. planning exercises or shopping for certain foods) as well as exercises to engage with levidex (e.g. mindfulness meditation audio exercises). New modules are activated successively after a waiting period, allowing participants to reflect on the content and

Figure 2. Levidex module overview (final version).

complete tasks and exercises before starting a new module. Optional e-mails and short text messages inform participants about newly available modules. In addition, brief messages are sent to provide lifestyle-related information or brief therapeutic or motivational suggestions. Handouts in PDF format (worksheets and module summaries) and all audio recordings previously encountered can be accessed directly via a menu option. Optional self-monitoring questionnaires (e.g. daily mood check-ups, weekly assessments of physical activity) with individualised feedback and scores for self-reported behaviour performance are included, to visualise achievements over time. The menu also contains an instruction manual and a glossary with additional explanations for 62 terms. Sample screenshots of levidex are given in Supplemental File 2.

Feasibility testing and piloting with PwMS

Characteristics of the participating 23 PwMS (15 in the feasibility and eight in the pilot study) are shown in Table 2. Participants were predominantly female and middle-aged. The majority had RRMS with mild impairment and had been living with MS for more than 5 years. PwMS key quotes are given in Table 3. Supplementary qualitative data are provided in Supplemental File 3.

Ease of use and appearance. The feasibility study consistently showed that the technical use of levidex was feasible. Moreover, the participants generally appreciated the layout and easy navigation (13 out of 15). However, to facilitate the usability of the programme, a print-out version of the instruction manual was compiled to be sent to future participants along with the login details.

Table 1. Levidex subject areas and content.

Subject area	Content
Psychological well-being and sleep management (5 modules)	• EBPI on the potential impact of stress reduction, positive emotion, and sleep on the immune system and MS • Assessment of individual sleep quality and possible difficulties • Set of evidence-based CBT techniques for overcoming insomnia • Personalised suggestions for healthy sleep habits • Mindfulness practice and meditation (e.g. audio recordings and individually tailored exercises)
Dietary habits (3 modules)	• Assessment of individual dietary habits through screening questions • EBPI and dietary guidelines on healthy dietary patterns • Set of behaviour change techniques [e.g. goal-setting, action-planning and mental contrasting (of pros and cons or goal obstacles and solutions)] to increase the intake of recommended food groups (e.g. vegetables, whole grain, fish) and reduce the consumption of processed foods (e.g. processed meat, snacks) which potentially increase inflammation
Physical activity (2 modules)	• Reflection about the participants' current level of physical activity • EBPI on the impact of physical activity on MS symptoms • Set of behaviour change techniques (e.g. goal-setting, action-planning) to promote the adoption of optimised physical activity behaviour
Booster modules (4 modules)	• Recapitulation of essential content from previous modules • Discussion of the participants' progress • Provision of supporting techniques for long-term maintenance of achieved behaviour change

CBT, cognitive behavioural therapy; EBPI, evidence-based patient information; MS, multiple sclerosis.

Piloting of levidex generally indicated good levels of acceptance and practicability. It was even appreciated by one participant who usually did not use digital applications. Some participants (4 out of 8) were not satisfied with the module length and considered it too long. However, participants appreciated that breaks were possible at any time. Similar to a real human conversation, the modules are designed as simulated dialogues that can only be accessed once. Here, some participants struggled with the limited repeatability of modules. One participant criticised the lack of opportunity to reread the content he had worked through in the past. Another participant even claimed a restriction of the freedom for information. Based on this feedback, short handouts available at any time including key messages were incorporated for every module. Beyond that, information provided in the modules is repeated within the last four booster modules. Information regarding the limited repeatability of the modules was additionally added to the instruction manual to avoid false expectations.

Content quality and personalisation. The majority of PwMS in the feasibility cohort agreed or strongly agreed that the content provided in levidex was understandable (14 out of 15). Whereas some participants (feasibility: 5 out of 15, piloting: 1 out of 8) perceived the optional email and short text message reminder system as excessive or annoying, this feature was appreciated by all other participants. All feasibility participants agreed or strongly agreed that levidex was trustworthy. The references, including the plain language summaries provided, were considered helpful by almost all participants who used them (12 out of 15). Some participants (feasibility: 4 out of 15, piloting: 4 out of 8) noted that the simulated dialogue offered restricted answering options and suggested including neutral answers. The additional material (e.g. audio exercises, handouts) and the glossary were helpful for all participants who used them (feasibility: 12 out of 15, piloting: 5 out of 8).

Satisfaction and perceived benefit. By using a German-style school grades format ranging from 1 (very good) to 6 (insufficient), levidex was graded as good (grade 2) in the feasibility cohort, even though some participants (4 out of 15) only perceived it as satisfactory (grade 3). In the pilot study, levidex was graded as good (grade 2) by 6 out of 8 participants. While many participants perceived levidex as relevant or highly relevant for newly diagnosed PwMS (feasibility: 10 out of 15,

Table 2. Demographic and clinical characteristics of the samples of PwMS..

	Feasibility testing (*n* = 15)	Piloting (*n* = 8)
Age in years, median (range)	53 (26–60)	47 (23–54)
Female, *n*	11	4
Male, *n*	4	4
Education level		
Secondary school, *n*	6	1
High school/A-levels, *n*	5	4
University degree, *n*	4	3
Disease duration in years, median (range)	7 (1–19)	9 (2–25)
PDDS, median (range)	1 (0–7)	3 (1–4)
0–normal, *n*	3	–
1–mild disability, *n*	5	3
2–moderate disability, *n*	2	–
3–gait disability, *n*	3	4
4–early cane, *n*	–	1
5–late cane, *n*	–	–
6–bilateral support, *n*	–	–
7–wheelchair/scooter, *n*	2	–
8–bedridden, *n*	–	–
MS type		
RRMS, *n*	10	5
SPMS, *n*	4	1
PPMS, *n*	1	2

MS, multiple sclerosis; PDDS, patient determined disease steps; PPMS, primary progressive MS; PwMS, persons with MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

piloting: all participants), some already felt familiar with the content and thus perceived it as less relevant for themselves (feasibility: 5 out of 15, piloting: 5 out of 8). Nevertheless, five participants in the pilot study reported having implemented lifestyle changes through programme usage. While some participants felt that levidex was particularly suitable for newly diagnosed PwMS, others pointed out that the amount of information might be too much for this target group. Finally, the majority of all participants (20 out of 23) indicated that they would be likely or even very likely to recommend levidex to a friend or colleague who might need help regarding the handling of the disease.

Feasibility testing with MS experts

From 15 recruited MS experts, 11 signed informed consent, but only eight MS experts completed feasibility testing. The MS experts (five neurologists, two nutrition scientists, and one sports scientist) were middle-aged (median 54, range 32–54) and six were male. Expert key quotes are given in Table

Table 3. PwMS key quotes.

Evaluation criteria	PwMS key quote
Empowerment for lifestyle adaptation	"That would have been THE perfect thing after diagnosis! To know that there are other possibilities (scientifically proven) beyond stand-alone medication. This returns a sense of trust in your own body."[P14]
Barriers to digital health	"In principle, I was really pleasantly surprised, because I am not someone who actually enjoys sitting in front of a computer or playing with an app. So it really was the content I was interested in, rather than the format and yet I was surprised how well I got along with it." [PP05]
Quantity and depth of information	"Yes, a lot of details that I quite simply didn't know and that I have never seen brought together in this way before, particularly tailored to MS. Usually it's all rather generalised and I was really surprised by the depth of information, its thoroughness. And how in actually every area there was something I hadn't come across or heard about previously." [PP05]
	"I'm relatively deeply immersed in the material. For newly diagnosed patients it's way too much input. Less is more!" [P09]
Readyness	"To begin with you just want to be left in peace, or you are all-consumed with your own self and not yet. . . Caught up with your psyche and all that . . . This could very well be helpful then, but everyone is wired differently." [PP04]

MS, multiple sclerosis; PwMS, persons with MS.

Table 4. MS expert key quotes.

Evaluation criteria	MS expert key quote
Attitude towards disease modifying therapies (before revision)	"And generally I think that while the realm of drug therapy is well depicted, it probably does speak more to the sceptical viewpoint here, and what doesn't come through strongly enough, I think, is that there are patients with highly active MS who really do benefit from immunotherapy, and less so in other cases." [E03]
Quantity, quality and depth of information	"I think the glossary is really good, and these are absolutely the themes that are often raised in seminars and in consultations and they are the ones I must be ready to offer an opinion on. [. . .]So it is very serious, and very readable, and I believe that an impacted person who is in search of an answer to a particular point, and many people affected are on such quests in my experience, will truly find an answer. [. . .] And I think for those who want to know more, this [the plain language abstracts] is wonderful. And it remains an individual choice, what to click on or not. And above all the scope of the description of the study is just right. Short and to the point and all the essentials are in there."[E05]
MS and diet	"In my opinion it's a confidence-building measure to say, okay, we know there are these other things circulating on the internet at the moment, and this is our position on those." [E04]
	"How should I change my nutrition, how should I optimise my sleep? It would be best to work on physical exercise, too, not forgetting whatever else, stress management, say. But at some point, it could all get a little much, right? [. . .] I have to think of too many things at once. And just when I'm familiarising myself with one subject, the next one is already tapping at the door." [E06]

MS, multiple sclerosis.

4. Additional qualitative expert data are provided in Supplemental File 4.

Ease of use and appearance. Most participants (7 out of 8) regarded the arrangement of modules within levidex as plausible. The majority (7 out of 8) perceived it as visually appealing. Only one expert (neurologist) perceived the visualisation as rather monotonous and very text-heavy, which is why he recommended including videos and more images for more graphic variety.

Content quality and personalisation. Findings confirmed understandability, as most experts (6

out of 8) agreed that it was understandable for PwMS. One expert (sports scientist) perceived the content tailoring of the modules on physical activity as appropriate, but overloaded. The participating experts also generally perceived the introductory module as too long and complex. Some of the participating neurologists particularly expressed their concern about a too critical review of immunotherapies in the introductory module. As immunotherapy decision-making is not at the core of the intervention, this part was excluded from levidex. After the revision, levidex now only encourages immunotherapy decision-making and refers users to the treating neurologist for further immunotherapy-related matters (see 'Final levidex programme'). In addition, the first module was split into two parts. More break options and a progress bar were incorporated throughout the modules, to visualise the remaining module duration. Six of eight experts rated levidex as highly trustworthy and relevant for PwMS. The implemented plain language summaries and the glossary were highly appreciated. Moreover, two experts (a nutrition scientist and a neurologist) appreciated the evidence communication regarding MS and nutrition, as well as on lifestyle in general, being aware of the complex evidence situation in this field. Some of the participating neurologists pointed out that the answer options in the simulated dialogues were too limited, which is why they perceived them as predefined and out of context in places.

Satisfaction and perceived benefit. Overall, levidex was graded as good (grade 2), even though some participants (3 out of 8) only perceived it as satisfactory (grade 3). The experts were also asked to assess the motivational potential for long-term use of levidex. The feedback in this regard was mixed. Although almost all experts (7 out of 8) ranked the application as rather motivating to highly motivating, they stressed that motivation is highly individual and that not all PwMS might be amenable to behaviour change based only on a digital health application. Some participants were afraid that levidex might be too demanding with regard to parallel behaviour changes in many different areas. To make the pursued behaviour change more attainable, three experts recommended including more targeted and specific goal-setting, based on positive formulations and practical examples. For this reason, more frequent and more targeted nutritional impulses were added to the optional emails and short text message reminders.

Discussion

This article reports on the development, feasibility testing, piloting, and revision of a new digital health application (levidex) for PwMS based on the MRC framework. Throughout the development phase, relevant findings for modifications were gathered, and the initial version of levidex was adapted accordingly. Levidex was rated as comprehensive and complex, but our results consistently show that it is feasible and well accepted by both MS experts and PwMS. Most relevantly, trust in levidex and perceived relevance for newly diagnosed PwMS was high. While some MS experts raised concerns regarding the complexity of some content, it was rated as understandable and easy to navigate by PwMS. Nevertheless, concerns expressed by PwMS and MS experts will be addressed in a mixed-methods process evaluation conducted in parallel to an ongoing RCT, to inform refinement of the intervention.[16] Participating PwMS particularly appreciated the glossary, summarising handouts and the audio exercises that were provided.

Levidex is an individually tailored digital health application that uses simulated dialogues to mimic a conversational flow, which is a special approach of the intervention. Moreover, a unique feature of levidex is that it conveys EBPI. Participating MS experts particularly appreciated the scientific citations and plain language summaries, which increase perceived credibility of the intervention. Participating PwMS expressed a special interest in diet. This corresponds with survey data[21] showing a high unmet need of PwMS for evidence and education on the potential influence of dietary behaviour on MS disease course. However, the interpretation of the available evidence on diet and MS is very complex, as it is mostly based on observational studies. Conclusive RCTs investigating the influence of complex dietary patterns are lacking and supplementation studies with Vitamin D, fatty acids and other single nutrients have not yet demonstrated clear evidence.[9,10,34] Considering this, the question arises as to how complex evidence can be presented to PwMS. EBPI should be committed to both the comprehensive presentation of scientific evidence and patient-centeredness, and thus to delivering a comprehensible presentation of scientific information with practical relevance.[33,35] To

integrate both demands, different complexity levels of EBPI should be made accessible, based on individual health literacy and needs.[36] Responsive digital technologies such as broca, which was used for levidex, offer an ideal tool for this approach. However, possibilities for personalisation within the context of digital interventions designed as a simulated conversational flow are limited. Changing lifestyle habits is a difficult endeavour, and a wide range of domains such as knowledge acquisition, skill development, motivation, goal-setting, self-monitoring, and social support need to be addressed to successfully initiate and maintain behaviour change.[37,38] Although our data support the idea that levidex can motivate PwMS to initiate lifestyle changes, the question arises as to whether a digital health application can be enough to enable long-term behaviour change.

Very few studies have rigorously assessed the benefits of web-based interventions for MS.[39] However, recent meta-analytic evidence shows that the additional benefit of guided compared to unguided interventions might be small.[40] Compared to cost-intensive and time-consuming face-to-face interventions with high implementation barriers, levidex could become a cost-effective and supportive add-on to standard care that can easily be implemented even in remote regions. In light of the COVID-19 pandemic, the year 2020 clearly showed the feasibility and usefulness of web-based health care.[41] Levidex adds to this.

While levidex was initially developed for newly diagnosed PwMS, feasibility testing and piloting was performed with participants in later stages of MS and with advanced MS disease knowledge. This cohort was selected because newly diagnosed PwMS can be overwhelmed or even traumatised after receiving an MS diagnosis[3] and therefore might not yet be able to judge which stage of MS a lifestyle intervention might be most suitable for. Results indicated that it could be a helpful guide for all stages of MS. As participants were mostly at the age of about 50, levidex also appeared to be suitable for older adults, who are associated with lower eHealth literacy.[42] This offers potential for future adaptations of levidex. Building on our findings, preliminary data from a cohort of 40 PwMS in more advanced disease stages of MS indicate high acceptance of an adapted version specifically tailored to the needs of later MS stages. Nevertheless, levidex might be especially beneficial for PwMS in the early stage, as they are young and not substantially impaired or threatened in the short term, and thus qualified to induce behaviour change more easily. A currently ongoing RCT will therefore assess whether levidex can effectively change patient behaviour and impact on inflammatory disease activity among newly diagnosed PwMS.[16]

Limitations

The study findings are limited by the small sample size in feasibility testing and piloting. The sample consisted of PwMS who were diagnosed more than five years ago and mostly recruited via UKE's MS day clinic in Hamburg. As the programme covers at least 153 days in the intended participant timeline, at this stage, we were not able to test the whole sequence of modules. These limitations will be addressed in the ongoing RCT (NCT03968172) throughout Germany, targeting persons with a recent (<1 year) MS diagnosis and providing a follow-up of 1–2 years. It will assess whether levidex can effectively change patient behaviour, improve quality of life, and impact on inflammatory disease activity among newly diagnosed PwMS.[16] Based on the experience in the development of several individually tailored digital health applications,[14,15,20,43] levidex aimed to provide a broad range of pre-programmed response options. We are not aware of any other intervention delivering more individualisation while being completely software-based. However, possibilities for individialisation within the context of digital interventions designed as a simulated conversational flow are limited.

Conclusion

Levidex has the potential to close the gap between limited time in neurologist encounters and lifestyle-related information needs of PwMS. Beyond that, it can possibly enable PwMS to adjust to MS at an early stage, especially by optimising lifestyle habits.

Declarations

Ethics approval and consent to participate

The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015). Informed consent was obtained from all study participants. The subsequent RCT has been prospectively registered at ClinicalTrials.gov (NCT03968172).

Consent for publication

All study participants consented to a psyeudonymised publication of the data collected in this study.

Author contributions

Nicole Krause: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Visualisation; Writing – original draft.

Karin Riemann-Lorenz: Conceptualisation; Funding acquisition; Methodology; Resources; Supervision; Writing – review & editing.

Anne Christin Rahn: Conceptualisation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – review & editing.

Jana Pöttgen: Conceptualisation; Funding acquisition; Methodology; Resources; Writing – review & editing.

Sascha Köpke: Conceptualisation; Funding acquisition; Methodology; Resources; Writing – review & editing.

Björn Meyer: Conceptualisation; Funding acquisition; Resources; Software; Writing – review & editing.

Frithjof Thale: Conceptualisation; Resources; Software; Writing – review & editing.

Herbert Temmes: Conceptualisation; Funding acquisition; Writing – review & editing.

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Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CH has received research grants, speaker honoraria, and travel grants from Biogen, Celgene, Genzyme, Merck, and Roche. JP has received research grants, speaker honoraria, and travel grants from Bayer, Celgene, and Merck. BM and FT are employed by GAIA, the company that developed, owns, and operates levidex. NK, KR-L, ACR, SK, HT, and MvdL have nothing to declare.

Availability of data and material

All relevant data are within the manuscript and its supplemental material. The transcripts from the interviews contain sensitive data that could possibly give conclusions about the study participants.

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Supplemental material

Supplemental material for this article is available online.

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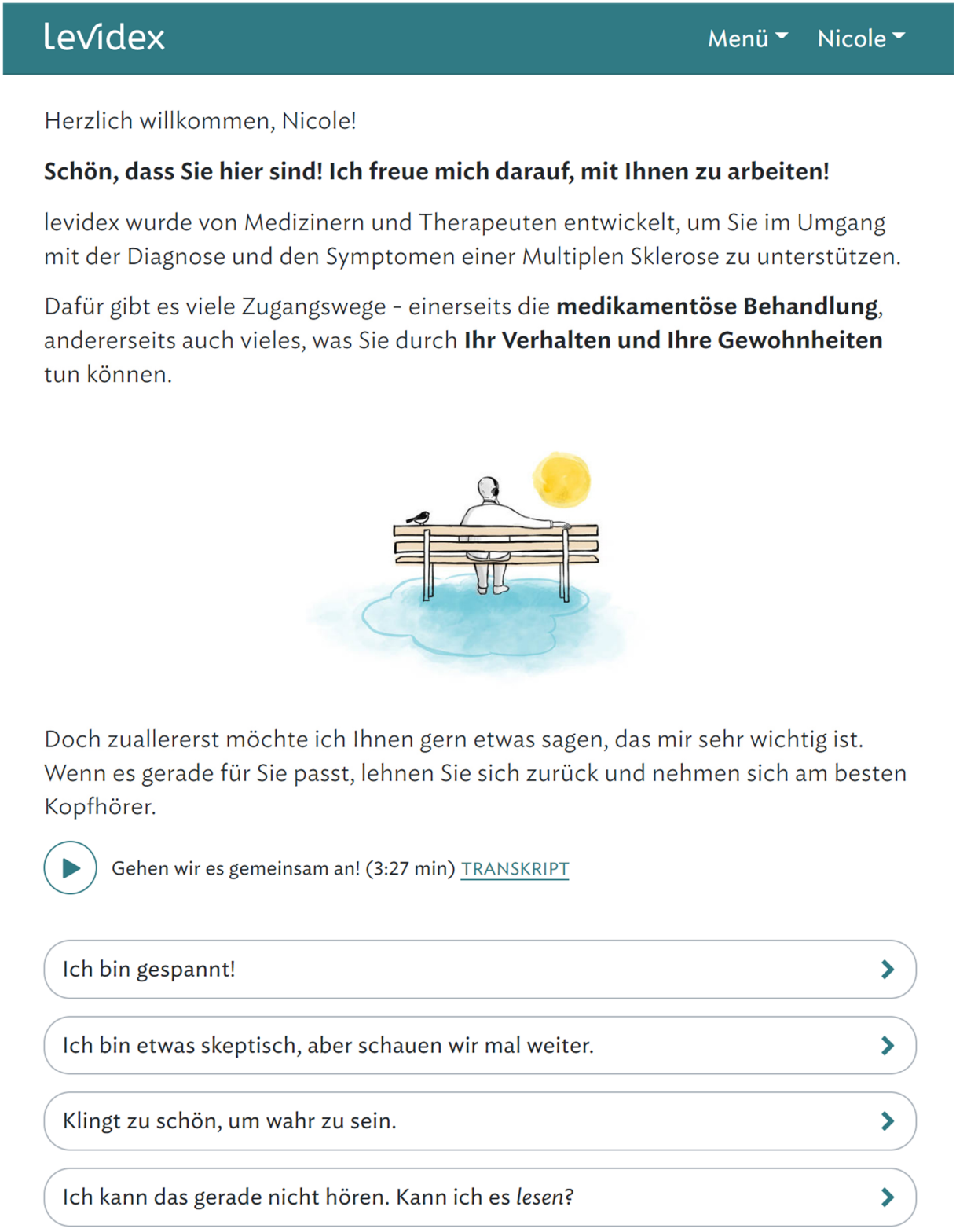
Supplemental file 1: Exemplary excerpt of plain language abstracts

Domain	Title, study design, abstract
Psychological well-being	**Morgan, N., Irwin, M. R., Chung, M., & Wang, C. (2014). The effects of mind-body therapies on the immune system: Meta-analysis. PLoS ONE, 9(7),e100903.** ***Meta-analysis*** In this so-called meta-analysis, all studies available to date that investigated the relationship between "mind-body" therapies, such as mindfulness meditation and immune system function, were reviewed. Based on 39 studies with over 2,000 patients, it was clearly shown that these therapies can reduce the activity of certain pro-inflammatory cytokines (e.g., C-reactive: medium effect, interleukin-6: not significant). Mindfulness exercises are therefore a good way to positively influence your immune system and thus your disease course. **Wellenzohn, S., Proyer, R. T., & Ruch, W. (2016). How do positive psychology interventions work? A short-term placebo-controlled humor-based study on the role of the time focus. Personality and Individual Differences, 96, 1-6.** ***Randomised controlled trial*** This intervention study tested whether humour-based forms of psychotherapy in the field of positive psychology are suitable for generating joy and alleviating depression. In a sample of almost 700 participants in an online intervention, it was shown that three different approaches were able to reduce depressive feelings and build up positive feelings. In addition, the study also identified two modes of action: Attention Shifting and Enjoying Positive Emotions.
Physical activity	**Latimer-Cheung, A. E., Pilutti, L. A., Hicks, A. L., Ginis, K. A. M., Fenuta, A. M., MacKibbon, K. A., & Motl, R. W. (2013). Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Archives of physical medicine and rehabilitation*, 94(9), 1800-1828.** ***Review, systematic*** The systematic review by Latimer-Cheung and colleagues summarised the results of 54 studies that examined the impact of exercise on fitness, mobility, fatigue, and quality of life. The authors concluded that there is sufficient evidence that regular exercise twice a week increases muscle strength and improves fitness. They also consider it possible that there are improvements in mobility, fatigue, and quality of life, although the studies' statements on this are inconsistent.
Dietary behaviour	**Ascherio A., Munger K.L., White R., Köchert K., Simon K.C., Polman C.H., Freedman M.S., Hartung H.P., Miller D.H., Montalbán X., Edan G., Barkhof F., Pleimes D., Radü E.W., Sandbrink R., Kappos L. & Pohl C. (2014). Vitamin D as an early predictor of multiple sclerosis activity and progression. JAMA neurology, 71(3), 306-314.** ***Cohort study*** In this observational study of 465 patients in early stages of MS (who were also receiving interferon therapy), lasting over 5 years, the relationship between vitamin D blood levels and disease activity or progression was investigated. This showed that higher vitamin D levels were associated with lower disease activity (relapse rate, MRI activity, brain volume loss) and slower disease progression. A normal vitamin D level (of greater than 50 nmol/L) in the first 12 months was associated with slightly lower disease activity (EDSS = -0.17) in the following 4 years.

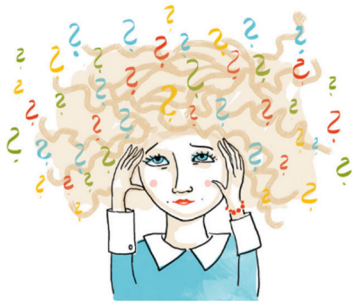
Supplemental file 2: Exemplary screenshots of the levidex programme



Prima. Ich hoffe, dass Sie sich gut zurechtgefunden haben.

Womöglich wissen Sie schon viel über MS. levidex können Sie als sichere Quelle nutzen für weitere gute und wichtige Informationen zu Ihrer Erkrankung.

Ich habe Ihnen alle wichtigen Informationen auch mit wissenschaftlichen Fakten untermauert. Dazu verweise ich sowohl auf Artikel aus Fachzeitschriften als auch auf Fachbücher und Ratgeber. Um mehr Informationen zu bekommen, können Sie auf Verweise wie diesen klicken: (1).



Es gibt so viele Informationen. Doch welche sind wichtig?

Bei all den Informationen, die man findet und die einem präsentiert werden fragt man sich natürlich:

Welche Informationen sind wirklich richtig und welche falsch?

oder

Sind all diese Informationen überhaupt für mich relevant?

Beide Fragen sind sehr berechtigt und vielleicht auch schon Ihnen durch den Kopf gegangen. Leider ist es für den Laien meist sehr schwer, Studien gut zu beurteilen und auch Ihre Ärzte und Therapeuten haben diese Erfahrung über Jahre entwickeln müssen.

Leider gibt es keine klaren Faustregeln wie "Alle Studien mit mehr als 100 Teilnehmern sind gut". Dies würde dem komplexen Thema nicht gerecht werden. Wenn Sie das Thema jedoch interessiert, werfen Sie gern einen Blick auf die Zusammenfassung, die ich Ihnen zusammengestellt habe.

Handout: Studien bewerten

Sie müssen das nicht gleich jetzt lesen, wenn Sie das nicht möchten. Sie finden das Dokument auch unter Mein Überblick im Menü.

Das soll es aber nun wirklich mit den einleitenden Worten gewesen sein, Nicole!

- Die Bewertung scheint wirklich ganz schön kompliziert zu sein. ›
- Die Studien interessieren mich nicht so sehr. Es wird schon stimmen, was Sie mir erzählen. ›
- Mal sehen, wie viele der Studien ich mir ansehe. ›

- Morgan, N., Irwin, M. R., Chung, M., & Wang, C. (2014). The effects of mind-body therapies on the immune system: Meta-analysis. *PLoS ONE, 9(7)*, e100903.

In dieser so genannten Meta-Analyse wurden alle bisher vorliegenden Studien gesichtet, die den Zusammenhang zwischen "Mind-Body"-Therapien, wie z.B. Achtsamkeits-Meditation, und der Funktion des Immunsystems untersucht haben. Anhand von 39 Studien mit über 2000 Patienten konnte klar gezeigt werden, dass diese Therapieformen die Aktivität bestimmter pro-inflammatorischer Zytokine reduzieren können (z.B. C-reaktives: mittlerer Effekt, Interleukin-6: nicht signifikant). Achtsamkeitsübungen sind also eine gute Möglichkeit, Ihr Immunsystem und somit Ihren Krankheitsverlauf positiv zu beeinflussen.

GESPRÄCH FORTFÜHREN

levidex – plain language abstract

Glossar

In diesem Glossar finden Sie Erklärungen zu den wichtigsten Begriffen rund um **MS**, **chronische Entzündung**, **Lebensstil** und **Immunsystem**.

Mehr Informationen erhalten Sie durch einen "Klick" auf den Begriff, der Sie interessiert.

A

- Aerobes vs. an-aerobes Training
- Adrenalin
- Antigen
- Antikörper
- Antioxidantien
- Apathie
- Arachidonsäure
- Aspartam
- Autoimmunerkrankungen

levidex – glossary excerpt

Levidex

8 Minuten – mehr braucht es nicht für Ihren Trainingsplan

Ihr Workout für Zuhause

Trainingsdauer gesamt: **8 Min.**

Dauer der einzelnen Übungen: **30 Sek.**

Pause zwischen den Übungen: **10-20 Sek.**

Übung 1: Hampelmann

Übung 2: Wandsitz

Übung 3: Liegestütze

Übung 4: Crunches

Übung 5: Stuhlsteigen

Übung 6: Kniebeugen

Übung 7: Trizeps-Stuhl-Dips

Übung 8: Plank

Übung 9: Auf der Stelle laufen

Übung 10: Ausfallschritt nach vorne

Übung 11: Liegestütz mit Rotation

Übung 12: Seiten-Plank

levidex – handout (exercise plan)

levidex – optional self-monitoring check-up (weekly assessment of physical activity)

Alles klar, unterhalten wir uns gerne weiter.

Herzlich willkommen, Nicole!
Es ist nun bereits drei Monate her, dass wir unser erstes Gespräch geführt haben. Ich freue mich, dass Sie so engagiert mitmachen!

Wissen Sie noch, was wir in der ersten Woche besprochen haben? Wenn nein: kein Problem! In der dritten Phase unseres Programms, die wir nun beginnen, werden wir alle wichtigen Informationen auffrischen und etwas vertiefen.

Super, dass Sie so weit gekommen sind!

In diesem und den folgenden drei Gesprächen soll es für Sie weiterhin spannend bleiben. Ich möchte Ihnen dazu neue Erkenntnisse aus der Wissenschaft präsentieren. Und gleichzeitig möchte ich mich mit Ihnen darüber unterhalten, wie es Ihnen mit der Optimierung Ihres Immunsystems eigentlich geht. Dazu gleich einmal eine Frage vorweg, Nicole, und ich bitte um eine ehrliche Antwort:

Haben Sie das Gefühl, dass Sie bisher aus unseren Gesprächen etwas für sich und Ihr Immunsystem mitnehmen konnten?

- Ja! Ich konnte viele der Tipps auf mein Leben übertragen. ›
- Bisher habe ich das Gefühl leider nicht. ›
- Bei mir sieht es gemischt aus. Manches konnte ich übernehmen, anderes nicht. ›

Supplemental file 3: Supplementary qualitative data

Piloting with persons with MS	
Evaluation criteria	**Quotation**
Content quality and personalisation	"I would feel very constrained and bossed about it [limited repeatability of modules]. A lot of resistance would build up in me, because, for me, it would feel like my personal decisions and freedoms were being interfered with." [PP05]
	"I could also imagine that having read through and worked through individual modules, which takes several weeks, saying: 'Hmm, how did that bit work again?' At which point you would definitely want to dip back in." [PP06]
Satisfaction and perceived benefit	"Well, I found it was generally a help, and I definitely wished that I had access to it when I… or rather at the time of my diagnosis." [PP01]
	"Exactly, you get input that is explained, but it really is a second step when the patient realises, my word, I actually have the possibility of doing something myself. It's not just a question of swallowing pills, I actually have this chance to turn my life around somehow so that I feel better, that's how it is." [PP03]
	"To begin with you just want to be left in peace, or you are all-consumed with your own self and not yet… Caught up with your psyche and all that… This could very well be helpful then, but everyone is wired differently." [PP04]
	"It is more motivating, because it is not mere chatter about all that may happen and what you won't be able do anymore, instead this is about ideas and approaches on how to achieve something, how to improve things, how a decline may be lessened by doing these things. It is positive, not negative." [PP06]
	"And the next thing is why wait five years, when there might be a piece of advice at the ready that just might lessen or even improve the disease course." [PP06]
Feasibility testing with MS experts	
Evaluation criteria	**Quotation**
Content quality and personalisation	"I do think that at certain points, it is very much the nature of the subject matter, with MRIs, for example, or explaining the diagnosis and so on […] I'm still not entirely convinced that a lay person can really follow all that […] And I always have a question in my mind about equipping patients with a pseudo-expertise in a subject and field that is so very complex, and whether we are really doing them a favour here. And whether they truly understand it. I'm not so sure about that." [E03]
	"And it is really a lot of new information. Looking again at all that's there on physical activity, say, just taking module four, it's really substantial. Even though there has been an attempt to keep each page as succinct as possible, which is great. […] I did get the feeling that it could be quite overwhelming, not least because of what it requires cognitively." [E06]
	"Yes, what I particularly liked primarily is how multifaceted it is, and that it covers so many aspects really well. Particularly all those lifestyle factors, this being an area that gets short shrift traditionally in doctor-patient discussions. When you ask along the lines: And what can I do for myself? And I believe what we have here is a platform that provides a great deal of information on all that side of things. I really appreciated that." [E03]
	"What evidence do we have on nutrition? What evidence is there on lifestyle? What recommendations are we able to make? So patients are looking for instructions, drawn from hard evidence from my experience with clinical studies, and I don't really have answers of that sort. Perhaps a salt-rich diet is good, and perhaps… We don't know any of this for sure yet. It's not something I would recommend to my patients, and the advice [in levidex] struck me as well-balanced." [E02]
	"Both these modules [on physical activity] can occasionally come across as a bit too instructive: "Do this, and you will feel better." It may be written repeatedly that "The decision, of course, is yours.", but it didn't feel a whole lot like my own decision by the end." [E06]
	"Yes, the choice of possible answers doesn't cover everything in the way you might respond yourself, of course, so often they are quite tightly defined, and then it's a question of considering which is the best fit? I would actually prefer to frame it differently, but there's not an option to skip to the next part. You have to select something. And that means it is really rather prescriptive." [E01]

	"When you're talking with a machine, so to speak, there will always be something of a sense of wondering where on earth has that question come from? In the flow of a conversation I'd have been expecting something quite different. But this is something of a preordained path, of course, and you have to follow it, and that is something you do notice now and again." [E02]
	"And then there was the question of how far to create standardisation whilst still leaving open the possibility for some kind of individualisation. It could be along the lines of, say, there is a different sequence of modules, so that one person may start with one, three and five, for example, sleep, nutrition and what not. And the other person begins with the physical exercise component… That's to say that everyone begins with something different, but it is standardised in the sense that he or she begins with what they feel like doing. Rather than what we have thought out or how the programme has been conceived. That would mean that the number of themes and their scope remained, but that people imposed their own order of carrying it out." [E06]
Satisfaction and perceived benefit	"I think it will definitely appeal to some patients and that they'll stick with it. I could imagine some others, however, finding it rather too arduous or complicated, as they click their way through. But I reckon that around two thirds would stick with it. That's a rough estimation on my part. Each person goes about information-gathering differently. I think that this is a particular approach that won't suit everyone, but may be a great fit for some. [E01]
	"There are patients who have a real need for lots of information and to be able to hand them something like this would be truly helpful. For others I have the feeling it might be too much. So I think it will depend very much on the individual how it is received." [E02]
	"Often people are a bit more on edge and – how should I put it – more serious. And I could imagine some may be put off by such a cheery, chummy approach that could come across as a little intrusive even. […] Personally I would prefer just a little more distance." [E04]
	"I think that the recipe part, for me, could do with being filled out a bit. The practical side of things, I mean. The information sections I found superb, including the nutrition section. That was really good. But at the end I was left thinking, how do I move forward with it now?" [E04]
	"Well, this business of I'll eat less of that, doesn't really help me. I need a practical alternative. I can eat more of these things in order to shift away from that. The more concrete the better. So, offering alternatives. And sometimes specifics and absolute clarity are called for. A generally positive formulation, I mean." [E05]
	"I think that people need a specific task or to select a specific task, their plan of action, right? That was something I was looking for in the daily emails, and missed. They provide more info. And that's well intended. And while I see the idea, or recognise the intention, I'm not entirely sure how to utilise it." [E06]

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	N/A
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3
	2b	Specific objectives or research questions for pilot trial	3
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	3-6
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	5-6
	4b	Settings and locations where the data were collected	5-6
	4c	How participants were identified and consented	5-6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4, 6-9
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	4-6
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N/A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N/A
Sample size	7a	Rationale for numbers in the pilot trial	5-6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			

Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	3-6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	9, 11
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5-6
	14b	Why the pilot trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9-10
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	9-12
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	9-12
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
	19a	If relevant, other important unintended consequences	N/A
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	14-15
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	13-15

Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	13-15
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	13-15
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	N/A
Protocol	24	Where the pilot trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16
	26	Ethical approval or approval by research review committee, confirmed with reference number	15

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

V Publikation 2

Krause N, Riemann-Lorenz K, Steffen T, et al. Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1). BMJ Open 2021;11:e041720. doi:10.1136/bmjopen-2020-0417206.2

BMJ Open

Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1)

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ABSTRACT

Introduction Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that mainly affects young adults. Uncertainty is a major psychological burden of the disease from diagnosis to prognosis, enhanced by the pressure to make early decisions on a diverse set of immunotherapies. Watchful waiting for 1–2 years while adapting goals and lifestyle habits to life with a chronic disease represents another reasonable option for persons with MS (PwMS). A behaviour change programme based on evidence-based patient information (EBPI) is not available in standard care. This randomised controlled trial (RCT) with an embedded process evaluation investigates the efficacy and cost-effectiveness of a web-based behavioural lifestyle programme to change lifestyle behaviour and reduce inflammatory disease activity in PwMS.

Methods and analysis A web-based behavioural intervention will be evaluated in an RCT aiming to recruit 328 persons with clinically isolated syndrome, suspected MS or confirmed MS for less than 1 year, who have not yet started immunotherapy. Moreover, a mixed-methods process evaluation and a health economic evaluation will be carried out. Participants will be recruited in at least 16 MS centres across Germany and randomised to an intervention group with 12 months of access to EBPI about lifestyle factors in MS, combined with a complex behaviour change programme or to a control group (optimised standard care). The combined primary endpoint is the incidence of new T2 lesions on MRI or confirmed relapses.

Ethics and dissemination The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015). Trial results will be communicated at scientific conferences and meetings and presented on relevant patient websites and in patient education seminars.

Trial registration number ClinicalTrials.gov Registry (NCT03968172); Pre-results.

Strengths and limitations of this study

- Patients were actively involved in the development process of the intervention group programme in order to address the complex needs of persons with newly diagnosed multiple sclerosis.
- This study provides an opportunity to test if lifestyle interventions can influence surrogate measures of disease activity in an immune-mediated disease.
- The intervention does not include personal consultation, which may limit the extent and sustainability of changes in lifestyle habits.
- We aimed to design a patient-centred pragmatic trial and thus selected patient-reported outcomes as secondary endpoints; however, objective measures, as for example, accelerometry, are not included.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system that affects about 240 000 people in Germany, typically first diagnosed during early adulthood.[1] Over the past decade, new diagnostic criteria[2] enabled earlier diagnosis of the disease and MRI has become a crucial diagnostic and prognostic instrument. Moreover, MRI is used for the evaluation of treatment success despite considerable limitations.[3] However, there is still no highly specific diagnostic marker and diagnosis may remain unclear for years. In addition, reliable prognosis remains difficult and it is hardly possible to estimate the long-term expected disability, especially when based on disease development during the first 1–2 years after onset. For this reason, diagnostic information about MS is often experienced as traumatising and can cause disappointment and distrust in the medical system at an early stage.[4] Although available immunotherapies reduce relapse

rates, the long-term benefit on disability progression remains unclear.[5 6] Nevertheless, early therapy directly after MS diagnosis is recommended.[7] Adherence to immunotherapy in the first 2 years, however, may be as low as 30%–50%.[8] These manifold uncertainties and the resulting psychological stress may have a negative effect on MS disease activity.[9] Surveys have shown that persons with MS (PwMS) are a patient group that frequently uses internet sources to gather information.[10] However, these sources often provide contradictory and poorly curated advice on lifestyle-related matters.[11] The existing care structures cannot meet the complex information needs of PwMS. Experimental research as well as several clinical studies have suggested that improved lifestyle management may have the potential to impact inflammatory and neurodegenerative processes in MS.[12 13] Rigorous studies are largely missing and systematic, evidence-based patient information (EBPI) about lifestyle factors in MS combined with a behaviour change programme is not available. Training and empowerment interventions in MS have so far mainly been studied in face-to-face or group programmes.[14] There are only very few examples for interventions that effectively change physical activity behaviour in MS. Motl *et al*[15] have demonstrated in a pilot study that an internet-based intervention may change walking behaviour as assessed by self-report. However, online interventions in MS have mainly been investigated for the management of symptoms such as depression and fatigue,[16 17] but not for change of overall lifestyle behaviour.

POWER@MS1 aims to encourage PwMS to find the best way of dealing with the disease on the basis of EBPI and a complex behaviour change intervention. The goal of the web-based behavioural lifestyle programme evaluated in this randomised controlled trial (RCT) is to optimise coping strategies and lifestyle habits, such as stress management, sleeping behaviour, physical activity and dietary behaviour. This may lead to decreased disease activity and lower distress to make an early treatment decision regarding use of immunotherapies. Together with the careful MRI monitoring of the disease dynamics in the study, this procedure might enable a more targeted immunotherapy initiation.

Objectives

This study investigates the hypothesis that EBPI about lifestyle factors in MS combined with a complex behaviour change programme (EBBC programme) can reduce inflammatory disease activity in MS and change patient behaviour.

Primary objective

To determine if the EBBC programme can reduce inflammatory disease activity in MS as measured clinically by relapses or by new T2 lesions on MRI.

Secondary objectives

The secondary objectives are to determine if the EBBC programme can:

- Strengthen patient autonomy and empowerment.
- Promote informed decisions on immunotherapy.
- Improve quality of life.
- Reduce anxiety and depression.
- Increase physical activity and a healthy dietary behaviour.
- Increase effectiveness of neurologist consultations.
- Fit with users and contextual factors.
- Save healthcare costs.

METHODS AND ANALYSIS

Study design

Based on developmental work following the Medical Research Council Framework for the development and evaluation of complex interventions,[18] a web-based behavioural intervention programme on lifestyle adaptation in MS was developed (for details see the Interventions section). In addition, a web-based control group programme was developed based on information material available from the German Multiple Sclerosis Society (DMSG). Details with regard to the development and adaptation process will be reported in a separate publication.

The intervention will be evaluated in a superiority, rater-blinded, randomised controlled, parallel group trial. This protocol is focusing purely on the RCT. Study participants will be randomised to the intervention group (IG) with access to the EBBC programme in addition to standard of care or to the control group (CG) with optimised standard care using an allocation ratio of 1:1. In addition, a mixed-methods process evaluation (see online supplemental appendix 1) and a health economic evaluation will be carried out.

Study setting

Recruitment and neurological encounters will take place in community clinics, private practices and academic hospitals with a specialisation in MS across Germany.

Eligibility criteria

Persons aged between 18 and 65 years with clinically isolated syndrome, suspected or confirmed MS for less than 12 months, who signed informed consent, will be included. Furthermore, they must have at least two MS-typical lesions on T2-weighted images on MRI scans and an MS typical cerebrospinal fluid finding with detection of oligoclonal bands. Internet access is mandatory for participation. PwMS who are not able to provide informed consent or have a substantial psychiatric disorder or a substantial cognitive deficit based on clinical impression will be excluded. PwMS who have been treated with glatiramer acetate, teriflunomide, dimethylfumarate or interferons within the last 6 months prior to study inclusion or have received corticosteroid therapy within 4 weeks prior to study inclusion will also be excluded. PwMS with a planned treatment start within 3 months after inclusion or PwMS who had received any other MS-specific

immunotherapy at any time in the past will not be eligible. Pregnancy and claustrophobia are also exclusion criteria.

Interventions

Eligible PwMS will be randomised to the IG programme or the CG programme. Both programmes will be offered online on the same platform with a similar design.

IG: EBBC programme

The IG programme is an MS-specific adaptation of the earlier developed 'Optimune'® tool by GAIA (https://gaia-group.com/en/). Based on current research and theory of the field,[19–21] it was developed for lifestyle management in patients with cancer based on empowerment[22] and cognitive–behavioural therapy (CBT) approaches, including acceptance/mindfulness-oriented techniques.[23–25] These techniques influence different theoretical domains as outlined in the theoretical domains framework[21] and thereby the participants' ability, motivation and opportunity to change their physical activity, stress management attitudes and dietary behaviour. For example, CBT techniques, such as behavioural activation and identifying and refuting unhelpful automatic thoughts and cognitive distortions, goal setting, goal review, agreeing on behavioural contracts, setting graded tasks, planning social support, action planning, weighing of pros and cons, preparing for/dealing with setbacks, self-motivational statements, constructing if–then plans, and formulating implementation intentions and positive emotion induction are incorporated throughout. Mental imagery exercises and mindfulness/acceptance exercises are integrated both in text format and as audio recording. Furthermore, EBPI, autonomy supportive intervention concepts based on self-determination theory,[26] the principles of responsiveness[27] and individual content-tailoring[28 29] are crucial components of the intervention format. The programme specifically attempts to avoid fear appeals and simple information provision (eg, 'lecturing'). The programme does not provide drug-specific information about available immunotherapies. The programme aims to translate evidence in the MS treatment and lifestyle management area in order to illustrate that decisions can be made. It follows the concept that every PwMS can develop an individual approach towards the disease, which might be a targeted immunotherapy initiation in one case or the development of a sophisticated food concept in the other.

The system is based on the Artificial Intelligence-based software platform broca®, which is the basis for several effective therapy support systems evaluated in earlier RCTs (eg, [16 23 30–32]). An optional email and short message service reminder system (eg, with lifestyle-related stimuli or reminders regarding programme usage and newly activated modules) aim to enhance involvement. Usage of the IG programme will be monitored biweekly and reacted on after 4 weeks of non-usage to ensure patient adherence.

The programme is designed as a highly individualised system that provides PwMS with narrative and coordinated information based on their existing health beliefs, interests and so on. Each text passage ends with a set of preprogrammed response options in multiple-choice format reflecting possible reader's feedback, such as 'Yes, that makes sense' or 'I do not quite understand this yet'. The participant is invited to tick the matching response and will be guided to the next page referring to the choice, for example, 'I'm glad that you can understand it' or 'No problem. Then let me explain it in a little more detail'. These simulated dialogues lead to a highly individualised way through the intervention, while on the other hand, the programme makes sure that every important area is touched. More precisely, disease management and lifestyle techniques as well as exercises will be taught in sequentially activated interactive learning units ('simulated dialogues') focusing on the following topics:

1. Diagnosis, prognosis and immunotherapy decision-making.
2. Support in coping.
3. Techniques for coping with stress/depressive symptoms and developing positive emotions.
4. Optimisation of dietary behaviour.
5. Optimisation of physical activity behaviour.
6. Sleep hygiene and methods for dealing with insomnia.

The modules are not ordered by priority. Altogether, the IG programme consists of 16 modules and will accompany each participant over a period of 12 months with initial two to three weekly modules, later only weekly reminders and modules every 2 weeks, and four booster sessions at the end.

CG: information from self-help societies

CG participants will receive access to an information platform with optimised standard care consisting of information compiled from DMSG information material to reflect current practice. It will also accompany participants over a period of 12 months and cover similar topics as in the IG. A reminder function as well as usage monitoring and adherence promotion will be applied as in the IG.

Patient and public involvement

PwMS were involved in the development phase of the intervention and also participated in the feasibility and pilot testing of the IG programme (see the Study design section). They were given access to the programme and invited to evaluate content, practicability, user-friendliness and comprehensibility of the programme, also considering the needs of newly diagnosed PwMS. The programme was revised based on the acquired feedback (eg, technical adjustments, inclusion of more break possibilities and a progress bar in the modules). In addition, suggestions for prospective adjustments, which were not possible due to technical limitations, such as the embedding of video material, were gathered. Details regarding the feedback and resulting programme changes will be communicated in a separate publication.

Criteria for discontinuation and relevant concomitant care

In case of new events (relapse or T2 lesion), formally the primary endpoint will be reached. However, study participants will be asked to remain in the study. Immunotherapy may be started during the trial period. Immunotherapy type, use and adherence rates will be collected during the clinical visits throughout the study.

Outcomes

Data will be collected over a period of 12 months, with a flexible follow-up of up to 24 months in early recruited PwMS. A list of outcomes, including measurement time points, is provided in table 1.

Primary outcome

The primary endpoint is the time to a new relapse or, as a surrogate for inflammatory disease activity, a new lesion on T2-weighted images on MRI scans, whatever occurs first. Occurrence of new T2 lesions will be assessed according to an MRI protocol (Localizer, 3D fluid-attenuated inversion recovery sagittal, eg, 3×3 mm, 3D image T1-weighted native sagittal, 1–3 mm, PD/T2-weighted axial 3 mm, protocol duration approximately 20 min.). MRI scans will be read centrally by an experienced rater, blinded to subject identity and group assignment.

Relapses will be clinically evaluated by participating neurologists. In case of a relapse, duration of complaints/impairment, relapse symptoms (worsened or newly occurred), degree of impairment due to the relapse and the degree of certainty with regard to the classification of the worsening as a relapse will be assessed.

Secondary outcomes

To assess risk knowledge, an abbreviated 10-item version of the MS risk knowledge questionnaire (Risk Knowledge in Relapsing Multiple Sclerosis V.2.0[33]) will be used.

As a surrogate of decision quality, preferred and realised role preference in decision discussions for or against immunotherapy based on the Control Preference Scale[34] will be assessed. Immunotherapy status will be assessed to determine whether an immunotherapy was newly started, aborted or changed.

The extent of patient activation (eg, expressed in the confidence and knowledge to take action as well as actually taking health-related action), based on the Patient Activation Measure[35] and the coping capability, based on two items (items 10 and 24) of the Coping Self-efficacy Scale[36] will be measured. In addition, patient expectancies based on items 1–3 of the credibility/expectancy questionnaire[37] will be assessed. Based on principles of the Health Action Process Approach,[38] readiness to change[39] will be estimated in order to determine the interventions impact on willingness to change lifestyle habits. Moreover, changes in perceived empowerment (based on [40], items 1, 3 and 4) will be measured.

Impairment in the Expanded Disability Status Scale[41] will be determined by the treating neurologist.

Table 1 Assessments and measurement time points

Instrument	Measurement time points								
	t_{-1}	t_0	V_1	V_2	V_3	V_4	V_5*	V_6*	t_x
Month	−1	0	1	3	6	12	18*	24*	X
Eligibility screen	X								
Informed consent	X								
Demographic data	X								
MRI		X		X	X	X	X	X	
Clinical visit		X	X	X	X	X	X	X	X
Relapse history		X	X	X	X	X	X	X	X
Immunotherapy status		X	X	X	X	X	X	X	X
EDSS		X				X			
RIKNO				X					
CPS						X			X
Decision satisfaction									X
Patient activation		X				X			
Emotional coping		X				X			
Changes in empowerment						X			
Expectancy			X						
Readiness to change		X		X		X			
HAQUAMS		X				X			
EQ-5D-5L		X			X	X	X	X	
HADS		X				X			
GLTEQ		X				X			
BSA		X				X			
QHOD2		X		X		X			
myfood24		X				X			
Process evaluation	X	X	X	X	X	X	X	X	
Health economic parameters		X			X	X	X	X	

t_{-1}=before enrolment; t_0=before allocation; V_1–V_6=post allocation (V_1=visit in month 1; V_2=visit in month 3; V_3=visit in month 6; V_4=visit in month 12; V_5=visit in month 18; V_6=visit in month 24); t_x=after reaching the primary endpoint.
*Only in early recruited PwMS.
BSA, Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise and Sport Questionnaire); CPS, Control Preference Scale; EDSS, Expanded Disability Status Scale; GLTEQ, Godin Leisure-Time Exercise Questionnaire; HADS, Hospital Anxiety and Depression Scale; HAQUAMS, Hamburg Quality of Life in Multiple Sclerosis Scale; PwMS, persons with multiple sclerosis; QHOD2, Questionnaire of Healthy Diet; RIKNO, Risk Knowledge in Relapsing Multiple Sclerosis.

Ideally, the lifestyle intervention leads to more general satisfaction with life but may also alleviate symptoms, such as depression, anxiety and fatigue. Quality of life will be measured with the Hamburg Quality of Life in MS Scale[42] and the generic EQ-5D-5L.[43] The Hospital Anxiety and Distress Scale[44] will be used as a measure for depression and anxiety.

Physical activity behaviour will be measured with the Godin Leisure-Time Exercise Questionnaire[45] and the Physical Activity, Exercise and Sport Questionnaire (Bewegungs- und Sportaktivität Fragebogen).[46]

The Questionnaire of Healthy Diet, an adapted version of the Mediterranean Diet Screener as used in [47] that was developed by the German Institute of Human Nutrition (DIfE), will be used to measure the frequency of intake of characteristic food groups within the last 7 days. To provide nutrient intake data, the 24-hour dietary recall myfood24[48] will be used, in each case three times within a time period of 1–3 weeks (2 weekdays, 1 weekend day).

Health economic outcomes

Health economic parameters will be assessed to determine the efficiency of the intervention by comparing the cost and outcome of the IG with the CG. All direct costs associated with the intervention as well as costs resulting from the consumption of health-related goods and services[49] and indirect costs due to productivity losses will be considered from the perspective of the German statutory health insurance and the society.

To determine efficiency of the intervention, a cost-effectiveness analysis will be performed in terms of additional costs per additional relapse or T2 lesion (clinical endpoint) averted and a cost-utility analysis, which aims to calculate the additional costs required for an additional improvement in quality-adjusted life years (QALYs). Incremental cost-effectiveness ratio and incremental cost-utility ratio will be calculated as the ratio of the difference in mean costs and difference in mean outcomes between IG and CG. QALYs will be measured by a well-established preference-based quality of life instrument (EQ-5D-5L) and evaluated by a German tariff to generate utilities.[43] A standardised instrument[50] will be used to record the healthcare consumption of study participants focusing mainly on outpatient doctor visits, visits to other health service providers, sick days, hospital stays and MS immune medication. Productivity losses will be estimated using the human capital approach.[51] The 95% CIs for the outcome of the analyses will be determined non-parametrically based on the distribution characteristics of costs using bootstrap procedures.[52] Univariate and probabilistic sensitivity analyses will be performed and cost-effectiveness acceptance curves will be executed to take uncertainty into account.[53]

Participant timeline

The time schedule is depicted in figure 1.

Sample size

Based on effect sizes resulting from an RCT for a stress management intervention[13] as well as data from cohorts on lesion development after an initial clinical event ([54] personal communication Michael Scheel, Charité Berlin), one event (relapse or at least one new T2 lesion) is expected in every second PwMS within 12 months in the CG. The 100 events result in a statistical power of 85% for a two-way significance level test of 5% and an assumed HR of 0.55, that is, a reduction of 45% by IG compared with the CG. Thus, with a mean observation time of 12 months, the 100 events required can be expected to be observed in 262 PwMS (131 per group). Assuming about 20% dropouts over 1 year, 328 PwMS will be randomised (164 per group, 20% dropout=33=131 per group). A sample size recalculation will be performed after 12 months to review the assumptions on event rates and dropouts.[55] If necessary, the number of cases will be increased to a maximum of 450 PwMS.

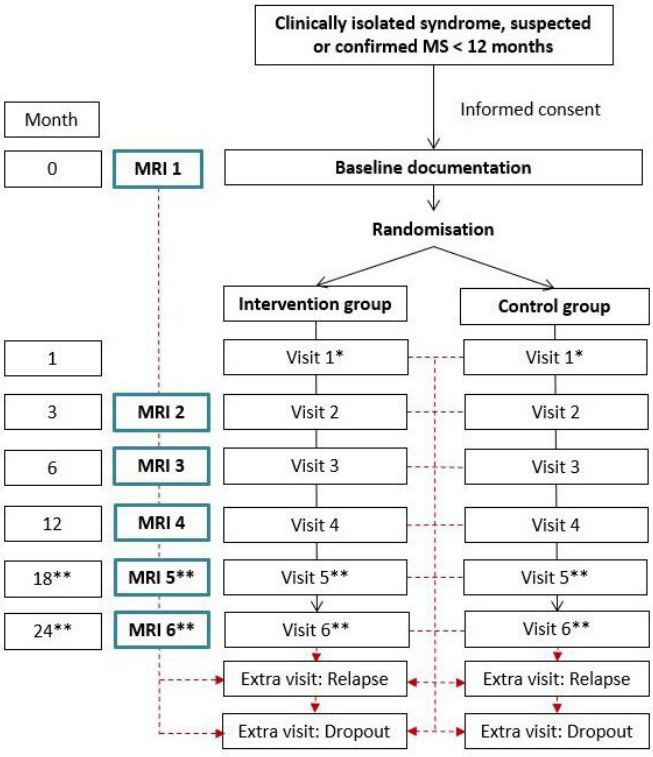

Figure 1 Participant timeline. *Visit 1 takes place in the MS centre to discuss the findings of the first MRI and by telephone through the study centre to clarify technical questions. **Visit 5 and visit 6 only in early recruited patients (flexible follow-up). MS, multiple sclerosis.

Recruitment

Eligible MS centres will be recruited by the coordinating centre in Hamburg (University Medical Center Hamburg-Eppendorf, UKE). Recruitment and inclusion of PwMS will take place in the participating MS centres through neurologists. In addition, POWER@MS1 will be advertised on the website of the DMSG. Overall, a recruitment period of 12 months is assumed with approximately 20 PwMS per centre, with one to two PwMS per month. Reasons for rejection will be documented.

Allocation

Group assignment will be undertaken externally and in a concealed manner through the electronic data capture system secuTrial® provided by the German MS Registry to prevent any manipulation of persons involved in the study.

Eligible study participants will be randomised into the IG or to the CG in blocks (1:1 allocation ratio) through a computer-generated system in secuTrial®. After baseline documentation and subsequent randomisation, PwMS will be provided with access (login) details to the IG or CG programme by an unblinded member of the study team.

Blinding

The study will be conducted as an investigator-blinded trial and participating MS centres will not be provided with any information about group assignment of a given PwMS. Blinding of the trial participants is pursued, but only possible to a limited extent. Participants and neurologists might realise their participation in the IG during encounters.

Data collection methods

Data will be obtained at different time points using paper-based and web-based questionnaires (see table 1). In case of missing data, participants will be contacted by a member of the UKE. All study relevant data will be entered into secuTrial® and provided online. Results of MRI scans (image data) will be saved on compact discs (CDs). In accordance with current procedures implemented in medical practice, CDs with MRI data will be sent to the study centre in sealed envelopes via regular mail. This has been reviewed and accepted by the reviewing ethics committees and is in compliance with current data protection rules and regulations in Germany. They will be quality-checked, pseudonymised and uploaded in a protected reading centre database. Data obtained with regard to nutrition behaviour will be collected via secured online platforms of the Humanstudienzentrum of the DIfE and Dietary Assessment Limited (University of Leeds spinout company), which act in accordance with European Union General Data Protection Regulation (Datenschutz-Grundverordnung). Data obtained through myfood24 will be stored on a server in the Netherlands, with a backup in the UK. After data collection, data will be transferred to secuTrial® and connected with the existing data sets. In addition, usage of the web-based programmes will be monitored.

Data management

The IG and CG programme will be provided via a secure online platform that meets all legal requirements (SSL Encryption). All study data will be used and evaluated pseudonymously. However, all participating MS centres will have a list with names and assigned pseudonyms. All electronic and paper-based data material will be stored at the UKE for a maximum period of 10 years and will be destroyed subsequently. Stored CDs containing MRI images will be destroyed directly after analysis of the study data. In case of withdrawn consent, pseudonymised data will be anonymised. A deletion of already anonymised data is not possible.

Statistical methods

The effect on the primary endpoint will be estimated in a Cox proportional hazards regression that, in addition to treatment, also includes study centre as a factor; it will be reported as HR with 95% CI and p value testing the null hypothesis H0:HR=1. Kaplan-Meier curves of the primary endpoint for both groups will be used to illustrate the treatment effect.

Secondary endpoints will be analysed using mean comparisons between IG and CG with adjustment for the baseline assessments and centre in analysis of covariance models. Least squares group differences will be reported with 95% CIs and p values testing the null hypothesis of no intervention effect. The number of portions/day or week for different food groups will be analysed, evaluated and compared with current recommendations. Data obtained through the 24-hour recall (myfood24) will be used to analyse intake of selected nutrients of interest comparing mean changes in intake from baseline with post intervention between IG and CG, adjusting for baseline intake. MRI lesion counts will be analysed using negative binomial regression models, adjusting for baseline MRI and centre. Adverse events will be summarised as frequencies and percentages by treatment group.

In addition, subgroup and moderator variable analysis is planned to be performed (eg, early therapy vs no therapy and women vs men).

Reasons for study withdrawal will be reported. In case of missing data, all PwMS will be analysed in the group they were randomised to (intention-to-treat analysis). Early study discontinuations will be treated as independent right censoring in the primary analysis. In case of substantial or differential study discontinuations, the validity of the independent censoring assumption will be explored in shared random effects models of the primary endpoint and time to study discontinuation. To handle missing data in baseline variables or follow-up assessments, multiple imputation models will be applied.

All details of the statistical analyses including definitions of analysis populations will be prespecified in a statistical analysis plan.

Monitoring

As part of a risk-based quality management, external independent data monitoring including onsite visits at the UKE and remote data checks in secuTrial® will be performed by the contract research organisation CTC North GmbH & Co.KG.

Safety and adverse events

As no significant harms (side effects, risks or complications) are to be expected, no stopping guidelines are planned. The performance of six MRIs over 2 years is close to clinical standard and can be regarded as harmless. Contrast media will not be used in order to minimise the risk of possible contrast media deposition in the basal ganglia, although no information on depositions is available for the contrast media currently used.[56] No auditing trials are planned or expected.

ETHICS AND DISSEMINATION

The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and the ethics committees of participating study centres.

Informed consent (see online supplemental appendix 2) will be obtained by the participating MS centres and a

copy will be sent to the study centre in Hamburg. Participants may withdraw their consent at any time. A financial compensation for participation in this study cannot be granted. In case of reaching the primary endpoint, PwMS are requested to remain in the study and continued access to the web tools will be guaranteed until the study end. Only the study team (investigators) and Alexander Stahmann (medical information scientist at the German MS Registry) will have access to the final trial data set. For publications, an anonymised data set will be used. If possible, an anonymised data set will be made available in the publication process in order to disseminate the study results.

Trial results will be communicated at scientific conferences and meetings (eg, at the yearly German Neurologists Society, the RIMS network) by the investigators and presented on the DMSG website and other relevant patient websites. Authorship will be shared between persons involved in the study following the current guidelines of the International Committee of Medical Journal Editors. Professional writers and persons not directly involved in the study will not be granted authorship.

DISCUSSION

This will be the first study assessing the impact of a lifestyle management programme combined with EBPI on inflammatory activity in MS. If successful, POWER@MS1 has a paradigm shifting potential. If successful, the trial could give lifestyle management a label as putative disease-modifying. This can impact guideline development.

Current trial status

Recruitment of PwMS has started in July 2019.

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Competing interests CH has received research grants, speaker honoraria and travel grants from Biogen, Celgene, Genzyme, Merck, Roche. J-PS receives research funding from Deutsche Forschungsgemeinschaft and reports grants from Biogen and Genzyme outside the submitted work. TF reports personnel fees from Bayer, BiosenseWebster, Boehringer Ingelheim, CSL Behring, Daiichi Sankyo, Enanta, Fresenius Kabi, Galapagos, Immunic, Janssen, LivaNova, Novartis, Relaxera, Roche, and Vifor; all outside this work.

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Appendix I: Process evaluation

A mixed methods approach (1) is used for the process evaluation based on standardised questionnaires and telephone interviews (see Table 2, Figure 2). Further, the outcome assessments of the main study are an important data source for the process evaluation. The process evaluation aims to clarify whether the intervention was delivered as intended (fidelity) and in which quantity (dose) the intervention was implemented (2, 3). Moreover, implementation barriers and facilitators will be explored. As shown in Table 2 and Figure 2, we will assess contextual factors, components associated with recruitment, delivery, responses and maintenance of centres and individuals (PwMS) as well as unintended consequences using different methods.

Sampling

Questionnaires will be provided to all participants. Interviews will be performed with 10 to 20 with PwMS from each study group until information saturation is reached. Of the healthcare providers, up to 10 neurologists and 5 radiologists will be interviewed based on a purposeful sampling strategy, i.e. aiming for a diversity of centres in organisational structure and size.

Timing

The process evaluation will be conducted in parallel to the main trial (see Table 2 for specific timing of assessments).

Data analysis

First, the process evaluation and trial data will be analysed separately. Afterwards, data will be combined and used to determine post-trial interview questions. Quantitative process evaluation data (questionnaires and evaluation forms) will be analysed descriptively using SPSS (International Business Machines Corporation (IBM), Armonk, United States of America) or R (R Development Core Team) software. Subgroup analyses considering study outcomes and patient characteristics will be performed (for example, start of immunotherapy and decision type) in order to explore the impact of the intervention on different groups. Interviews will be analysed by thematic analysis (4) using MAXQDA (5).

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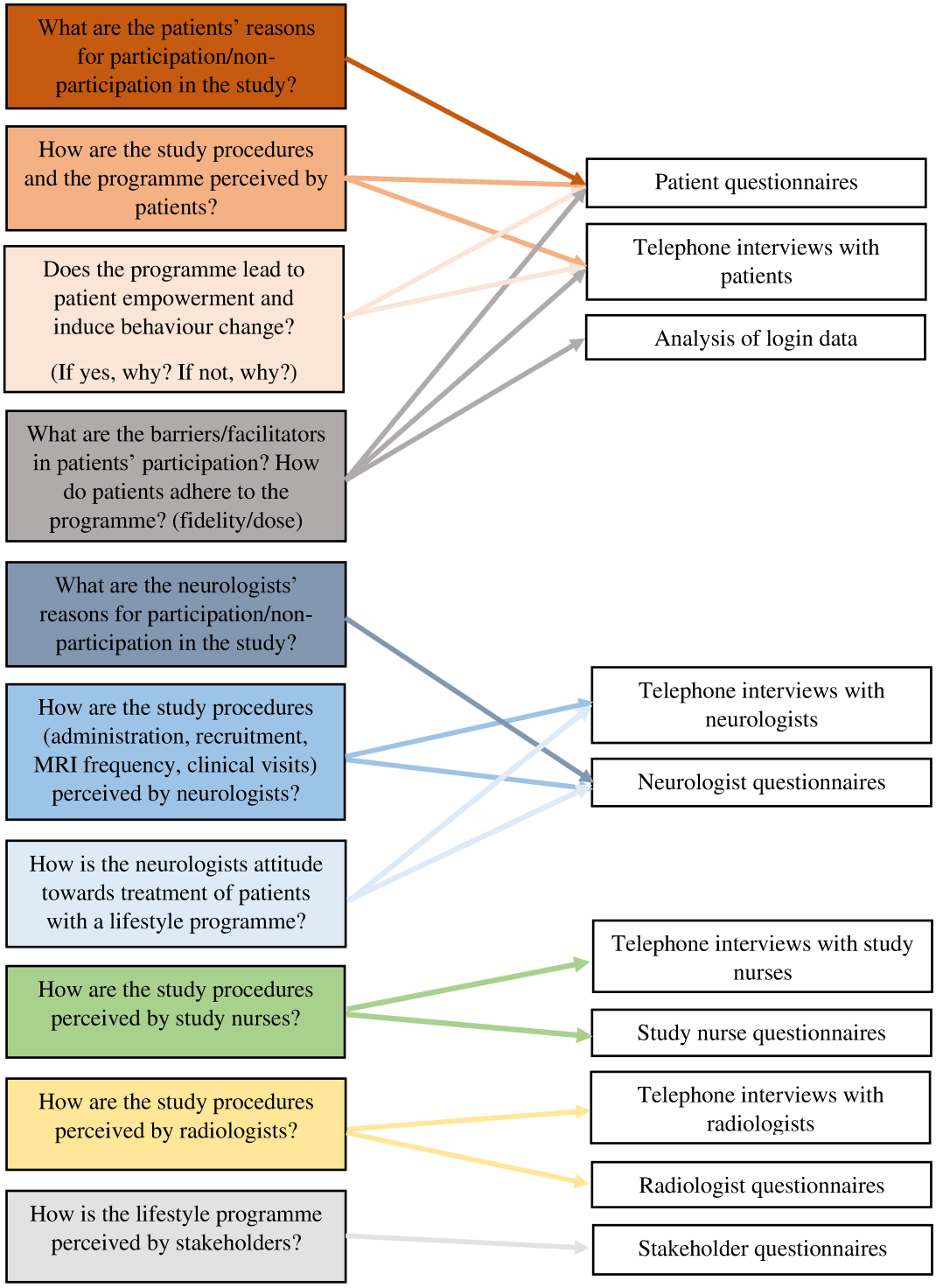
Overview process evaluation POWER@MS1			
Domain	**Objects of investigation**	**Ascertainment/Data collection tool**	**Time point**
Context	Context factors in Germany (health system)	Description	Pre-intervention
	Centre-specific structures and processes	Questionnaire, interviews	Pre-intervention
Recruitment of centres	Centre recruitment	Documentation of recruited centres, phone calls or visits in interested centres	Pre-intervention
	Reason for study participation/ for non-participation (promoting factors and barriers)	Questionnaire (neurologists)	Pre- and during intervention
Delivery to centres	Delivery of information (study management) to neurologists, study nurses and radiologists (participation, reach)	Provision of study materials about the intervention programme, initiation of study centres	Pre-intervention
	Delivery of the study monitoring platform access to all centres	Provision of access data	Pre-intervention
Response of centres	Attitude (neurologists, study nurses and radiologists) regarding the study procedures (e.g. administration, recruitment, clinical visits, MRI frequency) and the intervention	Evaluation forms, interviews	During and post-intervention
Maintenance of centres	Study centres: recruitment of patients	Documentation of recruited patients, evaluation forms, interviews	During and post-intervention
Recruitment of individuals	Recruitment of PwMS	Information video (provided online via YouTube and stakeholder websites/ social media/ network distributors/ magazines), study information leaflets, recruitment in the centres (screening lists, baseline questionnaires)	Pre-intervention
Delivery to individuals	Intervention group: delivery of the intervention to individuals (EBPI about lifestyle factors in MS combined with a complex behaviour change programme)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention

	Control group: delivery of the control intervention to individuals (web-based information on lifestyle factors consisting of optimised standard care material)	Provision of access (login) data, e-mail and text message reminders, monitoring of programme usage, evaluation forms, interviews	During and post-intervention
Response of individuals	E.g.: Satisfaction with the study procedures (e.g. frequency of MRIs and clinical visits) and the intervention, knowledge, attitude, empowerment, change in behaviour, barriers and facilitators	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	Post-intervention, after reaching the primary endpoint
Maintenance of individuals	PwMS (users of the programme): knowledge, empowerment, change in behaviour and reasons for usage	Questionnaires (primary and secondary endpoints RCT), evaluation forms, interviews	During and post-intervention
	PwMS (non-user of the programme): knowledge, empowerment, change in behaviour and reasons for non-usage	Contacting participants via e-mail or telephone, questionnaire, interviews	During and post-intervention
Unintended consequences	Patients: anxiety, depression, negative impact on disease specific quality of life	Evaluation form, interviews, secondary outcome measurement	During and post-intervention
	Neurologists: professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
	Study nurses: stress, professional relationship to patients, barriers for implementation	Evaluation form, interviews	During and post-intervention
Theory	EBPI, TDF, TPB, Empowerment	Application during study planning and the development of study materials, used in evaluation forms, in the programme and in secondary outcome measurement	Pre-, during and post-intervention
EBPI = evidence-based patient information; MRI = magnetic resonance imaging; MS = Multiple Sclerosis; PwMS = Persons with Multiple Sclerosis; RCT = randomised controlled trial; TDF = Theoretical Domains Framework; TPB = Theory of Planned Behavior			

Table 2: Overview process evaluation POWER@MS1

Figure 2: Process evaluation POWER@MS1: questions and methods



Appendix II: Model consent form

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Klinik und Poliklinik für Neurologie | Institut für Neuroimmunologie und Multiple Sklerose (INIMS)

Patienteninformation zur Studie „POWER@MS1“ – RCT (Version 1.3)

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Hamburg, 15.06.2020

Information und Einwilligung zur Studie:

Interaktive Webplattform zum EmPOWERment bei früher Multipler Sklerose (POWER@MS1) – Randomisiert kontrollierte Studie (RCT)

Sehr geehrte Studieninteressent*innen,

das Institut für Neuroimmunologie und Multiple Sklerose sowie der Bundesverband der Selbsthilfe (DMSG) danken Ihnen für Ihr Interesse an unserer Studie zum webbasierten Empowerment für Menschen mit Multipler Sklerose (MS). Die Studie wird öffentlich durch den Innovationsfond beim gemeinsamen Bundesausschuss (G-BA) gefördert.

Bitte lesen Sie diese Studieninformation sorgfältig durch. Ihre Ärztin oder ihr Arzt wird mit Ihnen auch direkt über die Studie sprechen. Bitte fragen Sie diesen oder diese oder kontaktieren Sie den unten genannten Studienleiter Prof. Dr. med. Christoph Heesen oder die Studienkoordinatorinnen Nicole Krause und Tanja Steffen, wenn Sie etwas nicht verstehen oder wenn Sie zusätzlich etwas wissen möchten.

Was ist das Ziel dieser Studie?

Bei Ihnen ist kürzlich ein MS Verdacht geäußert oder auch eine MS Diagnose gestellt worden. Diese Diagnose stellt für viele Patienten eine erhebliche Verunsicherung dar. Fragen die viele umtreiben sind zum Beispiel:

Wie sicher ist die Diagnose?

Werde ich einen eher gutartigen oder aktiveren Verlauf haben?

Brauche ich eine ganz frühe Immuntherapie?

Was kann ich tun, außer Medikamente zu nehmen?

Diese Fragen können im Rahmen von Arztbesuchen, beim Neurologen, nur begrenzt diskutiert werden. Im Internet gibt es eine Fülle von Informationen, deren Qualität oft zweifelhaft ist. Um Sie im ersten Jahr Ihrer MS Diagnose zu begleiten, haben wir verschiedene Materialien entwickelt, die Sie darin unterstützen sollen, einen eigenen Weg mit der Erkrankung zu finden.

Das Ziel dieser Studie ist es zu klären, ob diese von uns entwickelten und über das Internet bereit gestellten Materialien hilfreich sind. Im Verlauf von bis zu 2 Jahren wird insbesondere die Aktivität der MS im MRT (=Magnetresonanztomografie), mit Untersuchungen alle 6 Monate, sehr genau untersucht werden. Darüber hinaus erhalten Sie mehrmals Fragebögen zu möglichen Beeinträchtigungen, zu Ihrer Stimmungslage, aber auch zu Lebensstilfaktoren wie Ihrer sportlichen Aktivität und Ihren Ernährungsgewohnheiten.

Auf was müssen Sie sich als Teilnehmer/in einstellen?

In der Studie werden, in zwei Gruppen, unterschiedliche Informationsstrategien zu Lebensstilfaktoren verglichen. Die Zuordnung zu einer der Gruppen erfolgt zufällig (randomisiert). Wenn Sie sich für die Teilnahme entscheiden, erhalten Sie einen Zugangscode (Login) für eine Internetseite mit Informationen und Schulungsmaterialien. Dort melden Sie sich mit einer E-Mail-Adresse und einem selbst gewählten Passwort an. Die Webseite wird Ihnen über einen neutralen E-Mailabsender (ohne Bezug zur MS), in zeitlichen Abständen, immer wieder Informationen und Erinnerungen schicken. Auch per SMS können Sie auf eigenen Wunsch angesprochen werden. In diese Kontaktaufnahmen müssen Sie einwilligen. Dabei müssen Sie bedenken, dass jegliche Kommunikation über das Internet möglicherweise von Unbefugten abgehört werden kann und ein nicht sicher kalkulierbares Risiko besteht, dass bei der Nutzung von Internetplattformen Dritte an die eingegebenen Informationen gelangen können. Die Wahrscheinlichkeit, dass Ihnen damit jemand schadet ist jedoch sehr gering.

Wenn Sie innerhalb von 3 Monaten vor Studienbeginn ein geeignetes MRT bekommen haben, kann dieses für die Studie genutzt werden. Sollte kein geeignetes MRT vorliegen, erfolgt ein MRT zu Studienbeginn und nach 3, 6 und 12 Monaten. Für einen Teil der Patienten, die sehr früh eingeschlossen werden, erfolgen weitere MRTs zu Monat 18 und 24. Hier sollten die Aufnahmen bestenfalls immer am gleichen Gerät, in der gleichen Praxis erfolgen. Eine Kopie der Bilder wird an die Studienzentrale in Hamburg gesendet werden. Aufgrund der Anzahl an studienbedingten MRT-Untersuchungen entsteht durch die Teilnahme an der POWER@MS1 Studie ein zusätzlicher Zeitaufwand für Sie. Da das Verwenden von Kontrastmittel im Rahmen der Studie nicht notwendig ist, bestehen für Sie aber keine Risiken aufgrund der zusätzlichen MRT-Untersuchungen.

Zu Beginn der Studie und nach 12 Monaten erfolgt eine umfangreichere Erhebung mit Fragebogenmaterialien, aber auch im Verlauf der Studie (maximal 2 Jahre) benötigen wir Ihre Mitarbeit in Form der Bearbeitung von Fragebogenmaterial. Dies stellen wir entweder in Papierform mit Rücksendeumschlag zur Verfügung oder über ein persönliches Login im Internet für die gesicherte Forschungsdatenbank des MS-Registers der Deutschen Multiple Sklerose Gesellschaft (DSMG, Bundesverband e.V.), welche zur elektronischen Abbildung dieser Studie genutzt wird. Die Forschungsdatenbank wird von der MS Forschungs- und Projektentwicklungs-gGmbH in Hannover, einer 100%igen Tochter der DMS-Stiftung der DMSG, auf Servern in Deutschland betrieben. Das Ernährungsverhalten untersuchen wir mit zwei internetbasierten Erhebungsinstrumenten. Eines dieser Instrumente wird über eine gesicherte Online-Platt-

form des Humanstudienzentrums des Deutschen Instituts für Ernährungsforschung (DIfE) verwaltet. Das zweite Instrument wird von der Dietary Assessment Ltd (ein Spin-Out-Unternehmen der Universität Leeds) verwaltet, welche die erhaltenen Daten auf einem Server in den Niederlanden, mit einem Backup in England speichert. Beide Einrichtungen handeln in Übereinstimmung mit der Datenschutz-Grundverordnung (DSGVO) der EU und verarbeiten die Daten in pseudonymisierter Form (das heißt mit einem Code, ohne direkte Verbindung zu Ihrem Namen). Die Links zu den Ernährungserhebungen werden Ihnen über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studienzentrale in Hamburg zugesendet. Zum Schluss der Studie möchten wir noch mit einigen Teilnehmerinnen und Teilnehmern Interviews durchführen, die aufgezeichnet und verschriftlicht werden. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Hierzu werden Sie gesondert angesprochen und es erfolgt eine extra Einwilligung dafür.

Wer kann teilnehmen?

Sie können an der Studie teilnehmen, wenn:

1. Bei Ihnen im letzten Jahr eine MS Verdachtsdiagnose oder definitive Diagnose einer schubförmigen MS gestellt wurde.
2. Sie seit mindestens 6 Monaten keine Immuntherapie erhalten und in den nächsten 3 Monaten keine Immuntherapie geplant ist.
3. In den letzten 4 Wochen keine Cortisontherapie erfolgte und sie nicht schwanger sind.
4. Im Kernspin des Kopfes und Rückens mindestens 2 Entzündungsherde zu sehen sind.
5. Sie einen Internetzugang und ein internetfähiges Gerät (z.B. Laptop oder Tablet) haben.
6. Sie zwischen 18 und 65 Jahre alt sind.

Gibt es Risiken?

Risiken, jenseits der oben genannten zur Datensicherheit, liegen nicht vor.

Was passiert, wenn ich einen Schub habe oder neue Herde im MRT erscheinen?

Im Falle eines Schubes müssen Sie Ihren behandelnden Arzt aufsuchen. Dieser wird mit Ihnen zum einen über eine Schubtherapie und zum anderen über eine MS Immuntherapie entscheiden. Genauso liegt, bei Nachweis neuer Herde im MRT, eine Immuntherapieentscheidung an. Dabei kann die Entscheidung auch vertagt werden oder auch eine Entscheidung gegen eine Therapie gefällt werden. Direkt nach diesem Entscheidungsgespräch erfolgt, arzt- und patientenseitig, eine Bewertung. Zusätzlich möchten wir in diesem Fall aus der Studienzentrale eine kurze telefonische Befragung, innerhalb von 4 Wochen, mit Ihnen durchführen.

Was passiert mit meinen Daten?

Ihre Kontaktdaten werden an die Studienzentrale in Hamburg übermittelt. Ihre E-Mail-Adresse und Mobilfunknummer werden im Programm POWER@MS1 hinterlegt. Das Programm erinnert Sie regelmäßig, wenn neue Materialien für Sie bereit liegen. Dieser Kontakt erfolgt primär per E-Mail oder SMS. Ferner kann es sein, dass Sie kurze Verhaltenstipps per E-Mail oder SMS erhalten. Aus Datenschutzgründen sind E-Mail-Absender über das Programm so allgemein gehalten, dass nicht auf die MS rückgeschlossen werden kann. Hier müssen Sie darauf achten, dass die Nachrichten nicht im Spam-Ordner verschwinden. Zusätzlich kann es sein, dass Sie über die Studien-E-Mail (powerms1@uke.de) von Mitarbeitern/innen der Studien-

zentrale in Hamburg kontaktiert werden, mit der Bitte, bestimmte Studienfragen zu beantworten. Alle Patientendaten werden bis zum Studienende pseudonymisiert in einer Datenbank des deutschen MS-Registers gesammelt. Parallel dazu werden die Kernspindaten in Hamburg pseudonymisiert ausgewertet. Beide Datenbanken werden am Studienende verbunden und zusammen ausgewertet.

Zusätzlich werden die Zugriffszeiten auf der Studienwebsite erfasst, sodass wir abschätzen können, wie intensiv Sie sich mit den Materialien befasst haben. Diese Daten werden, wie alle anderen Daten, pseudonymisiert ausgewertet.

Nach Abschluss der Auswertung werden die Daten (inklusive Audiodaten) in Hamburg am INIMS auf einem geschützten Computer, über einen Zeitraum von 10 Jahren, sicher gelagert und anschließend vernichtet. Mit Ihrer Einwilligung werden darüber hinaus Ihre MS-bezogenen Daten in der Forschungsplattform des MS-Registers gespeichert (siehe Extraeinwilligung MS-Register). Ihre Einwilligung und die Teilnahme Ihres Zentrums am MS-Register vorausgesetzt, werden Ihre Daten gemeinsam mit dem Gesamtdatenbestand des MS-Registers, entsprechend Ihrer Einwilligung, ausgewertet. Die Daten können darüber hinaus der wissenschaftlichen Öffentlichkeit zugänglich gemacht werden, damit unsere Ergebnisse überprüft und gegebenenfalls auch mit anderen Ergebnissen verglichen werden können. Dazu werden die Daten anonymisiert, sodass keine Identifizierung mehr möglich ist. Stimmen Sie im Falle des Widerrufs Ihrer Einwilligungserklärung einer Weiterverwendung Ihrer sicher anonymisierten Daten nicht zu, ist eine Teilnahme an der Studie nicht möglich.

Teilnahme, Haftung, Versicherung, Aufwandsentschädigung

Die Teilnahme an der Studie ist freiwillig. Sie können Ihre Einwilligung jederzeit und ohne Angabe von Gründen widerrufen, ohne dass dadurch Nachteile für Sie entstehen.

Da es sich nicht um eine Studie zur Prüfung eines neuen Arzneimittels oder Medizinproduktes oder eines neuen Anwendungsgebietes handelt, ist keine besondere Studienversicherung (Probandenversicherung) zur Gefährdungshaftung vorgesehen. Es gelten die allgemeinen Haftungsgrundsätze.

Die wissenschaftliche Leitung hat Prof. Dr. med. Christoph Heesen (Telefon: 040-7410-53776). Die Studienkoordinatorin ist Nicole Krause (Telefon: 040-7410-54077). Sollten Sie noch weitere Fragen haben, stehen Ihnen der Versuchsleiter und die Studienkoordinatorin zur Beantwortung gerne zur Verfügung.

Für die Teilnahme an dieser Studie können keinerlei finanzielle Aufwandsentschädigungen gewährt werden.

Wir würden uns sehr freuen, wenn Sie dieses Projekt durch Ihre Teilnahme unterstützen.

Mit freundlichen Grüßen

Prof. Dr. med. Christoph Heesen

Nicole Krause

Datenschutzerklärung

Die erhobenen Daten unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen. Die Daten werden ausschließlich für wissenschaftliche Zwecke verwendet. Zugriff auf diese Daten haben die Projektleiter/Innen. Die Datenauswertung erfolgt durch Prof. Dr. Heesen und seine explizit autorisierten Mitarbeiter ohne Bezug zu den persönlichen Daten der Studienteilnehmer. Die in den Studien erhobenen Daten werden in pseudonymisierter[1] Form ausgewertet und für die Dauer von 10 Jahren gespeichert. Bei der Pseudonymisierung wird dem richtigen Namen ein Pseudonym (also ein Nummern- und Buchstabencode, z.B. A01, B01) zugeordnet. In den Dokumenten wird nur auf das Pseudonym und nicht auf den Namen verwiesen, sodass personenbezogene Daten nicht oder nur durch einen unverhältnismäßig großen Aufwand einer bestimmten Person zugeordnet werden können. Die personenbezogenen Daten sind gegen unbefugten Zugriff gesichert. Nach Beendigung der Studie werden die Tonaufnahmen der Interviews vernichtet. Ein individueller Widerruf der Erlaubnis zur Verwendung Ihrer Daten ist jederzeit möglich.

Eine Weitergabe der erhobenen Daten im Rahmen der Studie erfolgt nur in anonymisierter[2] Form. Die beteiligten Personen sind zur Verschwiegenheit verpflichtet. Gleiches gilt für die Veröffentlichung der Studienergebnisse.

Die Studienteilnehmer/innen haben das Recht, über die von Ihnen erhobenen personenbezogenen Daten Auskunft zu verlangen und über möglicherweise anfallende personenbezogene Ergebnisse der Studie ggf. informiert zu werden.
Diese Studie ist auch durch die zuständige Ethik-Kommission der Ärztekammer Hamburg beraten worden. Der zuständigen Landesbehörde kann ggf. Einsichtnahme in die Studienunterlagen gewährt werden. Im Falle des Widerrufs Ihrer Einwilligungserklärung werden die bereits erhobenen anonymisiert[2] und in dieser Form weiter genutzt.

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[1] *Pseudonymisieren ist das Ersetzen des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Identifizierung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a Bundesdatenschutzgesetz).*

[2] *Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Abs. 6 Bundesdatenschutzgesetz).*

Ergänzende Information für Studienteilnehmer gemäß Europäischer Datenschutz-Grundverordnung[3]:

Hiermit informieren wir Sie über die in der DSGVO festgelegten Rechte (Artikel 12 ff. DSGVO)**:**

Rechtsgrundlage: Die Rechtsgrundlage zur Verarbeitung der Sie betreffenden personenbezogenen Daten bildet bei klinischen Studien Ihre freiwillige schriftliche Einwilligung gemäß DSGVO sowie der Deklaration von Helsinki (Erklärung des Weltärztebundes zu den ethischen Grundsätzen für die medizinische Forschung am Menschen) und der Leitlinie für Gute Klinische Praxis. Zeitgleich mit der DSGVO tritt in Deutschland das überarbeitete Bundesdatenschutzgesetz (BDSG-neu) in Kraft.

Für die Datenverarbeitung verantwortliche Person: Der Studienleiter des Universitätsklinikums Hamburg-Eppendorf: **Prof. Dr. Christoph Heesen**

Recht auf Auskunft: Sie haben das Recht auf Auskunft über die Sie betreffenden personenbezogenen Daten, die im Rahmen der klinischen Studie erhoben, verarbeitet oder ggf. an Dritte übermittelt werden (Aushändigen einer kostenfreien Kopie) (Artikel 15 DSGVO, §34 BDSG-neu).

Recht auf Berichtigung: Sie haben das Recht, Sie betreffende unrichtige personenbezogene Daten berichtigen zu lassen (Artikel 16 und 19 DSGVO).

Recht auf Löschung: Sie haben das Recht auf Löschung Sie betreffender personenbezogener Daten, z. B. wenn diese Daten für den Zweck, für den sie erhoben wurden, nicht mehr notwendig sind (Artikel 17 und 19 DSGVO, §35 BDSG-neu).

Recht auf Einschränkung der Verarbeitung: Unter bestimmten Voraussetzungen haben Sie das Recht, eine Einschränkung der Verarbeitung zu verlangen, d.h. die Daten dürfen nur gespeichert, aber nicht verarbeitet werden. Dies müssen Sie beantragen. Wenden Sie sich hierzu bitte an Ihren Studienleiter oder an den Datenschutzbeauftragten des Prüfzentrums (Artikel 18 und 19 DSGVO).

Recht auf Datenübertragbarkeit: Sie haben das Recht, die Sie betreffenden personenbezogenen Daten, die Sie dem Verantwortlichen für die klinische Studie bereitgestellt haben, zu erhalten. Damit können Sie beantragen, dass diese Daten entweder Ihnen oder, soweit technisch möglich, einer anderen von Ihnen benannten Stelle übermittelt werden (Artikel 20 DSGVO).

Widerspruchsrecht: Sie haben das Recht, jederzeit gegen konkrete Entscheidungen oder Maßnahmen zur Verarbeitung der Sie betreffenden personenbezogenen Daten Widerspruch einzulegen (Art 21 DSGVO, § 36BDSG-neu). Eine solche Verarbeitung findet anschließend grundsätzlich nicht mehr statt.

Einwilligung zur Verarbeitung personenbezogener Daten und Recht auf Widerruf dieser Einwilligung: Die Verarbeitung Ihrer personenbezogenen Daten ist nur mit Ihrer Einwilligung rechtmäßig (Artikel 6 DSGVO). Sie haben das Recht, Ihre Einwilligung zur Verarbeitung personenbezogener Daten jederzeit zu widerrufen. Im Falle des Widerrufs müssen Ihre personenbezogenen Daten grundsätzlich gelöscht werden (Artikel 7, Absatz 3 DSGVO). Es gibt allerdings Ausnahmen, nach denen die bis zum Zeitpunkt des Widerrufs erhobenen Daten

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[3] *Verordnung (EU) 2016/679 des Europäischen Parlaments und des Rates vom 27. April 2016 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten, zum freien Datenverkehr und zur Aufhebung der Richtlinie 95/46/EG (Datenschutz-Grundverordnung)*

weiter verarbeitet werden dürfen, z.B. wenn die weitere Datenverarbeitung zur Erfüllung einer rechtlichen Verpflichtung erforderlich ist (Art. 17 Abs. 3 b DSGVO).

Möchten Sie eines dieser Rechte in Anspruch nehmen, wenden Sie sich bitte an den Studienleiter Ihres Prüfzentrums.

Außerdem haben Sie das **Recht, Beschwerde bei einer Aufsichtsbehörde/n einzulegen,** wenn Sie der Ansicht sind, dass die Verarbeitung der Sie betreffenden personenbezogenen Daten gegen die DSGVO verstößt. Wenn Sie Bedenken hinsichtlich des Umgangs mit Ihren personenbezogenen Datenhaben, können Sie sich an die für Sie zuständige Datenschutzbehörde wenden:

Die für das UKE beauftragte Behörde	**Datenschutz-Aufsichtsbehörde**
Datenschutzbeauftragter des Universitätsklinikums Hamburg-Eppendorf	Hamburgische Beauftragte für Datenschutz und Informationsfreiheit
Matthias Jaster	
Martinistraße 52 20246 Hamburg 040 / 7410 - 56890	Ludwig-Erhard-Str. 22 20459 Hamburg 040 / 42854 - 4040
m.jaster@uke.de	mailbox@datenschutz.hamburg.de

Einwilligungserklärung zur Teilnahme an der Studie POWER@MS1

Teilnehmer, Teilnehmerin (Name in Druckbuchstaben):

……

Bitte ankreuzen und unterschreiben

O Hiermit willige ich zur freiwilligen Teilnahme an der Studie ein.

Ich wurde mündlich ausführlich und verständlich über das Anliegen, die Bedeutung und die Tragweite der Studie aufgeklärt. Das Informationsschreiben zur Studie und zum Umgang mit den erfassten Daten habe ich gelesen und verstanden. Meine Fragen zur Studie wurden erläutert und beantwortet.

Zur Einwilligung hatte ich ausreichend Zeit. Meine Teilnahme ist freiwillig und kann jederzeit ohne Angaben von Gründen widerrufen werden, ohne dass für mich Nachteile entstehen. Ich habe keinerlei Kosten oder finanziellen Nutzen durch die Teilnahme an dieser Studie. Es gelten die Richtlinien des Datenschutzes.

Eine Kopie der Einwilligungserklärung habe ich erhalten und erkläre hiermit meine freiwillige Teilnahme an dieser Studie.

Ort, Datum	Unterschrift des Teilnehmers / der Teilnehmerin
……	……
Ort, Datum	Unterschrift des Arztes
……	……

VI Publikation 3 (im Druck)

Krause N, Derad C, von Glasenapp B, et al. Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial. Multiple Sclerosis and Related Disorders. 2023. doi:10.1016/j.msard.2023.105043

[EXT] Your Submission

em.msard.0.865ca6.a6db40c1@editorialmanager.com im Auftrag von Multiple Sclerosis and Related Disorders <em@editorialmanager.com>

Fr 29.09.2023 14:32

1. MSARD

An:Krause, Nicole <n.krause@uke.de>;

Ms. Ref. No.: MSARD-D-23-00404R2
Title: Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial
Multiple Sclerosis and Related Disorders

Dear Ms Nicole Krause,

We are pleased to inform you that your paper "Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial" has been accepted for publication in Multiple Sclerosis and Related Disorders in the present form.

Below are comments from the editor and reviewers.

Thank you for submitting your work to Multiple Sclerosis and Related Disorders.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

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Yours sincerely,

Christopher H Hawkes, MD FRCP FAAN
Managing Editor
Multiple Sclerosis and Related Disorders

Comments from the editors and reviewers:

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Journal Pre-proof

Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial

Nicole Krause , Carlotta Derad , Barbara von Glasenapp , Karin Riemann-Lorenz , Herbert Temmes , Markus van de Loo , Tim Friede , Thomas Asendorf , Christoph Heesen , the POWERMS1 study group

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Highlights

- Prevalence of anxiety and smoking is high in this early multiple sclerosis cohort
- Current smoking at disease onset is associated with a higher number of T2-lesions
- Unhealthy dietary habits are more common among current smokers
- A high need for stress management is prevalent and associated with disease severity

Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial

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Abstract

Background Receiving a multiple sclerosis (MS) diagnosis is a significant stressor. Therefore, highly individualised counselling is needed, especially in early MS. Modifiable risk factors (e.g. smoking and obesity) are gaining relevance in MS. Despite evidence for worse MS-related health outcomes, prevalence of adverse health behaviours, such as smoking and physical inactivity, is high across all MS stages. However, knowledge regarding health behaviours as well as their association with MS-related health outcomes among newly diagnosed PwMS in Germany is scarce. Currently, the efficacy of an interactive digital lifestyle management application intended to be used as an add-on to standard care among newly diagnosed PwMS in Germany is evaluated in an ongoing multicentre randomised controlled trial (RCT) ('POWER@MS1').

Objectives To describe baseline disease characteristics and health behaviours of the POWER@MS1 cohort and investigate associations between MS characteristics, quality of life (QOL), health behaviours and intention to optimise health behaviour habits.

Methods This study included 234 persons with early MS from 20 study centres located across Germany who participate in the POWER@MS1 RCT. Participants were recruited by treating neurologists from different regions and health-care settings in Germany. Baseline data was obtained using paper-based questionnaires and a web-based healthy diet screener between July 2019 and end of March 2022 and analysed descriptively.

Results In this early MS cohort (mean disease duration 4 months), a screening tool showed severe symptoms of anxiety in 15% of the participants. Better means for stress management appeared to be particularly relevant for the whole cohort. Moreover, 19% were current smokers, 16% were obese and 36% were insufficiently physically active. On average, participants only moderately adhered to dietary guidelines for recommended intake of key food groups (e.g. vegetables, fruits and fatty marine fish). Higher EDSS scores were associated with approximately 20% higher T2-lesion burden (rate ratio $RR = 1.2, p < 0.001$) and 13% higher relapse rate ($RR = 1.13, p = 0.02$) per EDSS disability level. Moreover, a higher T2-lesion burden was associated with current smoking ($RR = 0.76,\ p = 0.033$), resulting in approximately 24% less T2-lesions at disease onset among non-smokers. In addition, smoking was associated with unhealthier dietary habits according to lower diet scores (linear regression coefficient $\beta = -1.27,\ p < 0.001$). Higher EDSS scores ($\beta = 0.19,$

, $p < 0.001$) and higher BMI ($\beta = 0.013, p = 0.03$) were associated with higher HAQUAMS (lower QOL), while lower diet scores ($\beta = -0.044, p = 0.039$) were associated with lower HAQUAMS (higher QOL). Moreover, higher HAQUAMS indicated a higher intention to optimise stress management ($\beta = 0.98, p < 0.001$), physical activity ($\beta = 0.74, p = 0.046$) and sleep behaviour ($\beta = 1.82, p < 0.001$). Further, higher intention to optimise stress management was accounted for by higher EDSS scores ($\beta = 0.39, p = 0.004$) and a higher number of T2-lesions ($\beta = 0.029,\ p = 0.015$) in this newly diagnosed MS cohort.

Conclusion Results indicate a clear need for modifications of health behaviours among newly diagnosed PwMS participating in POWER@MS1. Individualised psychological and health behaviour counselling appears to be an important factor in treatment, also for similar early MS cohorts and particularly in those who demonstrate a more severe disease in clinical and MRI metrics.

KEYWORDS multiple sclerosis; early stage; disease activity; health behaviour; lifestyle management needs

1. Introduction

The prevalence of multiple sclerosis (MS) is increasing and new diagnostic criteria enable an earlier MS diagnosis (1, 2). Insufficient diagnostic information related to MS is a significant stressor that can cause distrust in the medical system at an early stage (3). Highly individualised counselling is needed, especially in early MS. Persons with MS (PwMS) want to actively participate in treatment decisions and take control to improve their health (4). Besides treatment with disease-modifying therapies (DMTs), adjustment of health behaviours is of growing importance in MS care (5) and maintaining a healthy lifestyle appears to be a key factor for successful self-management among PwMS (6). There are a number of known genetic, environmental and behavioural risk factors not only for developing MS but also for having a more severe MS course (7, 8). Among these are modifiable risk factors, such as smoking, low vitamin-D levels and obesity, which can be addressed through behavioural changes (5). Smoking, for instance, is associated with faster MS progression, worse long-term cognitive performance and higher premature mortality among PwMS (9-11). Moreover, low vitamin-D levels are associated with MS risk, higher disability and faster MS progression (5). Despite a lack of solid scientific evidence on the potential influence of dietary factors (e.g. specific diets or nutrients) (12, 13) or dietary modification (14) on MS outcomes, adherence to guidelines of a wholesome diet that takes MS-specific aspects into account is recommended (15). Further, regular physical activity (PA) is known to have a positive effect on balance (16), MS-associated fatigue (17), quality of life (QOL) and mood (18). Despite evidence for worse MS-related health outcomes among persons with adverse health behaviours, prevalence of physical inactivity, smoking, unhealthy dietary patterns and obesity appears to be high in PwMS across all disease stages (19-21). While presence of obesity at disease onset is already known to be associated with higher disability among PwMS in Germany (22), knowledge regarding dietary patterns, PA levels and smoking rates as well as their association with MS-related health outcomes among newly diagnosed PwMS in Germany is largely lacking. This is remarkable, as prompt and targeted optimisation of health behaviours at an early stage might have a positive impact on the further MS course. For this reason, the efficacy of an interactive digital lifestyle management application that is intended to be used as an add-on to standard care among newly diagnosed PwMS in Germany is currently evaluated in an ongoing multicentre randomised controlled trial (RCT) termed ‘POWER@MS1’ (23). The goal of this study is to describe baseline disease characteristics and health behaviours of the POWER@MS1 cohort that was recruited from different regions and health care settings in Germany. Moreover, we investigated whether there are associations between individual MS

characteristics, QOL and health behaviours as well as interest in and intention to optimise health behaviour habits. An overview of the research questions and underlying hypotheses is provided in Appendix A.

2. Methods

This study data was collected during baseline assessment of an ongoing RCT in Germany (23).

2.1 Inclusion criteria

Persons aged between 18 and 65 years with a clinically isolated syndrome, suspected or confirmed relapsing-remitting MS for less than 12 months, an MS-typical cerebrospinal fluid finding with detection of oligoclonal bands and at least two MS-typical lesions on T2-weighted images on magnetic resonance imaging (MRI) scans were eligible. From July 2019 to February 2021, only untreated patients were recruited. Based on a poor recruitment rate in the pandemic from March 2021 to March 2022, we broadened the inclusion criteria, including PwMS who are already treated with a DMT.

2.2 Recruitment of participants

Recruitment of participants took place from July 2019 until end of March 2022. Participants were recruited in 20 study centres in Germany comprising academic hospitals (40%), community clinics (35%) and private practices (25%) with a specialisation in MS. After eligibility screening, written informed consent was obtained in the study centres by participating neurologists.

2.3 Outcome measures and data collection methods

Data was obtained using paper-based questionnaires and a web-based healthy diet screener. Demographic and most clinical characteristics (e.g. comorbidities, relapse history) as well as height, weight and smoking status were obtained by the treating neurologist using standardised questionnaires (see Appendix B). T2-lesions were documented by the treating neurologist based on reports of radiologists involved in clinical care who determined the number of T2-lesions independently. Latest MRI scans (not older than 3 months) were sent to the leading study centre in Hamburg. A quality check for blurring and availability of at least two sequences (T1- and T2-weighted or FLAIR) at a minimum of 1.5 Tesla was performed. All other data were assessed using patient-reported outcome measures (see Appendix B). The Patient Activation Measure (PAM) (24) was used to measure the participants' engagement

level in care processes (e.g. based on the knowledge about their condition and treatments). Dietary behaviour was assessed through a healthy diet screener measuring the intake of 10 key food groups (e.g. vegetables, fruits and fatty marine fish) that are associated with a preventative potential for chronic diseases (25). For each food group, intake (e.g. portions/day) or frequency of intake within the last 7 days was assessed. Based on dietary guidelines of the German Nutrition Society (DGE) and additional evidence, 0 to 1 points are scored in all food groups (n=10) according to respective intake recommendations (low, moderate or high intake). A maximum diet score of 10 reflects perfect adherence to all intake recommendations. An overview of all food groups and intake recommendations is provided in Appendix C. Moreover, two open questions of the healthy diet screener assess self-reported deviations in dietary behaviour within the past week as well as self-reported special diets. Following the stage assessment of Lippke et al. (26), dietary behaviour expressed as fruit and vegetable intake as well as regular PA were assessed to classify participants into "non-active" behaviour stages (precontemplation, contemplation, preparation) or "active" behaviour stages (action, maintenance). For dietary behaviour, daily intake of at least two portions of fruits and three portions of vegetables was required to classify for active stages. Self-reported vitamin-D supplementation as well as the international units per week were assessed with a self-developed questionnaire. For PA, regular moderate or strenuous exercise (e.g. walking) of at least 30 minutes four times per week was required to classify for active stages. Moreover, the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (27) was used to measure frequencies of usual weekly PA of at least 15 minutes during leisure-time. Based on frequencies reported for moderate and strenuous activities, the GLTEQ health contribution score (GLTEQ HCS) was calculated to categorise participants as sufficiently, moderately or insufficiently active. Additionally, the Physical Activity, Exercise, and Sport Questionnaire (BSA-F) (28) was used to measure engagement in regular exercise activity within the past 4 weeks. A description of all other outcome measures and data collection methods is provided in the RCT study protocol (23).

2.4 Statistical analyses

Exploratory data analyses were performed to investigate associations between demographic or clinical characteristics and health behaviours. Continuous variables are described using mean and standard deviation (SD) or median and interquartile range (IQR) and categorical variables are expressed as total numbers (n) and relative frequencies (%). Cut-off values for high disease severity in early MS were defined as Expanded Disability Status Scale (EDSS) scores ≥ 3.0, ≥ 10 T2-lesions and a total of two relapses or more for disease activity. The association

of continuous dependent variables and continuous resp. binary explaining variables was quantified using linear regression models and the regression coeficients (β) are reported with 95% confidence intervals (CI). For number of relapses and T2-lesions (cranial and spinal), negative binomial regression was used to calculate associations and rate ratios (RR) are reported. Pearson's Chi-squared test was applied to investigate group differences for categorical variables. Multiple linear regression models were adjusted for age, sex, BMI, smoking status and educational status and missing values were removed. The best-fitting model was determined using the Akaike Information Criterion (AIC). To visualise these results, linear regression on a shifted log-transformed scale (log(x+1)) for QOL, number of lesions and EDSS was used. In this exploratory analysis, differences were considered significant at two-sided $p \leq 0.05$. Due to the exploratory nature of the analysis, no corrections for multiple testing were applied. Data were analysed using the statistical programming language R 4.2.1 (29).

3. Results

Overall, 351 PwMS were screened for eligibility and 117 PwMS were excluded (screening data is only available from seven study centres). Among all excluded PwMS (n=117), 66 did not meet inclusion criteria (e.g. due to treatment with a DMT, n=42), 18 declined participation (e.g., due to lack of time or interest) and 33 were excluded due to other reasons (e.g., distance to the study centre). Finally, 234 participants were recruited and successfully randomised. The sample consists of 78 participants who were randomised before and 156 participants who were randomised after the amendment of inclusion criteria in March 2021. Among all participants, two participants were diagnosed with MS 14 months prior to study inclusion, one participant had only one MS-typical lesion, and the last MRI was performed up to five months prior to study inclusion in 11 cases. Five participants did not have an MS typical cerebrospinal fluid finding with detection of oligoclonal bands and three participants had received corticosteroid therapy within 4 weeks prior to study inclusion. An overview of the number of participants per study centre is provided in Appendix D. Of all study centers (n=20), most participants (n=84, 36%) were recruited at the lead study centre in Hamburg, followed by Kiel (n=28, 12%), Cologne (n=22, 9%) and Bonn (n=17, 7%).

3.1 Demographics and disease characteristics

All demographic and clinical characteristics of the sample are shown in Table 1. Participants were predominantly female. The mean age at inclusion was 36.1 (SD 9.9) years. With two thirds of the sample having completed 12 or more school years, the education level is high.

The majority was employed with mostly sedentary work. On average, participants were diagnosed with MS four months before study enrolment. With a median EDSS of 1 (IQR 0-2), the level of disability was mild. At baseline, participants had 10 (median; IQR 5-14) T2-lesions (cranial and spinal) and experienced one relapse. In total, 30% of our sample were treated with a DMT, which included n=50 PwMS treated with a category 1 DMT (e.g., Beta-Interferones, Dimethyl fumerate), n=4 PwMS treated with a category 2 DMT (e.g., Ozanimod, Cladribine) and n=16 PwMS treated with a category 3 DMT (e.g., Ocrelizumab, Natalizumab) (30). Comorbidities were documented by the treating neurologist for almost 60% of the sample. Among these, 20% (n=27) had other neurological or psychiatric disorders, 19% (n=26) had another autoimmune disease, 11% (n=15) suffered from hypertension and 6% (n=8) showed other cardiovascular diseases (complete list of comorbidities is listed in Appendix E). Around 42% of participants were overweight or obese with a BMI of ≥25kg/m^2. With a total average score of 1.7 (SD 0.5) in the Hamburg Quality of Life in MS Scale (31), QOL was high in this cohort (see Appendix E for subscale data). Symptoms of moderate to severe anxiety, measured by the Hospital Anxiety and Distress Scale (32), were present in about one third and symptoms of moderate to severe depression in about 11% of the sample.

Table 1: Demographic and clinical characteristics of the early MS cohort

	Baseline (n = 234)
Age in years (at inclusion), mean (SD)	36.1 (9.9)
Female, n (%)	184 (78.6)
Education, n (%)[a]	
Less than 12 years	74 (32.9)
12 years and more	151 (67.1)
Employed persons, n (%)[b]	213 (91.4)
None or rather little sedentary work, n (%)[b]	52 (24.6)
Rather more or much sedentary work, n (%)[b]	159 (75.4)
Disease duration in months, mean (SD)	4.4 (4.0)
EDSS, median (IQR)	1 (0-2)
Number of relapses, median (IQR)	1 (1-2)
Number of T2-lesions (cranial and spinal), median (IQR)	10 (5-14)
Cranial T2-lesions, median (IQR)	9 (4-12)
Spinal T2-lesions[c], median (IQR)	1 (0-2)
Current DMT use, n (%)	70 (29.9)
Persons with comorbidities, n (%)[b]	135 (57.9)

Body-Mass-Index (kg/m^2), mean (SD)[b]	25.2 (5.6)
Underweight (< 18.5 kg/m^2), n (%)	7 (3.0)
Healthy weight (18.5-24.9 kg/m^2), n (%)	128 (55.4)
Overweight (25.0-29.9 kg/m^2), n (%)	61 (26.4)
Obesity (≥ 30.0 kg/m^2), n (%)	35 (15.2)
HAQUAMS total score, mean (SD)	1.7 (0.5)
HADS anxiety score, mean (SD)	6.7 (3.7)
Moderate to severe symptoms of anxiety (8-17), n (%)	78 (33.3)
Severe symptoms of anxiety (11-17), n (%)	35 (15.0)
HADS depression score, mean (SD)	3.4 (3.3)
Moderate to severe depression (8-16), n (%)	25 (10.7)
Severe depression (11-16), n (%)	12 (5.1)

DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; HADS = Hospital Anxiety and Depression Scale; HAQUAMS = Hamburg Quality of Life in Multiple Sclerosis Scale; IQR = interquartile range; SD = Standard deviation.
[a] Missing values, n=9.
[b] Missing values, n=1-3.
[c] Missing values, n=51.

3.2 Health behaviour at MS onset

Self-reported health behaviours, including patient activation, active smoking, PA and dietary behaviour are shown in Table 2. According to the PAM score, the PwMS in this early MS cohort claimed active engagement in care processes. The proportion of current smokers was almost 20%. Considering all participating females (n=184), only 16% (n=30) were smoking, whereas 30% (n=15) of all participating males (n=50) were smoking. With a mean diet score of 5.1 (SD 1.4), on average participants only moderately adhered to intake recommendations for key food groups. The maximum score was 8.1 and 34% indicated that their reported dietary behaviour differed from the weeks before due to holidays, stress or other reasons. Participants deviated the most from intake recommendations for “whole grains” and “unsalted nuts” and performed best in the category "red meat", where 85% adhered to the low recommended intake (≤2 portions/week). Supplementary data for all food groups as well as a histogram with a density curve are provided in Appendix C. Among all, 34 (15%) participants reported to follow a vegetarian diet, 11 of those a vegan diet. Another 6% (n=14) indicated to follow other specific diets or dietary patterns (e.g. gluten free, intermittent fasting, low carb, Mediterranean Diet, Overcoming MS Diet). According to the stage assessment, 65% reported daily intake of at least 3 portions of vegetables and 2 portions of fruits (action and maintenance stage), whereas this was only reported by 8% (n=18) for the past week in the diet score. Vitamin-D was supplemented by 67% of this cohort. Among these, 10 particpants have

taken high doses (>4000 international units/day) above the recommended upper level for adults (33). Conforming to the GLTEQ health contribution score, 64% of the early MS cohort was classified as being sufficiently active, while more than one third was only moderately or insufficiently active. According to the BSA-F, only half of the study participants reported that they had engaged in regular exercise activity within the past 4 weeks. Of those, 66% (n=78) indicated that they had exercised for more than 120 minutes per week. Most commonly reported exercise activities included running (n=34, 29%), yoga (n=32, 27%), cycling (n=30, 25%), and strength training (n=19, 16%). According to the stage assessment for recommended PA, only 41% of the sample consisted of actors (action and maintenance stage). Generally, interest in health behaviour management options was high (mean score 8.8 on a scale of 0 to 10, with 10 indicating full agreement). Regarding the intention to change specific health behaviours, the optimisation of stress management was considered most relevant (mean score: 8.6), followed by the intention to change dietary behaviour (mean score: 7.3) and PA (mean score: 7.0). Change in sleep behaviour was only considered moderately relevant for this early MS cohort (mean score 6.0).

Table 2: Patient activation and health behaviour of the early MS cohort

	Baseline (n = 234)
PAM score, mean (SD)	67.0 (11.1)
Active smokers, n (%)[a]	45 (19.2)
Smoking duration in years, mean (SD)[b]	18.1 (10.0)
Healthy diet score, mean (SD)	5.1 (1.4)
Stage of change – fruit and vegetable consumption, n (%)[a]	
Precontemplation (non-intenders)	5 (2.2)
Contemplation (non-intenders)	17 (7.3)
Preparation (intenders)	59 (25.3)
Action (actors)	40 (17.2)
Maintenance (actors)	112 (48.1)
Vitamin-D supplementation, n (%)[a]	157 (67.1)
≤ 1000 international units per day, n (%)[c]	43 (34)
> 1000 to ≤ 4000 international units per day, n (%)[c]	73 (58)
> 4000 international units per day, n (%)[c]	10 (8)
GLTEQ HCS, mean (SD)[d]	24.6 (19.1)
Insufficiently active (below 14), n (%)	40 (18)
Moderately active (14-23), n (%)	42 (17.5)

Sufficiently active (24 and above), n (%)	146 (64.0)
BSA-F – regular exercise activity, n (%)[a]	119 (51.1)
< 30 minutes/week	5 (4.2)
≥ 30 to < 120 minutes/week	36 (30.3)
> 120 minutes/week	78 (65.6)
Stage of change – physical activity, n (%)	
Precontemplation (non-intenders)	9 (3.9)
Contemplation (non-intenders)	44 (18.8)
Preparation (intenders)	85 (36.3)
Action (actors)	32 (13.7)
Maintenance (actors)	64 (27.4)
Interest in health behaviour management options, mean (SD)*[a]	8.8 (1.6)
Intention to change physical activity	7.0 (2.9)
Intention to change dietary behaviour	7.3 (2.5)
Intention to change sleep behaviour	6.0 (3.1)
Intention to optimise stress management	8.6 (2.1)

BSA-F = Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität Fragebogen); GLTEQ HCS = Godin Leisure-Time Exercise Questionnaire health contribution score; PAM = Patient Activation Measure; SD = Standard deviation.
[a] Missing values, n=1-3.
[b] Missing values, n=7.
[c] Missing values, n=31.
[d] Missing values, n=6.
* Likert scale ranging from 0 ("completely disagree") to 10 ("fully agree").

3.3 Association of MS characteristics and health behaviours

Higher EDSS scores were associated with a higher age at diagnosis ($\beta = 2.4, 95\%\text{-CI: } [1.16, 3.64], p < 0.001$), a higher relapse rate ($RR = 1.13$; 95%-CI:[1.01,1.25], $p = 0.02$), a higher T2-lesion burden ($RR = 1.2$; 95%-CI:[1.08,1.32], $p < 0.001$) and worse QOL ($\beta = 0.185, 95\%\text{-CI: } [0.12, 0.25], p < 0.001$) in early MS. More precisely, the number of T2-lesions increased by about 20% and the relapse rate increased by about 13% when moving from one EDSS disability level to the next higher. T2-lesion burden was not associated with QOL or current DMT use. When examining differences in MS characteristics according to recruitment time (before amendment in March 2021 vs. after amendment), univariate analysis did not reveal significant differences between groups. However, a multiple logistic regression with group allocation as dependent variable and sex, age at diagnosis, T2-lesion count, relapse rate, QOL and EDSS as explaining variables, revealed a significant influence of QOL on group allocation (Odds Ratio = 1.95, 95%-CI: [1.06, 3.75]) with lower QOL being associated with PwMS recruited prior to the amendment. However, mean differences of QOL are

comparably small (1.65, 95%-CI:[1.53-1.76] before amendment vs. 1.78, 95%-CI:[1.69-1.85] after amendment).

Smoking

Education level was lower among smokers compared to non-smokers ($\chi^2 = 25;\ p < 0.001$). Moreover, current smoking was associated with lower diet scores ($\beta = -1.26;$ 95%-CI: $[-1.75, -0.78], p < 0.001$; see Figure 1) and a higher T2-lesion burden ($RR = 0.76;$ 95%-CI:$[0.59,0.97], p = 0.033$; see Figure 1). With a mean expected number of T2-lesions of 15.53 (95%-CI: $[12.4, 19.47]$) among smokers and 11.8 (95%-CI: $[10.54, 13.2]$) among non-smokers, non-smokers had about 24% less T2-lesions at disease onset. Current smoking was not associated with age at the time of diagnosis, EDSS or relapse rate.

Figure 1: Association of current smoking with dietary behaviour and T2-lesion burden (violin plots). The violin plots show the distribution and density curve in each group.

Dietary behaviour and BMI

Diet scores were higher among persons with a higher education level ($\beta = 0.89;$ 95%-CI: $[0.47,1.31], p < 0.001$). Besides current smoking, unhealthy dietary habits expressed as low diet scores were also associated with worse QOL expressed as high HAQUAMS ($\beta = -0.044,$ 95%-CI: $[-0.09, -0.002], p = 0.039$). Moreover, low diet scores were associated with high BMI values ($\beta = -0.05,$ 95%-CI: $[-0.09, -0.01], p = 0.008$), supporting convergent validity of these outcome measures. BMI was higher among persons with lower education level ($\beta = -1.82;$ 95%-CI: $[-3.37, -0.27], p = 0.02$). High BMI was also associated with lower QOL according to high HAQUAMS ($\beta = 0.013,$ 95%-CI: $[0.001, 0.03], p = 0.03$), but not with current smoking. Further, diet scores as well as BMI were not associated with age at the time of diagnosis, relapse rate, EDSS, number of T2-

lesions or PA. No association between obesity and individual MS characteristics could be shown. See Table 3 for a detailed summary of results.

Physical activity

While low education levels were associated with insufficient PA according to the GLTEQ health contribution score ($\beta = 10.02$; 95%-CI: $[3.97,16.06], p < 0.001$), the total level of movement and exercise activities assessed by BSA-F was not associated with education level. Moreover, PA was not associated with age at the time of diagnosis or individual MS characteristics.

Interest in health behaviour management options and willingness to change

Individual MS characteristics measured as age at the time of diagnosis, EDSS, relapse rate, number of T2-lesions and QOL were not associated with general interest in health behaviour management options in early MS. Associations of individual MS characteristics and the intention to optimise stress management are provided in Appendix F. In newly diagnosed PwMS, higher intention to optimise stress management was accounted for by higher EDSS scores ($\beta = 0.388$, 95%-CI: $[0.12, 0.65], p = 0.004$) and more T2-lesions ($\beta = 0.029$, 95%-CI: $[0.006, 0.05], p = 0.015$). A lower QOL expressed by high HAQUAMS indicated a higher intention to optimise stress management ($\beta = 0.982$, 95%-CI: $[0.47, 1.49], p < 0.001$). T2-lesion burden was not associated with the intention to change any other specific health behaviour and no associations were observed for number of relapses. To explain the intention to optimise stress management, the best fitting multiple linear regression model (adjusted $r^2 = 0.23$) included number of T2-lesions ($\beta = 0.037, p = 0.002$) and QOL ($\beta = 0.836, p = 0.001$). For a detailed summary of analyses see Table 3.

Table 3 Univariate linear regression coefficients. RR: Rate Ratio, β: Slope coefficient of linear regression, p: two-sided p-value for null hypothesis H_0: $\beta = 0$, χ^2: test statistic of the Chi-Square test

Dependent variable	Explanatory variable	Regression coefficient	95%-CI	p-value
Age at the time of diagnosis	EDSS	$\beta = 2.4$	$[1.16, 3.64]$	$p < 0.001$
Relapse rate	EDSS	RR $= 1.13$	$[1.01, 1.25]$	$p = 0.02$
Number of T2-lesions	EDSS	RR $= 1.2$	$[1.08, 1.32]$	$p < 0.001$
QOL	EDSS	$\beta = 0.19$	$[0.12, 0.25]$	$p < 0.001$
Education	Smoking	$\chi^2 = 25$		$p < 0.001$
Healthy diet score	Smoking	$\beta = -1.27$	$[-1.75, -0.78]$	$p < 0.001$

Number of T2-lesions	Smoking	RR = 0.76	[0.59, 0.97]	$p = 0.033$
Healthy diet score	Education	$\beta = 0.89$	[0.47, 1.31]	$p < 0.001$
QOL	Healthy diet score	$\beta = -0.044$	$[-0.09, -0.002]$	$p = 0.039$
QOL	BMI	$\beta = 0.013$	[0.001, 0.025]	$p = 0.03$
BMI	Education	$\beta = -1.82$	$[-3.37, -0.27]$	p =0.02
GLTEQ HCS	Education	$\beta = 10.02$	[3.97, 16.06]	$p = 0.001$
Intention to…				
optimise stress management	EDSS	$\beta = 0.39$	[0.12, 0.65]	$p = 0.004$
optimise stress management	Number of T2-lesions	$\beta = 0.029$	[0.006, 0.05]	$p = 0.015$
optimise stress management	QOL	$\beta = 0.98$	[0.47, 1.49]	$p < 0.001$
change physical acitivity	QOL	$\beta = 0.74$	[0.015, 1.48]	$p = 0.046$
change sleep behaviour	QOL	$\beta = 1.82$	[1.08, 2.56]	$p < 0.001$

BMI = Body-Mass-Index; EDSS = Expanded Disability Status Scale; GLTEQ HCS = Godin Leisure-Time Exercise Questionnaire health contribution score; HAQUAMS = Hamburg Quality of Life in Multiple Sclerosis Scale; QOL = quality of life (measured by HAQUAMS).

Associations of disease characteristics and the intention to change PA as well as sleep management are provided in Appendix F. A higher intention to optimise PA was also accounted for by higher EDSS scores ($\beta = 0.39$, 95%-CI: $[0.01, 0.77], p = 0.043$) and lower QOL measured by high HAQUAMS ($\beta = 0.745$, 95%-CI: $[0.01, 1.47], p = 0.046$). In addition, lower QOL indicated a higher intention to change sleep behaviour ($\beta = 1.82$, 95%-CI: $[1.08, 2.56], p < 0.001$). There was no association between EDSS scores or lower QOL and the intention to change dietary behaviour.

4. Discussion

This study reports on clinical characteristics and health behaviours of the POWER@MS1 cohort that consists of newly diagnosed PwMS from different regions and clinical settings in Germany. Sex, number of relapses, level of disability measured as EDSS and T2-lesions as well as presence of comorbidities fit data reported for PwMS in other large German cohort studies (22, 34), while age at disease onset was higher among our participants (37 vs 31 years). Moreover, the frequency of depressive symptoms fits data reported for newly diagnosed PwMS in the German NationMS cohort (35) and the frequency data of symptoms of anxiety corresponds to a meta-analysis on emotional outcomes in early MS (36). In

particular, similar to earlier studies (37) a high prevalence of severe symptoms of anxiety (15%) was detected in our study with a screening measure and psychological support in terms of improvement in stress management was considered highly relevant, which both might be explained by the substantial emotional burden and high stress levels following an MS diagnosis (3, 37). Interestingly the need for improvements in stress management was more pronounced in those who demonstrate a more severe disease in clinical and MRI metrics.

The proportion of current smokers is a little lower in our cohort than in both the general German population (28%) (38) as well as in a comparable German early MS cohort (32%) (22). Considering the negative impact of smoking on the MS-related disease course (10, 11), the prevalence of smokers is nevertheless worrying, especially among males (30% smokers). Smoking cessation is particularly relevant in early MS, since smokers in this cohort showed a higher disease severity (T2-lesions) at a very early stage. This fits with other data showing that earlier smoking cessation seems to have stronger effects on MS disease outcomes (39). Further, smoking was associated with unhealthy dietary behaviour and co-occurrence of these risk factors might lead to an acummulation of negative impacts (40). Ideally, health behaviours should be addressed early through multiple health behaviour change interventions (41). We found no associations between smoking and EDSS or relapse rates, which might be explained by the generally low relapse rate and mild impairment of this early MS cohort. Associations of disability, increased disease severity and smoking might only become apparent over a further disease course. In general, only small to medium effects were observed for associations between health behaviours and individual MS characteristics, which might be more pronounced in more physically impaired PwMS.

Regarding the presence of obesity, our data is in line with a nationwide longitudinal cohort study involving newly diagnosed PwMS (22). While obesity at disease onset was associated with higher EDSS in this cohort, this was not reflected in our data. As obesity has shown to be associated with cardiovascular risk factors as well as increased MS-related disease severity and progression (42, 43), this highlights the need for optimisation of diet and exercise habits in this early MS cohort. To address this issue, dietary counselling might primarily focus on weight problems. PA level needs optimisation in more than one third of this early MS cohort. Remarkably, the proportion of PwMS classified as sufficiently active according to the GLTEQ was substantially higher in this early MS cohort than in a German web-based survey study (44), where only 45% were sufficiently active. However, these participants were characterised by a longer disease duration and higher disability. Stage assessment data on

fruit/vegetable intake and PA did not match other outcome measures. More specific instruments (e.g. diet screeners) might be more adequate to monitor dietary patterns.

Lower QOL was associated with unhealthy dietary habits, high BMI as well as higher intention to optimise stress management, PA and sleep behaviour. To increase QOL among newly diagnosed PwMS comparable to this cohort, support to adjust these health behaviours should be provided. While sleep disorders seem to be common in MS, they have not been rigorously studied with monitoring tools, which is why population-based studies are needed (45) to develop treatment strategies.

Due to the pragmatic study design and the resulting heterogeneity of MRI scans (e.g. regarding software used, slice thickness) as well as assessors, we chose the number of T2-lesions as the major inflammatory MRI measure. Considering the scope of the RCT, which is the optimisation of health behaviours, those with very unhealthy habits who are not at all willing to change their health behaviour might especially be underrepresented. Supporting this assumption, the PAM validation study (24) revealed that those with higher patient activation scores, as observed in this study, are generally more likely to exercise regularly, have healthier dietary habits, and do not smoke. Therefore, we assume an underestimation rather than an overestimation of risk in this cohort.

In conclusion, this study indicates a clear need for counselling and modifications of health behaviours in comparable cohorts of persons with early MS. However, as a relevant proportion of PwMS in this cohort showed severe symptoms of anxiety, these participants might only be ready to modify their health behaviours after having received psychological support to address relevant coping issues. Moreover, stress management appears to be particularly relevant. Therefore, we believe that individualised psychological counselling and coping support should be provided for similar early MS cohorts. Results of the ongoing RCT (23) are expected to help better understand whether digitally administered health behaviour change is feasible and whether these changes affect relevant health outcomes in MS (e.g. T2-lesion burden, relapse rate, EDSS or QOL) over time.

Declarations

Ethics approval and trial registration

The study has been approved by the Ethics Committee of the Hamburg Chamber of Physicians (PV6015) and written informed consent was obtained from all participants. The RCT has been prospectively registered at ClinicalTrials.gov (NCT03968172).

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Declaration of competing interests

CH has received research grants, speaker honoraria and travel grants from Biogen, Celgene, Genzyme, Merck and Roche; all outside of this work. HT has no personal pecuniary interests to disclose, other than being the Secretary General of the German MS Society, federal association, which receives funding from a range of public and corporate sponsors, recently including Bundesgesundheitsministerium (BMG), The German Innovation Fund (G-BA), The German MS Trust, Biogen, Bristol Myers Squibb, Merck Serono, Novartis, Roche, Sanofi, Viatris (former Mylan); none resulted in a conflict of interest. TF reports personnel fees from Bayer, BiosenseWebster, Boehringer Ingelheim, CSL Behring, Daiichi Sankyo, Enanta, Fresenius Kabi, Galapagos, Immunic, Janssen, LivaNova, Novartis, Relaxera, Roche, and Vifor; all outside this work. DB has received speaker honoraria and travel grants from Bayer, Novartis, Roche, Genzyme; all outside this work. AB has received consulting and/or speaker fees from Alexion, Biogen, Celgene, Horizon, Novartis, Roche and Sandoz/Hexal and his institution has received compensation for clinical trials from Alexion, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme; all outside this work. KG has received compensation as investigator, advisor and speaker as well as travel fees from Abbvie, Almirall, Aristo, Bayer, Biogen, BMS, Celgene, Genzyme, Ipsen, Janssen, Merck, Novartis and Roche; all outside this work. SM has received financial support for consulting activities from Roche; all outside this work. PO received research support as well as speaking fees and travel fees from Alexion, Bayer Health Care, Biogen, Janssen, Merck Serono, Novartis, Pfizer, Roche, Sanofi Genzyme, TEVA; all outside this work. HR has received speaker honoraria from Roche, MerckSerono, and Novartis and participated in advisory boards for Novartis, Teva, and Hexal; all outside this work. SSch has received research grants, speaker honoraria and travel compensations from BayerVital, Biogen, Genzyme, Merck, Novartis, Roche, Teva; all outside

this work. AS received speaker honoraria from Bayer and Biogen, and participated in AdBoards for Merck Serono; all outside this work. KHS has received speaker honoraria or travel grants from Biogen, Bristol Myers Squibb, Merck and Roche; all outside this work. CW has received institutional honoraria and/or grant support from Novartis, Sanofi-Genzyme, Alexion, Janssen, Merck, Biogen, and Roche; all outside this work. All other authors have nothing to declare.

Author contributions

Nicole Krause: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualisation, Writing – original draft. **Barbara von Glasenapp:** Conceptualisation, Project administration, Writing – review & editing. **Karin Riemann-Lorenz:** Conceptualisation, Funding acquisition, Methodology, Writing – review & editing. **Carlotta Derad & Thomas Asendorf:** Data curation, Formal analysis, Visualisation, Writing – review & editing. **Tim Friede:** Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Herbert Temmes & Markus van de Loo:** Resources, Writing – review & editing. **Christoph Heesen:** Conceptualisation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft. **POWER@MS1 study group:** Recruitment, Study conduct, Writing – review & editing.

Abbreviations

AIC: Akaike Information Criterion

BMI: Body-Mass-Index

BSA-F: Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität Fragebogen)

CI: conficence interval

DMT: disease-modifying therapy

EDSS: Expanded Disability Status Scale

GLTEQ: Godin Leisure-Time Exercise Questionnaire

HAQUAMS: Hamburg Quality of Life in Multiple Sclerosis Scale

HADS: Hospital Anxiety and Depression Scale

IQR: interquartile range

MRI: magnetic resonance imaging

MS: multiple sclerosis

PA: physical activity

PAM: Patient Activation Measure

PwMS: person with multiple sclerosis

QOL: quality of life

RCT: randomised controlled trial

RR: rate ratio

SD: standard deviation

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Appendix

Appendix A: Overview of research questions and hypotheses

Research question 1: Are individual MS characteristics of persons with early MS (measured as EDSS, number of T2-lesions and QOL) associated with each other or DMT treatment?

Hypotheses:

1.1 A higher number of T2-lesions is associated with higher EDSS scores.

1.2 A higher number of T2-lesions is associated with lower QOL.

1.3 A higher number of T2-lesions at disease onset is associated with DMT treatment.

1.4 Higher EDSS scores are associated with lower QOL.

Research question 2: Are demographics or individual MS characteristics of persons with early MS (measured as age at the time of diagnosis, EDSS, relapse rate, number of T2-lesions and QOL) associated with health behaviours or comorbidities?

Hypotheses:

2.1 The education level is lower in PwMS who smoke.

2.2 MS manifests earlier and more severely in PwMS who smoke.

2.3 The education level is lower in PwMS with lower physical activity.

2.4 MS manifests earlier and more severely in PwMS with lower physical activity.

2.5 The education level is lower in PwMS with lower diet scores.

2.6 MS manifests earlier and more severely in PwMS with lower diet scores.

2.7 The education level is lower in PwMS with higher BMI values.

2.8 MS manifests earlier and more severely in PwMS with higher BMI values.

2.9 The education level is lower in PwMS with lower patient activation.

Research question 3: Are health behaviours of persons with early MS associated with each other or comorbidities?

Hypotheses:

3.1 Physical activity is lower in PwMS who smoke.

3.2 Diet scores are lower in PwMS who smoke.

3.3 Comorbidities are more frequent in PwMS who smoke.

3.4 BMI values are higher in PwMS who smoke.

3.5 BMI values are higher in PwMS with lower physical activity.

3.6 BMI values are higher in PwMS with lower diet scores.

3.7 Comorbidities are more frequent in PwMS with higher BMI values.

Research question 4: Are individual MS characteristics of persons with early MS (measures as EDSS, relapse rate, number of T2-lesions and QOL) associated with the interest in health behaviour management options, the intention to optimise health behaviours or stages of change?

Hypotheses:

4.1 Interest in health behaviour management options is higher among pwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL).

4.2 The intention to optimise physical activity is higher among pwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL).

4.3 The intention to optimise dietary behaviour is higher among pwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL).

4.4 The intention to optimise sleep management is higher among pwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL).

4.5 The intention to optimise stress management is higher among pwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL).

4.6 PwMS with higher disease severity (measured as higher EDSS scores, higher relapse rate, higher number of T2-lesions and lower QOL) are in lower stages of change (regarding physical activity and dietary behaviour).

Appendix B: Clinical assessments and patient-reported outcome measures

Clinical assessment (by neurologists)	**Patient-reported**
Demographic data	Education
Height and weight	HAQUAMS
Smoking status	HADS
Comorbidities	PAM
MRI history	Healthy diet screener
T2-lesions	Vitamin-D supplementation
Relapse history	GLTEQ
Immunotherapy history and status	BSA-F
EDSS	Stages of change

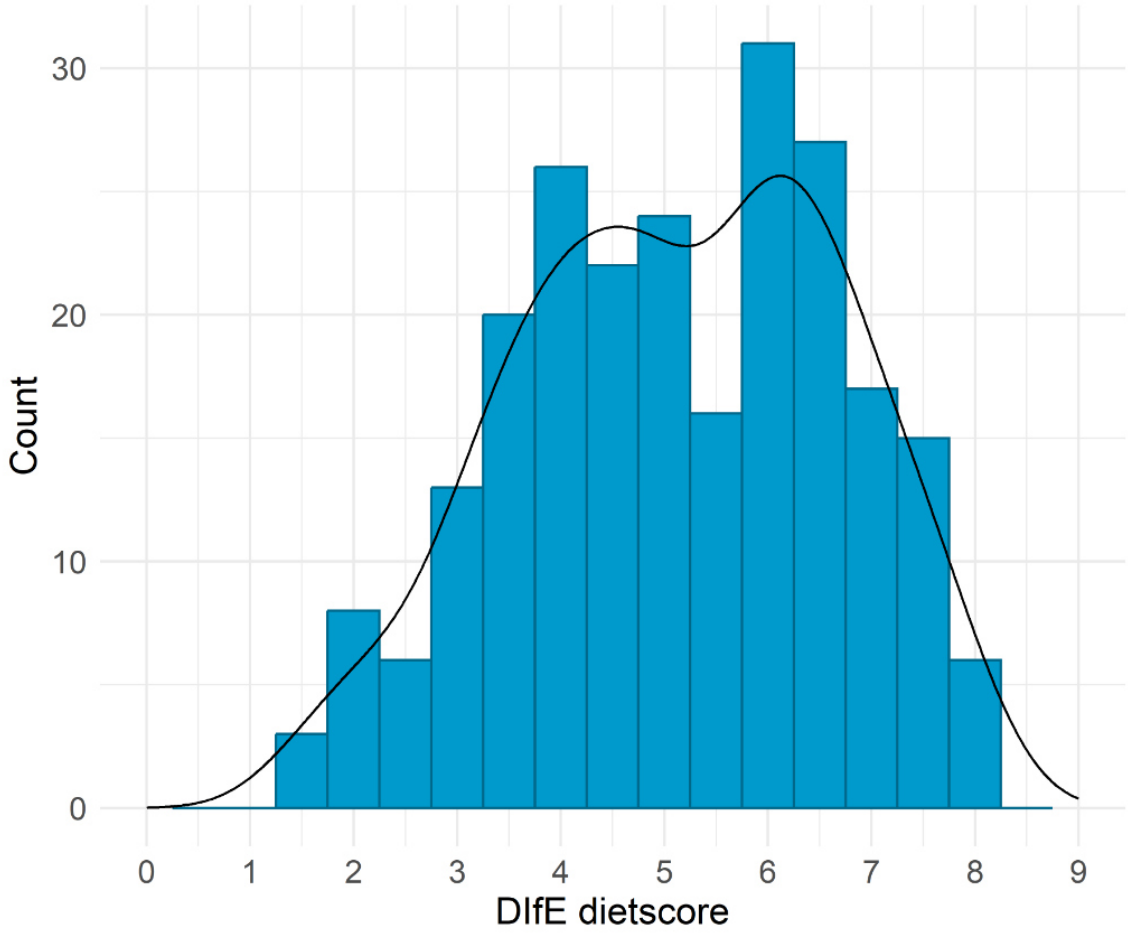
BSA-F = Physical Activity, Exercise, and Sport Questionnaire (Bewegungs- und Sportaktivität Fragebogen); EDSS = Expanded Disability Status Scale; GLTEQ = Godin Leisure-Time Exercise Questionnaire; HADS = Hospital Anxiety and Depression Scale; HAQUAMS = Hamburg Quality of Life in Multiple Sclerosis Scale; MRI = magnetic resonance imaging; PAM = Patient Activation Measure.

Appendix C: Healthy diet score – food groups according to Jannasch et al. 2022

	Mean score (n=234)	Max. score possible	Recommended intake	Adherence to recommendation, n (%)
Healthy diet score	5.1	10	N/A	N/A
Bread and Cereals, overall intake	0.29	0.5	Moderate (3-5 portions/day)	37 (15.8)
Proportion of Whole Grains[a]	0.26	0.5	High (100%)	22 (9.6)
Fermented Dairy Products	0.44	1	Moderate (1-2 portions/day)	98 (41.9)
Raw and Cooked Vegetables	0.49	1	High (≥ 3 portions/day)	35 (15.0)
Fruits	0.58	1	High (≥ 2 portions/day)	93 (39.7)
Legumes	0.43	1	High (≥ 2 portions/week)	79 (33.8)
Unsalted Nuts	0.2	1	Moderate (7 portions/week)	25 (10.7)
Fish (overall intake)	0.18	0.5	Moderate (2 portions/week)	42 (17.9)
Proportion of Fatty Marine Fish[b]	0.26	0.5	High (100%)	32 (20.8)
Meat, Processed Meat	0.29	0.5	Low (≤ 1 portion/week)	105 (44.9)
Red Meat	0.46	0.5	Low (≤ 2 portions/week)	198 (84.6)
Vegetable Oils, intake	0.23	0.5	High (≥ 7 times/week)	70 (29.9)
General use for food preparation	0.42	0.5	High (100%)	122 (52.1)
Sugar-Sweetened Beverages	0.61	1	Low (≤ 1 glass/week)	112 (47.9)

[a] Only applicable for n=228 participants who reported intake of bread and cereals.

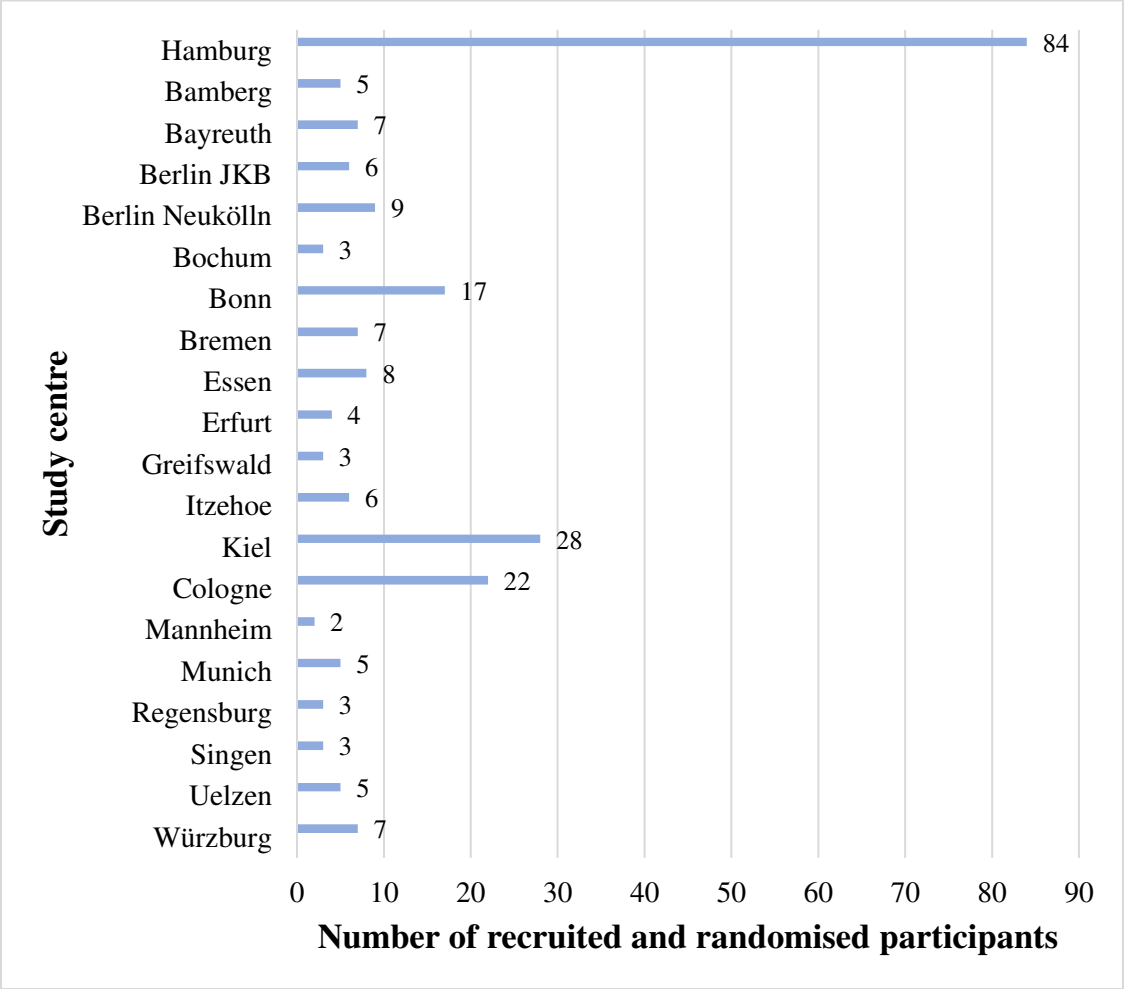
[b] Only applicable for n=154 participants who reported intake of fish.



Histogram of the DIfE dietscore with density curve.

*DIfE: German Institute of Human Nutrition (Deutsches Institut für Ernährungsforschung)

Appendix D: Recruitment of study participants per study centre

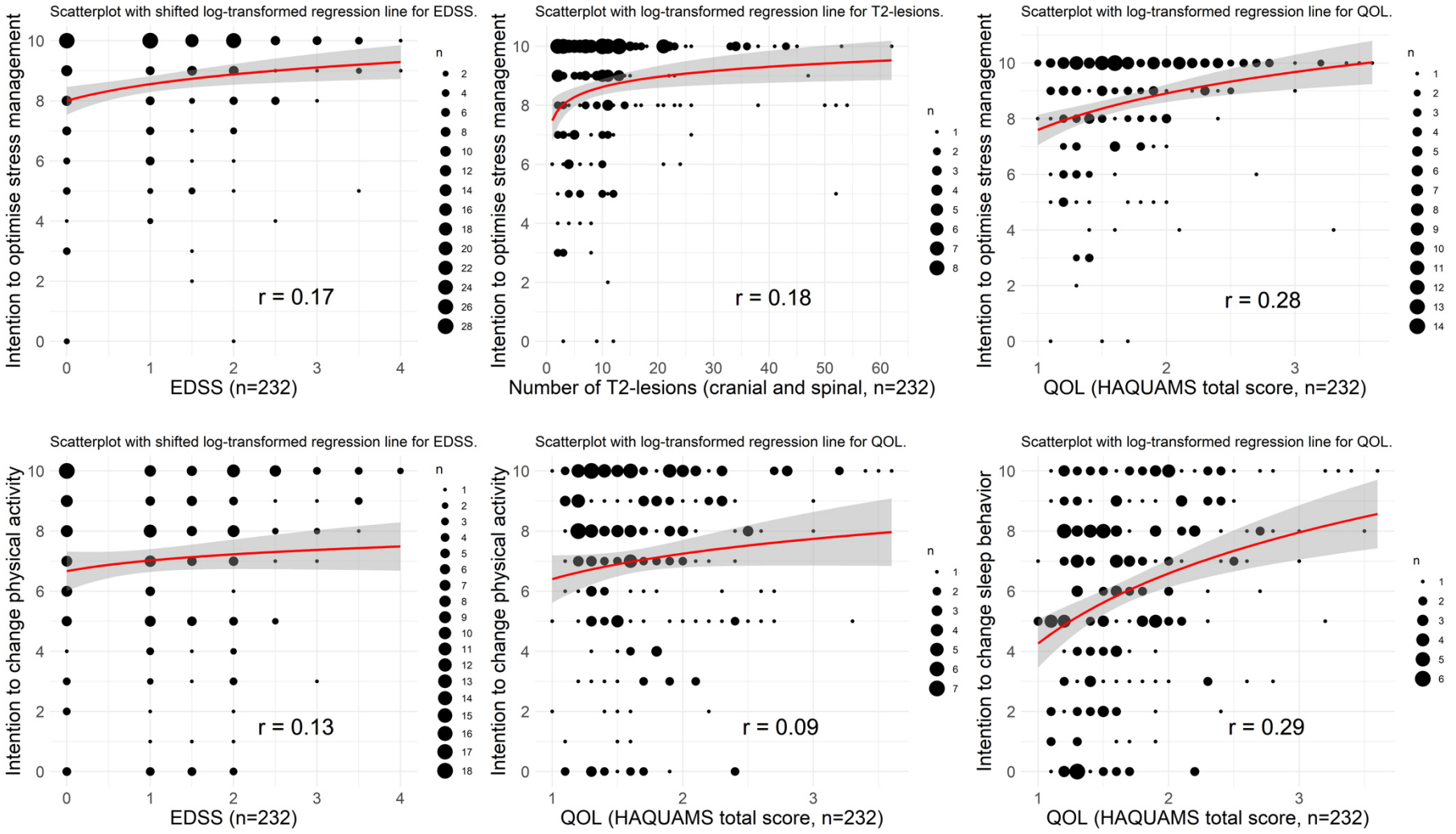


Appendix E: Comorbidities and HAQUAMS subscales

	Baseline (n = 234)
Comorbidities, n (%)[a]	135 (58.0)
Allergies	37 (27.4)
Obesity	35 (25.9)
Neurological/psychiatric disorders	27 (20)
Autoimmune diseases	26 (19.3)
Metabolic diseases	15 (11.1)
Hypertension	15 (11.1)
Cardiovascular diseases	8 (5.9)
Gastrointestinal diseases	9 (6.7)
Cancer	5 (3.7)
Osteoporosis	2 (1.5)
Kidney/urogenital diseases	2 (1.5)
Other comorbidities	40 (29.6)
HAQUAMS subscale scores, mean (SD)	
Fatigue/Thinking	2.0 (1.0)
Cognition	2.0 (0.9)
Mobility/Lower limb	1.4 (0.7)
Mobility/Upper limb[a]	1.1 (0.4)
Social function[a]	1.7 (0.7)
Mood[a]	2.1 (0.8)

HAQUAMS = Hamburg Quality of Life in Multiple Sclerosis Scale.
[a] Missing values, n=1.

Appendix F. Association of disease characteristics and interest in health behaviour management options



Appendix F: Association of disease characteristics (EDSS, T2-lesions, QOL) and intention to optimise stress management as well as intention to change PA and sleep behavior. Pearson correlation (r) is reported.

VII Weitere Arbeit (zur Publikation eingereicht)

Krause N, von Glasenapp B, Heesen C, et al. Diet and multiple sclerosis: Application of behaviour change techniques, the Behaviour Change Wheel and the Theoretical Domains Framework to characterise a digital health application.

Abstract

Background Multiple sclerosis (MS) is a chronic disease affecting the central nervous system. Persons with MS (PwMS) have a high need for lifestyle-related information and motivation to change dietary behaviour tends to be high among PwMS. This study aimed to provide a comprehensive understanding of the behaviour change techniques (BCTs) targeting three dietary behaviour modules in "levidex", a digital lifestyle application for PwMS with 16 modules covering physical activity, diet, stress and sleep.

Methods The BCT Taxonomy based on the Theoretical Domains Framework was used to report BCTs and connect them to theoretical mechanisms of action of levidex. BCTs were independently coded by two raters using MAXQDA 2022 and disagreements were resolved by a third rater. BCTs were mapped to the Behaviour Change Wheel. Inter-rater reliability was assessed as percentage agreement and coefficient kappa.

Results Overall, 28 BCTs were identified, with 202 BCT codings across all levidex components targeting dietary behaviour. Most commonly used BCTs are 'instruction on how to perform the behaviour', 'information about health consequences' and 'credible source'. Identified BCTs serve a variety of Behaviour Change Wheel components.

Conclusions A broad range of BCTs focussing on skill development and information provision from credible sources is utilised in levidex to facilitate the adoption of health-promoting dietary habits. BCT taxonomy coding is a feasible approach to analyse BCTs applied in online interventions.

KEYWORDS multiple sclerosis, dietary behaviour, digital health application; behaviour change techniques, mechanisms of action

Background

Although the disease course of multiple sclerosis (MS) seems to be more benign in recent years (1), reliable prognosis estimates remain extremely difficult, and receiving an MS diagnosis is often experienced as traumatising (2). Even though MS is associated with significant health care costs related to prescriptions of disease-modifying drugs, around 30% of persons with RRMS are not on immunotherapies (3) because of various reasons, including limited efficacy, side-effects and risks associated with immunotherapies (4). If no immunotherapy is chosen, persons with MS (PwMS) are often left with no other treatment and disease management options. This might be one reason why PwMS have a high need for lifestyle-related information to manage and improve their health (5). Moreover, PwMS with active coping strategies who aim to acquire a better understanding of MS and search for possibilities to take action themselves (e.g., through a change in health behaviour) seem to adjust better to MS (6).

Modifiable risk factors, such as dietary behaviour, are not only considered increasingly relevant in research on MS progression (7), but are also of high interest among PwMS in Germany (8, 9). While special MS diets to manage symptoms and disease progression are promoted in various internet sources (10), scientific evidence on the potential influence of specific diets or single nutrients on MS is insufficient (10-12). According to current evidence, PwMS are recommended to adhere to a healthy dietary pattern as defined in national guidelines and consider MS-specific aspects (8, 13). Although motivation to change dietary behaviour seems to be high among PwMS (14), dietary advice provided by neurologists and health professionals after an MS diagnosis is perceived as unsatisfactory by PwMS (15). In Germany, time for dietary advice is limited in standard care and PwMS report that consultation durations with their physicians tend to be too brief (16). For this reason, digitally delivered behaviour change interventions could potentially improve the provision of evidence-based lifestyle-related information and, thereby, help improve dietary behaviour among PwMS. However, the modification of lifestyle habits is complex, and numerous medical and behavioural disciplines have been working on this topic for a long time. The classification of behaviour change techniques (BCTs) has recently gained increased attention in health psychology. Interventions that were developed based on an assessment of appropriate intervention strategies and behavioural targets that take theories of behaviour change into account seem to be more effective than interventions that are not theory-based (17). While theory-based development of interventions as well as the incorporation of specific

BCTs is recognised as the best-practice approach for effective nutrition interventions (18, 19), to our knowledge, evidence regarding the specific BCTs implemented in behaviour change interventions targeting dietary behaviour among PwMS is lacking.

The aim of this study was to provide a comprehensive example description of the BCTs targeting dietary behaviour in a digital health application for recently diagnosed PwMS termed "levidex". This intervention was developed by GAIA, a German small-to-medium enterprise (SME) that is focused on the development and research of digital health therapeutics. Levidex is an MS specific adaptation of "Optimune", which is a digital intervention to promote relevant health behaviours among breast cancer survivors (20). Optimune has shown improved dietary habits and quality of life based on the behaviour change technologies applied (21). The levidex programme is currently evaluated in a randomised controlled trial (RCT) in Germany (22). In this study, levidex was characterised descriptively according to the relevant guidelines and frameworks for the design and evaluation of behaviour change interventions (23, 24) to allow reproducibility and enable evidence syntheses regarding effective mechanisms of action.

Methods

Coding material: Digital health application levidex

Incorporated BCTs were identified in levidex, an individually tailored digital health application for recently diagnosed PwMS. Levidex is based on Optimune, a digital lifestyle management programme for breast cancer survivors, which has been shown to significantly improve quality of life and dietary habits (21). Specifically, significant improvements were observed regarding a healthy dietary pattern (e.g., eating more fruit, vegetables and fatty fish). Optimune engages users in a broad range of therapeutic techniques (e.g., BCTs and mindfulness-based techniques) and was mainly developed on the basis of cognitive behavioural therapy (CBT). The content (e.g. therapeutic topics and exercises) is provided in "simulated dialogues" that imitate a conversational flow by continuously inviting participants to select the most suitable response from several provided response options. Based on the selected responses, subsequent content is tailored to the participants' needs and preferences. In this way, different paths through the content are possible. While the largest amount of content is provided to participants with particularly high information needs, it is always ensured that core information is conveyed to all participants.

In accordance with the Medical Research Council guidance (25), PwMS and MS experts were involved in the development and adaptation process of levidex at early stages (26). The behaviour change strategies were transferred from Optimune, as to the best of our knowledge, there is no indication that the use of a highly specific set of BCTs is recommended in early MS. However, more on a patient information level, MS-specific topics and relating evidence were added to the levidex programme to meet the needs of PwMS. Besides dietary behaviour, this complex intervention is also targeting psychological well-being, sleep management, and physical activity (see Figure 1). For this study, only modules targeting dietary behaviour were evaluated, because the possible influence of dietary behaviour on the course of the disease is highly relevant for PwMS (8, 9) and evidence on effective behaviour change strategies to improve dietary behaviour among people with MS is largely lacking.

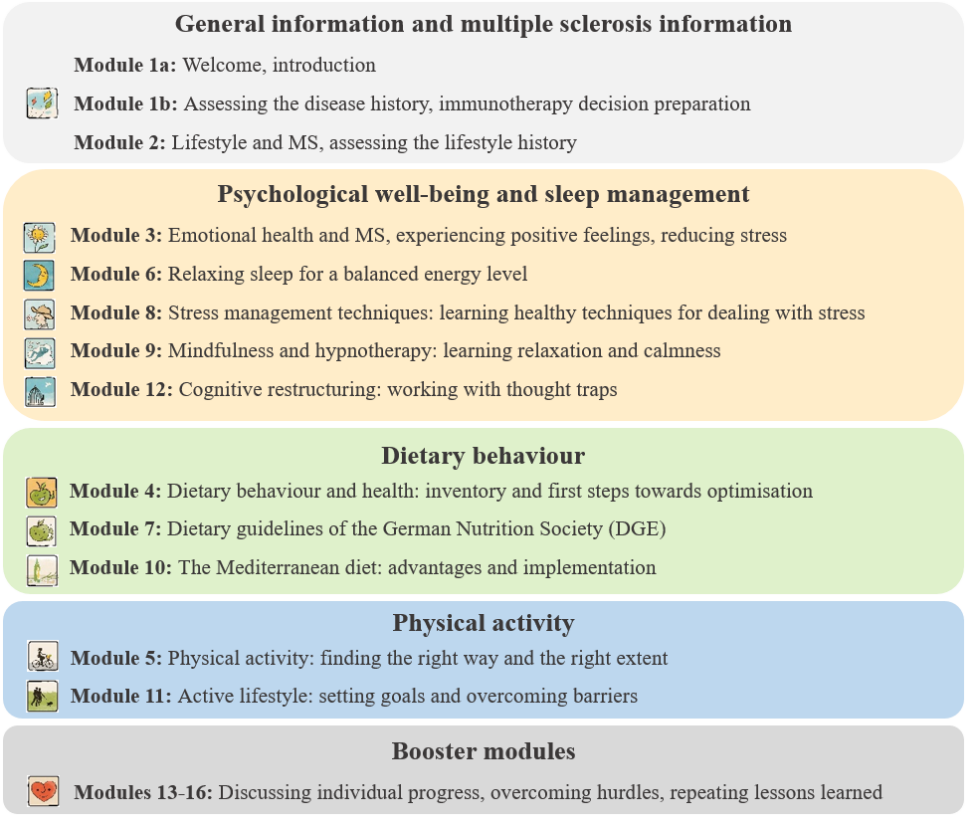


Figure 1: levidex domains and modules

Levidex was designed to be accessed over one year with each module taking about 30-45 minutes to be completed. The first module on diet and health (module 4) assesses current dietary behaviour through screening questions and provides an overview of what is discussed within the context of diet and MS. The second dietary behaviour module (module 7) provides participants with evidence-based information (EBPI) and dietary guidelines on potentially

healthy and unhealthy dietary patterns. The third dietary behaviour module (module 10) focusses on advantages of the Mediterranean diet and provides participants with recipes, grocery shopping lists and detailed cooking instructions. In the following, the dietary behaviour modules of levidex will be referred to as module 4, module 7 and module 10. In summary, the dietary behaviour modules aim to promote the adoption of improved dietary behaviour. More specifically, the modules aim to increase the intake of recommended food groups (e.g., vegetables, whole grain, fish) and reduce the consumption of processed foods (e.g., processed meat, fast food) and other foods that potentially increase inflammation. Levidex has a focus on EBPI, as all key statements provided in the modules are supported by relevant scientific article citations and plain language abstracts. Moreover, the dietary behaviour modules include tasks to be completed outside the programme (e.g., removing unhealthy foods from the refrigerator), self-talk exercises as well as optional audio exercises (e.g., mental imagery exercises). In addition, optional short messages including brief dietary information or motivational suggestions are sent to participants in SMS or email format. To visualise achievements regarding dietary behaviour, levidex also includes a self-monitoring questionnaire that is embedded in the programme. Users are prompted to complete this questionnaire once per week by answering five questions targeting (1) vegetable intake, (2) fruit intake, (3) consumption of processed foods, (4) intake of healthy fats (e.g., salmon, avocado, olive oil) and (5) consumption of whole-grain products. Based on the self-reported dietary behaviour, levidex provides individualised feedback and a weekly score. Between 1 (unhealthy/potentially pro-inflammatory) and 5 (healthy/potentially anti-inflammatory) points are assigned for each answer, resulting in a range of 5 to 25 points that can be achieved. Values of 15 or higher indicate a healthy diet. It is a pragmatic self-monitoring instrument and the scoring system is not validated.

Coding of BCTs

To provide an understanding of the mechanisms of action and allow reproducibility, levidex was characterised according to the active ingredients (present BCTs) that were implemented to promote healthy dietary habits among PwMS. The BCT Taxonomy v1 (BCTTv1) (27) consists of 93 hierarchically-clustered techniques and was used to identify and code the BCTs present in the levidex components addressing dietary behaviour: The three modules, optional short message reminders and an optional self-monitoring questionnaire. This was performed based on the actual programme text material. BCTs were coded by two raters (NK and BvG) who first of all underwent an online BCT Taxonomy training (28) consisting of six coding

sessions and two assessments. To improve coding accuracy, the raters shared and discussed results of the coding tasks provided in the online training. BCTs incorporated in the dietary behaviour components of levidex were thereupon coded using MAXQDA 2022.

First, the coders familiarised themselves with the coding material by reading through the text material. One dietary behaviour module was then coded independently by each rater. Subsequently, disagreements were discussed and coding strategies were optimised [see Additional file 1]. All dietary behaviour components were then coded independently by both raters. In the next step, the extent of coding agreement (inter-rater reliability) was checked and differences were discussed to optimise coding strategies. Independent coding was repeated until sufficient inter-rater reliability was achieved (see Data analysis). The resulting optimised coding strategies were recorded [see Additional file 2] and used as a guideline by both raters in a second independent coding process. Finally, the raters discussed the results of the second coding process to resolve disagreements and to achieve a consensus about implemented BCTs. Final agreement was achieved through discussion with a third rater (KR-L) who has experiences in the application of the Behaviour Change Wheel (BCW) and the Theoretical Domains Framework (TDF).

Data analysis. Inter-rater reliability between both raters was assessed by percentage agreement using MAXQDA 2022. In addition, coefficient kappa (29) was calculated in MAXQDA 2022 to establish inter-rater reliability of present BCTs. The following interpretation of the strength of agreement for kappa values (30) was adopted: < 0.00 = poor, 0.00-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-1.00 = almost perfect agreement. Substantial agreement (kappa 0.61-0.80) was set as a threshold for sufficient inter-rater reliability.

Mapping identified BCTs to theoretical mechanisms of action

According to the BCW and its core, the COM-B model, behaviour is a result of an interacting system that involves capability (e.g., knowledge and skills), opportunity (e.g., access, time resources) and motivation (23). To actually achieve behaviour change, an intervention needs to alter at least one of these components. In order to enable an understanding of the theoretical mechanisms of action targeted in levidex, an example was selected for each BCT (active component) that was used to change dietary behaviour among PwMS and all BCTs were mapped onto the COM-B. Moreover, the BCTs were linked to the domains (theoretical constructs) of the TDF (24), which is a more elaborated and integrative framework aiming to

understand behaviour. The allocation of the 14 validated theoretical domains to the COM-B system is provided in [Additional file 3].

In the final step, underlying intervention functions were linked to each TDF domain based on guidance provided by Michie et al. (17). As applied for coding of BCTs, the intervention functions, COM-B components and TDF domains were mapped independently by two raters (NK and BvG). Final agreement was achieved through discussion with a third rater (KR-L).

Results

The percentage agreement of the first coding process was 58.89% with a coefficient kappa value of 0.58, indicating moderate inter-rater reliability. After an optimisation of coding strategies to increase the strength of agreement, the second coding process resulted in substantial inter-rater reliability, with percentage agreement of 79.01% and a coefficient kappa value of 0.78.

BCTs applied in the dietary behaviour content of levidex

After resolving rater disagreements of the second coding process, 28 out of 93 BCTs included in the BCTTv1 were coded at least once. These BCTs cover 14 out of 16 BCT groups of the BCTTv1 (see Figure 2).

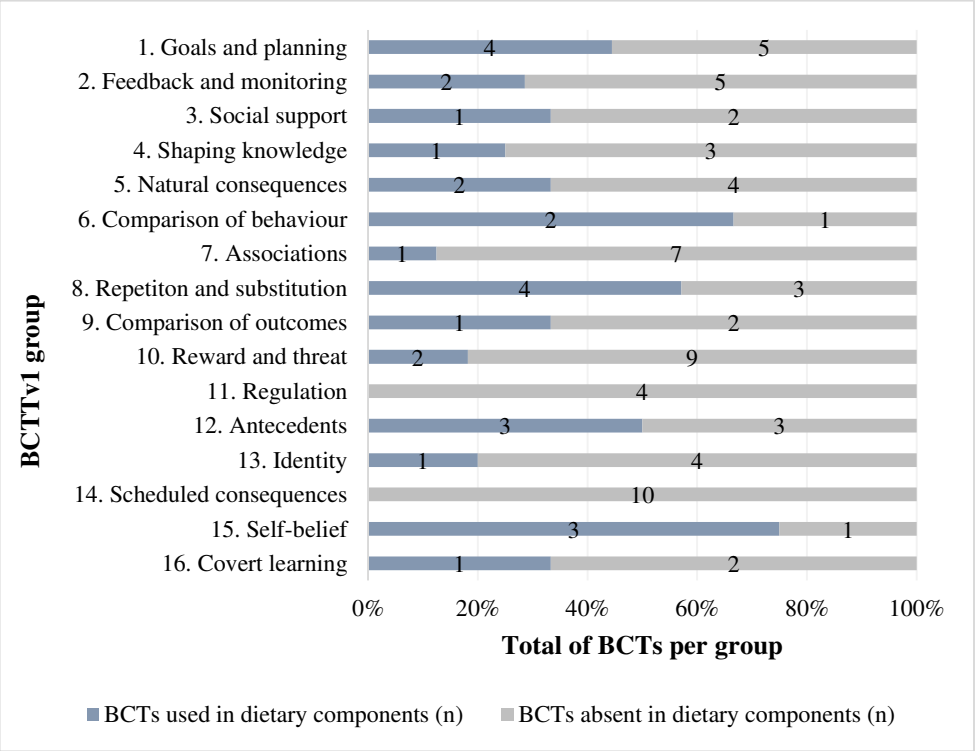


Figure 2: BCTs Utilised to Facilitate the Adoption of Health-promoting Dietary Habits according to the BCTTv1 Groups. The figure reads as e.g., 1.goals and planning: 4 out of 9 techniques from this area were addressed within the 3 modules.

BCTs of the groupings 'regulation' and 'scheduled consequences' were not identified in the dietary components of levidex. The specific BCTs applied in the dietary behaviour content of levidex as well as their respective frequency and occurrence in the intervention components are provided in [Additional file 4]. The greatest variety of BCTs (n=19) is used in module 10, which is more action-oriented and addresses the concept of the Mediterranean diet and contains recipes, grocery shopping lists and cooking instructions. This is followed closely by module 4, with a total of 18 different BCTs. Module 4 provides information about what is discussed within the context of diet and MS and contains an assessment of the participants` current dietary behaviour. To promote the adoption of healthy dietary habits among PwMS, the 28 identified BCTs are used 202 times across all components. The most frequently used BCTs are part of the BCTTv1 groups 'natural consequences', 'shaping knowledge', 'comparison of outcomes' and 'repetition and substitution'. Practical examples of frequently

used BCTs are provided in the following. Further examples for every BCT used in the dietary content of levidex are presented in [Additional file 5].

Frequently used BCTs. Across the dietary behaviour content of levidex, ‘information about health consequences’ is used most frequently to educate PwMS about possible health consequences. For example, participants are informed about health benefits of the Mediterranean diet or a generally healthy diet, which are both associated with a reduction in the risk of cardiovascular diseases, such as heart attacks and strokes. To motivate participants to change their dietary habits, levidex informs participants that the presence of certain risk factors for cardiovascular diseases (e.g. obesity) in newly diagnosed PwMS is associated with a higher risk of disease progression. Moreover, the BCT ‘credible source’ is applied frequently to confirm and reinforce information provided within the context of dietary behaviour (e.g. regarding health consequences). More precisely, all key statements are supported by plain language abstracts and relevant scientific article citations. For instance, information regarding the consumption of refined sugar given by the World Health Organization (WHO) is presented to participants to emphasise the associated risk of obesity, type 2 diabetes, high blood pressure and cardiovascular diseases. The BCT ‘instruction on how to perform the behaviour’ is frequently used in the form of grocery shopping lists, recommendations for grocery shopping facilities (e.g. farmer’s markets) or detailed cooking instructions for provided Mediterranean recipes. Beyond that, participants are advised to buy and store "basic ingredients" that are important for many healthy recipes, such as olive oil, herbs (fresh or dried), onions and garlic. Furthermore, participants are trained how to meet daily nutrient requirements through consumption of different kinds of fruit and vegetables and how to absorb vitamin D through consumption of certain foods (e.g. fatty fish, eggs or mushrooms) in addition to spending time in the sunlight. To reduce possible resistance towards dietary changes, levidex does not prohibit participants from eating certain unhealthy foods (e.g. processed foods), but rather advises them to reduce consumption of unhealthy foods and gradually replace them with healthy alternatives. This is reflected in the frequent use of the BCTs ‘behavioural practice/rehearsal’ and ‘behaviour substitution’, which are both applied in the form of tasks to be completed outside of levidex. For example, participants are prompted to try out at least one of the provided recipes or to remove unhealthy foods (e.g. white flour products) at home and replace them with healthy alternatives (e.g. whole-grain products) until the next module is activated. The least frequently used BCTs is ‘prompts/cues’, which is only used once to stimulate levidex users to hang up dietary goals on

their refrigerator as well as ‘social reward’, which is also used once to encourage participants to feel proud after having managed to remove unhealthy foods at home.

BCTs frequently used together. In total, 21 BCTs were used in combination with at least one other BCT. The most frequent combination (19 cases) is ‘information about health consequences’ provided together with ‘credible sources’. This is followed by ‘instruction on how to perform a behaviour’ (e.g. detailed cooking instructions), which is used together with a ‘demonstration of the behaviour’ (e.g. pictures of ready-prepared healthy dishes) seven times. Moreover, ‘behaviour substitution’ (e.g. prompt to consume natural foods rather than processed foods) is used together with an ‘instruction on how to perform the behaviour’ (e.g. how to prepare natural yoghurt with fresh fruit) in six cases to support the adoption of health-promoting dietary habits. A complete overview of the BCTs that are applied together is provided in [see Additional file 6].

Mapping of applied BCTs to theoretical mechanisms of action

The BCTs used in the dietary context of levidex cover a broad range of intervention functions and mapped on all COM-B components and all 14 TDF domains, with most BCTs mapping on multiple domains. Accordingly, the dietary content is not focused on specific areas. To visualise the even distribution of the theoretical mechanisms of action targeted in levidex, Table 1 provides the mapped COM-B components and TDF domains for each BCT used to facilitate the adoption of health-promoting dietary habits among PwMS.

Table 1: COM-B Components and TDF Domains mapped for BCTs used in the Dietary Content of levidex

	COM-B components													
	Capability				Opportunity		Motivation							
	Physical	Psychological			Social	Physical	Reflective						Automatic	
	TDF domains													
BCT	S	K	MAD	BR	SI	EN	B Cap	B Con	S/P ID	O	I	G	EM	R
1.1				■							■	■		
1.2				■			■	■						
1.4				■							■	■		
1.9							■			■	■	■		
2.2		■						■						
2.3				■										
3.1					■				■					
4.1	■	■												
5.1		■						■					■	
5.6		■						■					■	
6.1	■	■	■	■										
6.2					■		■		■					
7.1			■	■		■								

8.1														
8.2														
8.4														
8.7														
9.1														
10.4														
10.9														
12.1														
12.3														
12.5														
13.2														
15.1														
15.2														
15.4														
16.2														

BCT = Behaviour change technique; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

For example, ‘demonstration of the behaviour’ (BCT 6.1) mapped onto four different TDF domains, including ‘skills’, ‘knowledge’, ‘memory, attention and decisional processes’ as well as ‘behavioural regulation’. The three domains that were targeted by the largest number of BCTs include ‘behavioural regulation’ (n=12), ‘beliefs about capabilities’ (n=8) and ‘knowledge’ (n=7). An example for the links between the BCTTv1, the BCW and the TDF domains for the most frequently used BCT (‘information about health consequences’) is provided in [Additional file 7]. The selected example is educational, as it provides knowledge about the health consequences (e.g. lowered likelihood of cardiovascular diseases) of a healthy diet to promote healthy eating. At the same time, it is persuasive by generating positive feelings about the health consequences that are associated with a healthy diet. Moreover, the newly acquired knowledge about healthy dietary behaviour addresses the psychological capability of the participant as well as the reflective motivation, as it induces beliefs about the consequences and outcomes of the wanted behaviour (healthy eating). [Additional file 5] provides text examples for each BCT used in the dietary content of levidex as well as an overview on the mapped intervention functions, COM-B components and TDF domains.

Discussion

This paper reports on the characterisation of BCTs in the dietary components of a new digital health application (levidex) for PwMS. Although usage of the BCTTv1 was complex, it was feasible and many different BCTs were identified. According to Webb et al. (31), larger effects on behaviour were observed with increasing number of BCTs used in interventions,

but it is a matter of ongoing research to classify which number and combination of BCTs used in behaviour change interventions can be classified as effective (32, 33). Moreover, the identified variety of BCTs enables a precise description of the active ingredients of levidex and, in combination with the currently ongoing RCT (22), there is a chance to gain more insights into effective BCTs for behavioural interventions. Remarkably, the BCTs used in the content targeting dietary behaviour mapped onto all intervention functions, all COM-B components and all TDF domains. This enables an understanding of the hypothesised mechanisms of action and underlying processes of change targeted in levidex.

PwMS search for possibilities to manage their health and levidex offers the possibility to adjust lifestyle-related issues that potentially affect their health. Various lifestyle-related aspects are addressed in levidex, such as the topic of dietary behaviour. In accordance with the transtheoretical model of behaviour change (34), the dietary behaviour components of levidex try to reach PwMS who have some knowledge about or interest in diet but may still be at the stage of precontemplation. It is aimed to at least bring them to the stage of contemplation, in which a reflection about their current dietary behaviour takes place. Two of the core techniques that were identified in the dietary behaviour components of levidex are 'information about health consequences' as well as 'credible source', which reflects the major focus on EBPI and trustworthiness of the programme. This is accompanied by instructions for healthy eating as the desired behaviour, aiming to help participants to achieve the next stages, namely preparation and action. However, this only applies to the dietary behaviour content, and the focus of other intervention components targeting psychological well-being, sleep management or physical activity might deviate. Nevertheless, for the field of diet and nutrition this might be an appropriate method to achieve behaviour change, as information needs in this regard are unmet in standard care and PwMS are confronted with contradictory information on dietary approaches (35). Moreover, as levidex is intended to be accessed over one year, it is also aimed to achieve the stage of maintenance. This is especially targeted through a discussion of the individual change process and possible barriers as well as through a repetition of lessons learned in the booster modules of levidex.

For short-term improvements in dietary behaviour (e.g., fruit, vegetable and fat intake), a systematic review of brief nutrition interventions indicates that 'generalisation of target behaviour', 'reduce negative emotions' and 'verbal persuasion about capability' are the most effective BCTs (18). This review also showed that tailored educational interventions

providing feedback, such as levidex, are more effective in improving short-term dietary behaviours than non-tailored interventions. According to another systematic review on interventions for overweight and obese adults, goal setting and self-monitoring were most effective in promoting and maintaining healthy dietary patterns (36). Yet a scoping review of nutrition interventions for people with neurological diseases, including MS, showed that most commonly used BCTs are 'instruction on how to perform a behaviour', 'credible source' and 'behavioural practice/rehearsal' (37). Although this clearly supports the BCTs that were mainly implemented in the content covering dietary behaviour in levidex, due to the heterogeneity of review results for nutrition interventions it is still unclear which BCTs are most effective for such interventions. The inconsistent evidence base leaves researchers and counselling people unsure which BCTs to use. Moreover, there is a general lack of evidence regarding the effectiveness of currently available nutrition programmes for adults with neurological diseases, which is why further studies on such programmes are needed (37). Other programmes that are produced with the same software and functioning as levidex have already demonstrated effectiveness in several RCTs (38-42). Given that Optimune, the digital health application that formed the basis for levidex, has proven its efficacy regarding the improvement of healthy dietary behaviour in breast cancer survivors (21), we expect that levidex could also be effective in this regard, and results from the ongoing RCT will clarify whether this is the case. Nevertheless, especially long-term effects of digital interventions on dietary behaviour change and other relevant outcomes need to be investigated (43).

Limitations

Levidex was developed based on years of experience in the development of CBT-based online interventions by a multidisciplinary team of primarily psychologists, psychotherapists, physicians and software engineers affiliated with GAIA. Even though this team has produced several online interventions that have demonstrated merit in RCTs, the fact that the efficacy of levidex is still unknown can be regarded as a limitation of this study. However, Optimune with the same behaviour change approach in a breast cancer context has shown its efficacy in a randomised controlled study (21). Another limitation is that only one aspect of levidex was examined in this paper – the extent to which it utilises certain BCTs. Of note, levidex could also be analysed from other vantage points, such as the programme's user-friendliness, the comprehensiveness or accuracy of its content, or the extent to which specific CBT techniques or common factors of psychotherapeutic effectiveness are implemented within the intervention. A related limitation is that the intervention content was only characterised for

the components targeting dietary behaviour, and it remains unclear whether other levidex modules utilise a different set of BCTs. We also note the limitation that, due to the large number of BCTs in the BCTTv1, it was very difficult to achieve a high level of agreement between two raters. The large number of techniques is not taken into account in the calculation of agreement, as only coded BCTs were considered. If agreement regarding BCTs that were not coded by both raters had been taken into account, the level of agreement might have been higher, as more than two thirds of the available BCTs were consistently not identified by both raters.

Conclusion

The framework of BCTs is a useful tool to develop and evaluate behaviour change interventions. A broad range of BCTs focusing on knowledge and skill development through information provision from credible sources and instructions was identified in the components targeting dietary behaviour in the example digital health application levidex. This approach can help to better understand the mechanisms of interventions and to continuously improve behaviour change approaches. Outcomes of effectiveness studies can possibly be matched to the active ingredients and ideally, evidence syntheses might enable the identification of a core set of BCTs.

List of abbreviations

BCT: behaviour change technique

BCTTv1: Behaviour Change Technique Taxonomy v1

BCW: Behaviour Change Wheel

CBT: cognitive-behavioural therapy

COM-B: Capability-Opportunity-Motivation-Behaviour

EBPI: evidence-based patient information

MS: multiple sclerosis

PwMS: person with multiple sclerosis

RCT: randomised controlled trial

TDF: Theoretical Domains Framework

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets (i.e. the text corpus of the levidex modules targeting dietary behaviour) analysed in the current study are not publicly available as they belong to GAIA, the company that developed, owns and operates levidex.

Competing interests

CH has received research grants, speaker honoraria and travel grants from Biogen, Celgene, Genzyme, Merck and Roche. BM is employed by GAIA, the company that developed, owns and operates levidex, but he was not involved in any coding process or related analyses. NK, BvG and KR-L declare that they have no competing interests.

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Authors' contributions

KR-L is the principle investigator and led the planning and conduction of the study with support from NK, BvG, CH and BM. BM contributed to the development of the content of levidex and optimune (the digital intervention that formed the basis of levidex), and CH and KR-L (along with BM and several other GAIA employees not listed as authors) contributed to the revision of levidex content to improve suitability for an MS population. NK and BvG conducted the coding of BCTs with support from KR-L. NK wrote the first draft of the paper. KR-L, CH, BvG and BM commented on the manuscript providing scientific content. All authors read and approved the final manuscript.

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Additional files

Additional file 1: Adjusted BCT coding rules (first coding process)

Additional file 2. Optimised BCT coding rules (second coding process)

Additional file 3. Subdivision of the COM-B Model (23) according to the TDF Domains (24)

Additional file 4: Frequency of BCTs applied

Additional file 5: Mapping of the BCTTv1 onto the BCW and TDF to describe levidex

Additional file 6. BCTs frequently coded together

Additional file 7. Information about health consequences' – Mapped BCW Components, TDF Domains and Intervention Functions

TIDieR Checklist

Additional file 1: Adjusted BCT coding rules (first coding process)

1. Read the whole text material at least once before starting to code BCTs.
2. Pure reflections on recent dietary behaviour are not sufficient to code a BCT.
3. Do not code generally valid recommendations for a healthy diet (e.g., from the DGE) as "4.1 Instruction on how to perform the behaviour", if the participant is not directly addressed.
4. Code grocery shopping lists for recipes and the relating cooking instructions as one BCT ("4.1 Instruction on how to perform the behaviour") and not separately.
5. Code recommendations on nutrients, dietary fibre, food supplements, etc. as "5.1 Information about health consequences". BUT: only code this BCT for recommendations related to food supplements in capsule or tablet form, as injections fall into the category of drugs.
6. Always code "5.1 Information about health consequences" and "9.1 Credible source", if information on health consequences of a specific diet is provided from a credible source.
7. If a text passage contains several aspects of the same BCT, the whole text should be coded only once. Do not code individual sentences separately that apply to the same BCT.

Additional file 2: Optimised BCT coding rules (second coding process)

General coding rules

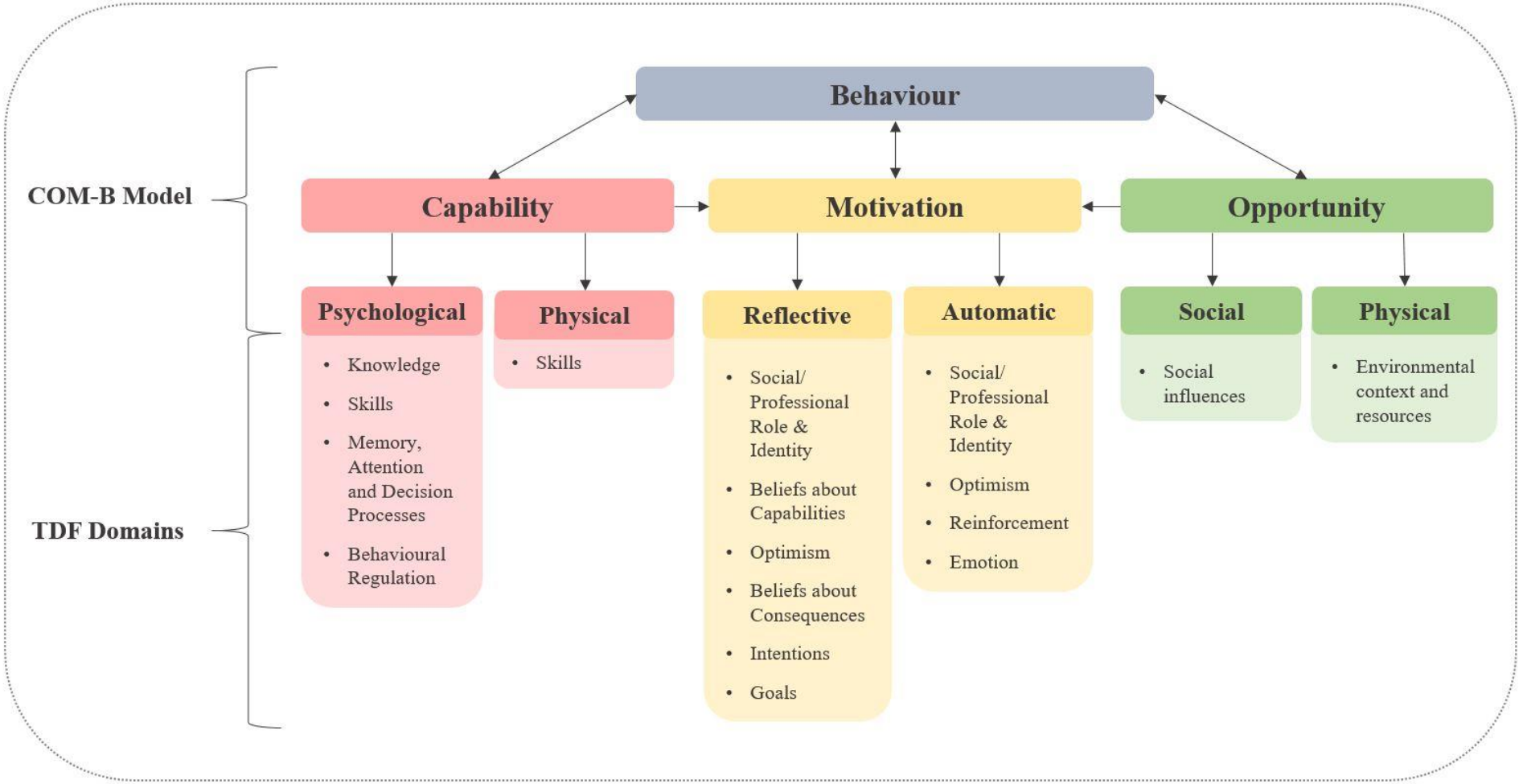
1. Before assigning a BCT, always read the coding description in the BCT Taxonomy (v1) as well as the adjusted and optimised coding rules.
2. If a text passage contains several aspects of the same BCT, the whole paragraph is coded only once. Do not code individual sentences separately that apply to the same BCT.
3. Pure reflections on recent dietary behaviour are not sufficient to code a BCT.
4. Do not code a BCT if only examples are given that are not directly prompted to the participant.
5. Do not code headlines.

BCT specific coding rules

BCT No. and Label	Additional Coding Rules
1.2 Problem solving	Must always include two components (barriers and strategies to overcome these barriers) and only targets other BCTs in rare cases.
1.4 Action planning	Only code if details of implementation are given.
1.8 Behavioural contract	Only code if there is a witness. The levidex programme also counts as a witness.
3.1 Social support (unspecified)	Always code as soon as friends, family etc. are involved. Also code when participants are asked to involve friends, family, etc.
4.1 Instruction on how to perform the behaviour	If recipes are provided, the accompanying lists of ingredients should also be coded as soon as a person is prompted to. A prompt to visit a doctor is not specific enough for the practice of behaviour. Do not code handout headings as well as general instructions of behaviour change methods not directly targeting dietary behaviour.
5.1 Information about health consequences	Only code if health consequences of dietary behaviour are provided.
6.2 Social comparison	Code case studies of different people separately.
7.7 Exposure	Only code when it is clear that the exposure is something "feared". Mere mental imagery exercises of exposures are not sufficient for coding.
8.1 Behavioural practice/rehearsal	Only code when the participant is prompted to perform a behaviour (e.g., invitation to recreate provided recipes).
8.2 Behaviour substitution	Only code when a participant is directly asked to choose the healthier alternative rather than potentially unhealthy foods.
8.7 Graded tasks	Only code if it explicitly refers to dietary behaviour. Do not code for general recommendations regarding graded tasks.
9.1 Credible source	Only code if it is described whether something about the dietary

	behaviour is health-promoting or harmful and a reference to the behaviour is clear. If more than one source is provided, always code the entire paragraph if they refer to the same dietary behaviour.
10.9 Self-reward	Always code when a participant is asked to be proud of themselves because of a positive accomplishment.
12.3 Avoidance/reducing exposure to cues for the behaviour	Only code when a participant is asked directly to avoid/reduce exposure to cues for the behaviour.
15.2 Mental rehearsal of successful performance	Only code if it relates to healthy dietary behaviour. A reference to a generally healthy lifestyle is not sufficient for coding.
16.2 Imaginary reward	Only code if it is an imaginary reward.

Additional file 3: Subdivision of the COM-B Model (23) according to the TDF Domains (24)



Additional file 4: Frequency of BCTs applied

BCT No. and Label	M4	M7	M10	oSMQ	oSM	Total (%)
1.1 Goal setting (behaviour)	✓		✓			6 (2.97)
1.2 Problem solving	✓				✓	4 (1.98)
1.4 Action planning			✓			2 (0.99)
1.9 Commitment			✓			3 (1.49)
2.2 Feedback on behaviour				✓		2 (0.99)
2.3 Self-monitoring of behaviour				✓	✓	5 (2.48)
3.1 Social support (unspecified)			✓			4 (1.98)
4.1 Instruction on how to perform the behaviour	✓	✓	✓		✓	30 (14.85)
5.1 Information about health consequences	✓	✓	✓		✓	32 (15.84)
5.6 Information about emotional consequences	✓	✓				2 (0.99)
6.1 Demonstration of the behaviour	✓		✓			7 (3.47)
6.2 Social comparison			✓			2 (0.99)
7.1 Prompts/cues			✓			1 (0.50)
8.1 Behavioural practice/rehearsal	✓	✓			✓	18 (8.91)
8.2 Behaviour substitution	✓	✓	✓		✓	13 (6.44)
8.4 Habit reversal		✓	✓			3 (1.49)
8.7 Graded tasks	✓	✓		✓		6 (2.97)
9.1 Credible source	✓		✓			21 (10.40)
10.4 Social reward		✓	✓			1 (0.50)
10.9 Self-reward	✓					2 (0.99)
12.1 Restructuring the physical environment	✓		✓		✓	8 (3.96)
12.3 Avoidance/ reducing exposure to cues for the behaviour	✓					3 (1.49)
12.5 Adding objects to the environment	✓		✓		✓	6 (2.97)
13.2 Framing/ reframing	✓	✓			✓	6 (2.97)
15.1 Verbal persuasion about capability	✓		✓			2 (0.99)
15.2 Mental rehearsal of successful performance	✓		✓			5 (2.48)
15.4 Self-talk			✓			3 (1.49)
16.2 Imaginary reward	✓		✓			5 (2.48)

M4 = Module 4, “Dietary behaviour and health: inventory and first steps towards optimisation”; M7 = Module 7, “Dietary guidelines of the German Nutrition Society (DGE)”; M10 = Module 10, “The Meditteranean diet: advantages and implementation”; oSMQ = optional Self-monitoring Questionnaire; oSM = optional short messages.

Additional file 5: Mapping of the BCTTv1 onto the BCW and TDF to describe levidex

			Capability				Opportunity		Motivation							
			Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT	**Functions**	**Exemplary text description***	**S**	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**
1.1 Goal setting (behaviour)	Enablement	The participant is prompted to set a goal for a new, healthier dietary behaviour (e.g., eat fresh vegetables and fruits every day instead of fast food and sweets) and to write it down.														
1.2 Problem solving	Enablement	The participant is prompted to identify and write down barriers for healthy eating as well as possible solutions to overcome these barriers in an "if - then" format. The person is asked to visualise exactly what he or she will do when the expected obstacle occurs.														
1.4 Action planning	Enablement	The participant is encouraged to formulate detailed plans for new dietary behaviour and provided with examples for such plans (e.g., "From now on, I will eat five portions of fruits and vegetables a day").														

* Since only one example of each coded BCT is provided here, the examples may not represent all possible links to COM-B components and TDF domains.

BCT = Behaviour change technique; Functions = Intervention functions; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

			Capability				Opportunity		Motivation							
			Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT	**Functions**	**Exemplary text description***	**S**	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**
1.9 Commitment	Enablement	The participant is asked to use "I will" statements to affirm strong commitment regarding the targeted change in dietary behaviour and is provided with examples of possible statements (e.g., "I will eat more natural and natural food. I don't need convenience food! There's too much salt, sugar and fat in it. Instead, I will buy my ingredients fresh and pay attention to good quality.").							■			■	■	■		
2.2 Feedback on behaviour	Education, Persuasion	The participant is provided with feedback (a score and information) on the dietary performance of the last week based on an optional self-monitoring questionnaire.		■						■						
2.3 Self-monitoring of behaviour	Enablement	The participant is asked to record his or her dietary behaviour based on five questions covered in a weekly optional self-monitoring questionnaire.				■										
3.1 Social support (unspecified)	Enablement	The participant is advised to discuss his or her dietary intentions in detail with the partner, a friend or family members.					■				■					
4.1 Instruction on how to perform the behaviour	Education	The participant is provided with a grocery shopping list and detailed instructions on how to prepare ratatouille.	■	■												

* Since only one example of each coded BCT is provided here, the examples may not represent all possible links to COM-B components and TDF domains.

BCT = Behaviour change technique; Functions = Intervention functions; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

			Capability				Opportunity		Motivation							
			Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT	**Functions**	**Exemplary text description***	**S**	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**
8.1 Behavioural practice/rehearsal	Training	The participant is prompted to cook one of the provided recipes or something else healthy at least once until the next conversation.														
8.2 Behaviour substitution	Enablement	The participant is prompted to avoid sugary drinks (e.g., lemonade) and to drink water or unsweetened tea instead.														
8.4 Habit reversal	Training, Enablement	The participant is prompted to use herbs and spices where he or she previousely used a lot of salt and sugar.														
8.7 Graded tasks	Training, Enablement	The participant is asked to reduce sugar in tea and coffee as well as to mix sweet drinks with mineral water step by step until the beverage tastes good without sugar.														
9.1 Credible source	Persuasion	The participant is provided with recommendations of the WHO to emphasise the importance of low consumption of dietary energy from added sugars.														
10.4 Social reward	Incentivisation	The participant is congratulated for already having implemented changes in dietary behaviour.														
10.9 Self-reward	Incentivisation	The participant is encouraged to feel proud after having managed to remove unhealthy foods at home.														

* Since only one example of each coded BCT is provided here, the examples may not represent all possible links to COM-B components and TDF domains.
BCT = Behaviour change technique; Functions = Intervention functions; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

			Capability				Opportunity		Motivation							
			Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT	**Functions**	**Exemplary text description***	**S**	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**
12.1 Restructuring the physical environment	Environmental restructuring, Restriction, Enablement	The participant is advised to remove the sweets at home and replace them with something else that is good for the immune system (e.g., frozen blueberries or other fruits).														
12.3 Avoidance/ reducing exposure to cues for the behaviour	Environmental restructuring, Restriction, Enablement	The participant is suggested to not have certain unhealthy foods at home which have been the reason for unhealthy snacking.														
12.5 Adding objects to the environment	Environmental restructuring, Enablement	The participant is prompted to fill the gap that was caused by a removal of unhealthy foods with foods that support the immune system.														
13.2 Framing/ reframing	Persuasion, Enablement	The participant is encouraged to view the preparation of demanding recipes (fish fillet with vegetables) as delicious foods which are good for his or her health.														
15.1 Verbal persuasion about capability	Persuasion	The participant is informed that he or she can successfully resist the temptations of the food industry.														
15.2 Mental rehearsal of successful performance	Training, Persuasion	The participant is advised to imagine very precisely and in detail eating a healthy and delicious fruit salad. The participant is also advised to imagine the colorful fruits, the sweet smell, the fresh, fruity taste as well as how good this healthy fruit salad is for their body.														

* Since only one example of each coded BCT is provided here, the examples may not represent all possible links to COM-B components and TDF domains. BCT = Behaviour change technique; Functions = Intervention functions; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

			Capability				Opportunity		Motivation							
			Physical	Psychological			Social	Physical	Reflective						Automatic	
BCT	**Functions**	**Exemplary text description***	**S**	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**
15.4 Self-talk	Training, Persuasion	Participants are prompted to tell themselves loudly that they will eat more natural food, that they don't need convenience food and will buy fresh ingredients and pay attention to good quality and prepare their food deliciously and gently - even if it is a bit more time-consuming.														
16.2 Imaginary reward	Incentivisation	Participants are prompted to be proud of themselves and enjoy the great feeling after having managed to resist temptations after being exposed to unhealthy foods in their imagination.														

* Since only one example of each coded BCT is provided here, the examples may not represent all possible links to COM-B components and TDF domains.

BCT = Behaviour change technique; Functions = Intervention functions; S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

Additional file 6: BCTs frequently coded together

BCT No. and Label	1.1	1.2	1.4	1.9	3.1	4.1	5.1	5.6	6.1	8.1	8.2	8.4	8.7	9.1	10.9	12.1	12.3	12.5	13.2	15.2	15.4	16.2
1.1 Goal setting (behaviour)			2	3							1	1									3	
1.2 Problem solving											1					2	1	1				
1.4 Action planning	2			2																	2	
1.9 Commitment	3		2								1	1									3	
3.1 Social support (unspecified)						1																
4.1 Instruction on how to perform behaviour					1		3	1	7	3	6		3	1		2	1	3				
5.1 Information about health consequences						3				2	3			19								
5.6 Information about emotional consequences						1																
6.1 Demonstration of the behaviour						7																
8.1 Behavioural practice/rehearsal						3	2				2		2			2			2			
8.2 Behaviour substitution	1	1		1		6	3			2		3				1	1	1			1	
8.4 Habit reversal	1			1							3										1	
8.7 Graded tasks						3				2						1	1					
9.1 Credible source						1	19															
10.9 Self-reward																						1
12.1 Restructuring the physical environment		2				2				2	1		1				1	4				
12.3 Avoidance/reducing exposure to cues for the behaviour		1				1					1		1			1						
12.5 Adding objects to the environment		1				3					1					4						
13.2 Framing/reframing										2												
15.2 Mental rehearsal of successful performance																						4
15.4 Self-talk	3		2	3							1	1										
16.2 Imaginary reward															1					4		

Additional file 7: 'Information about health consequences' – Mapped BCW Components, TDF Domains and Intervention Functions

5.1 Information about health consequences

Exemplary text description:

The participant is informed that a healthy diet lowers the likelihood of cardiovascular diseases and thus lowers the risk of a worse MS prognosis through provision of written information.

Intervention functions: Education, Persuasion

Capability				**Opportunity**		**Motivation**							
Physical	**Psychological**			**Social**	**Physical**	**Reflective**						**Auto**	
S	**K**	**MAD**	**BR**	**SI**	**EN**	**B Cap**	**B Con**	**S/P ID**	**O**	**I**	**G**	**EM**	**R**

S = Skills; K = Knowledge; MAD = Memory, Attention and Decisional Processes; BR = Behavioural Regulation; SI = Social Influences; EN = Environmental Context and Resources; B Cap = Beliefs about Capabilities; B Con = Beliefs about Consequences; S/P ID = Social/Professional Role and Identity; O = Optimism; I = Intentions; G = Goals; EM = Emotion; R = Reinforcement.

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	2	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	3-5	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	3-5	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	3-5	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	N/A	
	HOW		
6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	3	

	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	N/A	
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	4	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	3-5	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	N/A	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

VIII Zusammenfassung auf Deutsch und auf Englisch

Hintergrund: Nach einer Diagnose der Multiplen Sklerose (MS) müssen Betroffene frühzeitig Therapieentscheidungen treffen und ein Bewältigungskonzept entwickeln. Veränderbare Risikofaktoren und die Aufrechterhaltung eines gesunden Lebensstils werden in der MS-Forschung zunehmend als relevant angesehen. Darüber hinaus ist der lebensstilbezogene Informationsbedarf bei MS-Betroffenen hoch.

Methoden: Eine neue digitale Gesundheitsanwendung („levidex") wurde entwickelt und in einer Machbarkeits- und Pilotstudie mit MS-Betroffenen und MS-Expert:innen getestet. Levidex vermittelt evidenzbasierte Patient:inneninformationen zu Lebensstilfaktoren bei MS unter Einsatz von Verhaltensänderungstechniken (BCTs). Die ernährungsbezogenen Komponenten wurden mithilfe einer BCT-Taxonomie deskriptiv beschrieben. Zudem wurde levidex in einer deutschlandweiten randomisierten kontrollierten Studie (RCT) mit begleitender Prozessevaluation und einer gesundheitsökonomischen Evaluation untersucht. Die Basisdaten der Teilnehmenden zum Zeitpunkt des Studieneinschlusses wurden explorativ analysiert.

Ergebnisse: Die finale levidex-Version umfasst 16 Gespräche, 177 Referenzen und zahlreiche weitere Funktionen. Die Machbarkeits- und Pilotstudie bestätigten eine gute Machbarkeit und hohe Akzeptanz von levidex. Die Ergebnisse zeigten Verbesserungspotenzial (z.B. hinsichtlich der Länge), aber auch, dass levidex verständlich, vertrauenswürdig und relevant ist. Insgesamt wurden in den ernährungsbezogenen Komponenten 28 BCTs identifiziert. Für das RCT wurden in 20 Studienzentren insgesamt 234 Erstbetroffene mit MS rekrutiert. Die Mehrheit der Teilnehmenden ist weiblich, hat ein Durchschnittsalter von 36 Jahren und eine leichte MS-Beeinträchtigung. Zudem besteht in dieser Kohorte von Erstbetroffenen mit MS Bedarf hinsichtlich einer Optimierung ihres Gesundheitsverhaltens.

Diskussion: Levidex wird von MS-Betroffenen und MS-Expert:innen gut angenommen und hat das Potenzial, den lebensstilbezogenen Informationsbedarf von MS-Betroffenen zu decken und sie durch eine Optimierung ihres Gesundheitsverhaltens frühzeitig auf die MS einzustellen. Die Wirksamkeit von levidex im Hinblick auf eine mögliche Verringerung der Krankheitsaktivität und Verbesserung der Lebensqualität wird durch das RCT untersucht.

Background: After a multiple sclerosis (MS) diagnosis, persons with MS (PwMS) are often urged to make early therapy decisions, while they have to develop a coping concept in parallel. Modifiable risk factors and the maintenance of a healthy lifestyle are considered increasingly relevant in MS research. Moreover, lifestyle-related information needs are high among PwMS.

Methods: A new digital health application ("levidex") was developed and tested with PwMS as well as MS experts. Levidex conveys evidence-based patient information about lifestyle factors in MS and engages PwMS in a broad range of behaviour change techniques (BCTs). The levidex components targeting dietary behaviour were characterised descriptively according to a BCT Taxonomy. Levidex was evaluated in a randomised controlled trial (RCT) across Germany. In addition, a mixed-methods process evaluation and a health economic evaluation was carried out. Exploratory data analyses were performed to explore the baseline data of the participants at the time of study inclusion.

Results: The final levidex version includes 16 modules, 177 references and a broad range of other functions. Feasibility and piloting of levidex confirmed good feasibility and high acceptance. Results revealed potential for improvement (e.g., regarding the length) but showed that levidex is understandable, trustworthy, and relevant. A total of 28 BCTs were identified in the dietary behaviour components of levidex. In the RCT, 234 participants with early MS were recruited in 20 study centres. The majority of the participants is female with a mean age of 36 years and mild MS impairment. Moreover, results indicate a need for modifications of health behaviours in this cohort of persons with early MS.

Discussion: Results suggest that levidex is feasible and well-accepted by PwMS and MS experts. It has the potential to meet lifestyle-related information needs of PwMS and might help them to adjust to MS early by optimising their health behaviours. Optimally, it can promote a reduction of disease activity and improve quality of life. Insights regarding the effectiveness of levidex are expected from the results of the RCT.

IX Erklärung des Eigenanteils an den Publikationen

Publikation 1: Krause N, Riemann-Lorenz K, Rahn AC, et al. 'That would have been the perfect thing after diagnosis': development of a digital lifestyle management application in multiple sclerosis. Therapeutic Advances in Neurological Disorders. January 2022. doi:10.1177/17562864221118729

Eigenanteil: Nicole Krause war substantiell an der Konzeption und Durchführung der Studie beteiligt. Sie führte die Datenerhebung sowie alle statistischen und qualitativen Analysen durch, interpretierte die Ergebnisse und bereitete diese zwecks Überarbeitung des Interventionsprogramms (levidex) auf. Sie verfasste unter alleiniger Erstautorenschaft den ersten Entwurf des Manuskriptes und übernahm als Hauptverantwortliche den Einreichungs- und Reviewprozess.

Publikation 2: Krause N, Riemann-Lorenz K, Steffen T, et al. Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1). BMJ Open 2021;11:e041720. doi:10.1136/bmjopen-2020-0417206.2

Eigenanteil: Nicole Krause war maßgeblich an der Konzeption der gesamten randomisiert kontrollierten Studie sowie dem Einholen des zugehörigen Ethikvotums beteiligt. Sie registrierte außerdem die Studie und verfasste den ersten Entwurf des Studienprotokolls. Als alleinige Erstautorin und Hauptverantwortliche übernahm sie den Einreichungs- und Reviewprozess.

Publikation 3 (im Druck): Krause N, Derad C, von Glasenapp B, et al. Association of health behaviour and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial. Multiple Sclerosis and Related Disorders. 2023. doi:10.1016/j.msard.2023.105043.

Eigenanteil: Nicole Krause war maßgeblich an der Konzeption und Durchführung der Studie (inkl. Datenerhebung), der Ausarbeitung von Forschungsfragen und Hypothesen sowie der Analyse und Interpretation der Daten beteiligt. Sie verfasste unter alleiniger Erstautorenschaft den ersten Entwurf des Manuskriptes und übernahm als Hauptverantwortliche den Einreichungs- und Reviewprozess.

Weitere Arbeit (zur Publikation eingereicht): Krause N, von Glasenapp B, Heesen C, Meyer B, Riemann-Lorenz K. Diet and multiple sclerosis: Application of behaviour

change techniques, the Behaviour Change Wheel and the Theoretical Domains Framework to characterise a digital health application.

Eigenanteil: Im Rahmen dieser Arbeit war Nicole Krause maßgeblich an der Planung und Durchführung der Studie beteiligt. Sie sichtete alle ernährungsbezogenen levidex Inhalte, führte die Kodierung der BCTs durch und interpretierte die Ergebnisse. Als alleinige Erstautorin verfasste sie zudem den ersten Entwurf der Arbeit und reichte diesen ein.

X Danksagung

Zunächst möchte ich mich ganz herzlich bei allen an den Studien beteiligten MS-Betroffenen bedanken, deren Unterstützung und positives Feedback zu dieser Forschungsarbeit stets ein großer Motivationsfaktor für mich war.

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XI Lebenslauf

Lebenslauf entfällt aus datenschutzrechtlichen Gründen

Lebenslauf entfällt aus datenschutzrechtlichen Gründen

XII Schriftenverzeichnis

In dieser Dissertation einbezogene Publikationen

Krause N, Riemann-Lorenz K, Steffen T, Rahn AC, Pöttgen J, Stellmann JP, Köpke S, Friede T, Icks A, Vomhof M, Temmes H, van de Loo M, Gold SM and Heesen C. Study protocol for a randomised controlled trial of a web-based behavioural lifestyle programme for emPOWERment in early Multiple Sclerosis (POWER@MS1). BMJ Open. 2021;11:e041720. Doi: 10.1136/bmjopen-2020-041720.

Krause N, Riemann-Lorenz K, Rahn AC, Pöttgen J, Köpke S, Meyer B, Thale F, Temmes H, van de Loo M, Gold SM and Heesen C. 'That would have been the perfect thing after diagnosis': development of a digital lifestyle management application in multiple sclerosis. Therapeutic Advances in Neurological Disorders. 2022;15. Doi:10.1177/17562864221118729.

Krause N, Derad C, von Glasenapp B, Riemann-Lorenz K, Temmes H, van de Loo M, Friede F, Asendorf T, Heesen C, POWERMS1 study group. Association of health ehavior and clinical manifestation in early multiple sclerosis in Germany – Baseline characteristics of the POWER@MS1 randomised controlled trial. Multiple Sclerosis and Related Disorders. 2023. doi:10.1016/j.msard.2023.105043. (Im Druck)

Krause N, von Glasenapp B, Heesen C, Meyer B and Riemann-Lorenz K. Diet and multiple sclerosis: Application of behaviour change techniques, the Behaviour Change Wheel and the Theoretical Domains Framework to characterise a digital health application. (Zur Publikation eingereicht)

Weitere Publikationen

Goldin K, Riemann-Lorenz K, Daubmann A, Pöttgen J, **Krause N**, Schröder H and Heesen C. Health behaviors of people with multiple sclerosis and its associations with MS related outcomes: a German clinical cohort. Frontiers in Neurology. 2023;14:1172419. doi: 10.3389/fneur.2023.1172419.

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Riemann-Lorenz K, **Krause N**, Marck CH, Daubmann A and Heesen C. (2023) Diet and Multiple Sclerosis – Development and mixed methods feasibility testing of a comprehensive Nutritional Information Resource (NUTRIMS). Patient Education and Counselling. (Zur Publikation eingereicht)

*geteilte Erstautorenschaft

XIII Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: