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Habilitationsschrift

Naturheilkunde, Komplementäre und Integrative Medizin bei chronischen Erkrankungen

zur Erlangung der Lehrbefähigung für das Fach

Experimentelle Innere Medizin mit Schwerpunkt Naturheilverfahren/Naturheilkunde

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Abkürzungen

- BMI – Body-Mass-Index
- CAM – Complementary and Alternative Medicine
- CIM – Complementary and Integrative Medicine
- CRP – C-reaktives Protein
- DALYs – Disability-Adjusted Life Years
- DASH diet – Dietary Approaches to Stop Hypertension
- DGE – Deutsche Gesellschaft für Ernährung
- EbM – Evidence-based Medicine
- HDL – High-Density-Lipoprotein
- HOMA-Index – Homeostasis Model Assessment-Index
- HRV – Herzratenvariabilität
- IBS-SSS – Irritable Bowel Syndrome – Severity Scoring System
- IM – Integrative Medizin
- MBM – Mind-Body Medizin
- MBSR – Mindfulness-Based Stress Reduction
- MBLM – Meditation Based Lifestyle Modification
- mTor – mammalian Target of Rapamycin
- LDL – Low-Density-Lipoprotein
- MMR – Mixed-Methods Research
- NCDs – Non-Communicable Diseases
- NCCIH – National Center for Complementary and Integrative Health
- NHK – Naturheilkunde
- NHV – Naturheilverfahren
- NIH – National Institutes of Health
- PBD – Plant-Based Diet
- PSS – Perceived Stress Scale
- RCT – Randomized Controlled Trial
- TCM – Traditionelle Chinesische Medizin
- TEM – Traditionelle Europäische Medizin
- TIM – Traditionelle Indische Medizin
- TMS – Traditional Medicine Systems
- WHO – World Health Organization
- WMS – Whole Medical System
- WSR – Whole Systems Research

1. Einleitung

Chronische Krankheiten zählen in Industriestaaten und zunehmend auch in weniger wohlhabenden Ländern zu den häufigsten und gesundheitsökonomisch bedeutsamsten Gesundheitsproblemen [1]. Insbesondere Herz-Kreislauf-Erkrankungen, Übergewicht und Adipositas, Diabetes mellitus Typ 2, Krebserkrankungen, sowie zunehmend auch stressassoziierte Erkrankungen, zeigen weltweit eine zunehmende Prävalenz und beeinflussen Lebensqualität, Arbeitsfähigkeit und Sterblichkeit [1-5].

Die Therapiemethoden der Naturheilkunde fokussieren auf gesundheitsfördernde Lebensstilmaßnahmen und Verfahren wie Bewegung, Ernährung, strukturierte Stressreduktion und Ordnungstherapie sowie Hydrotherapie. Sie sind im globalen Kontext in kulturell verorteten Formen der Traditionellen Medizin (TM) verankert. Umfragen zeigen, dass ein großer Teil der Bevölkerung in Europa im Krankheitsfall zusätzlich zur konventionellen Behandlung mit evidenzbasierten Verfahren der Komplementärmedizin und Naturheilkunde im Rahmen einer Integrativen Medizin behandelt werden möchte [6-8]. Auch in den Gesundheitsberufen, insbesondere in Pflege und Ärzteschaft, besteht ein wachsendes Interesse für evidenzbasierte Interventionen der Komplementärmedizin [9-11].

Hierbei handelt es sich explizit um komplementäre und integrative Medizin (Englisch: *Complementary and Integrative Medicine*, CIM) und nicht um Alternativmedizin. Die CIM kombiniert evidenzbasierte Naturheilkunde und Komplementärmedizin mit etablierten Verfahren der konventionellen Medizin [12]. Als „alternative“ Therapien werden meist Verfahren bezeichnet, deren Wirksamkeit nicht oder nur unzureichend belegt ist und/oder die als Methode keine Plausibilität aufweisen [12].

1.1 Definition der Begriffe Naturheilkunde, Komplementär- und Integrative Medizin

Im angloamerikanischen Raum hat sich den letzten Jahrzehnten der von der amerikanischen Gesundheitsadministration *National Institutes of Health* (NIH) geprägte Begriff *Complementary and Alternative Medicine* (CAM), in der letzten Dekade abgeändert zu *Complementary and Integrative Medicine* (CIM) durchgesetzt [12]. In Deutschland ist der Begriff Komplementärmedizin inzwischen akademisch etabliert, in der

Bevölkerung sind jedoch eher die Begriffe Naturheilkunde (NHK) und Naturheilverfahren (NHV) verbreitet.

Die Kombination von konventioneller Medizin, Komplementärmedizin und patientenzentrierten Ansätzen wird seit den 1940er Jahren unter dem Begriff "Integrative Medizin" (IM) zusammengefasst [12]. Die bisher umfassendste Definition stammt von Brinkhaus/Esch, die die IM Definition des *Consortium of Acadamic Health Centres for Integrative Medicine* wie folgt adaptierten:

„Integrative Medizin und Gesundheit bekräftigt die Bedeutung der Beziehung zwischen Arzt und Patient, stellt den ganzen Menschen in den Mittelpunkt, stützt sich auf wissenschaftliche Erkenntnisse und nutzt alle geeigneten therapeutischen, präventiven, gesundheitsfördernden und lebensstilbezogenen Ansätze, Gesundheitsberufe und Gesundheitsdisziplinen, um eine optimale Gesundheit und Heilung zu erreichen, wobei die Kunst und Wissenschaft des Heilens im Vordergrund steht. Sie basiert auf einer sozialen und demokratischen sowie natürlichen und gesunden Umwelt“ (eigene Übersetzung des Autors) [12].

Die IM verbindet dabei die wissenschaftlichen Fortschritte der konventionellen Medizin mit den Erkenntnissen traditioneller Heilsysteme und der individuellen Patientenbetreuung in der Komplementärmedizin, um die Selbstwirksamkeit und die eigenen Fähigkeiten der Patienten zur Genesung von Krankheit und zur Erhaltung der Gesundheit zu stärken („*medicus curat, natura sanat“*) [12]. Es gibt ein in v.a. traditionellen Medizinsystemen (engl. *Traditional Medicine Systems*, TMS) über Jahrhunderte, teils Jahrtausende gewachsenes, naturheilkundliches Wissen, das zur Prävention und Therapie einer Vielzahl von Krankheiten genutzt wird und zunehmend in Gesundheitssystemen weltweit zum Einsatz kommt [13]. Insbesondere in den letzten Jahrzehnten erfolgte u.a. durch das NIH eine systematische Forschungsförderung im Rahmen des *National Center for Complementary and Integrative Health* (NCCIH) mit dem Ziel einer weiteren Evidenzgenerierung komplementär- und integrativmedizinischer Interventionen und um bisherige Strategien als Teil eines umfassenden Gesundheitsmanagements zu ergänzen [14].

In Europa und insbesondere im deutschsprachigen Raum gibt es eine lange Tradition der NHK [15, 16]. Die NHK ist die Lehre von NHV oder der Naturheilweisen bzw. Naturheilmitteln (z.B. Nahrung, Pflanzen, Wasser, Luft, Licht), die aus der Natur stammen oder der Natur nachempfunden sind [15]. NHV werden in klassische und erweiterte NHK-Interventionen eingeteilt [15]. Die fünf klassischen Bereiche der NHK sind:

- Ernährungs- und Fastentherapie
- Ordnungstherapie/Mind-Body Medizin
- Bewegungstherapie
- Hydro-, Balneo- und Thermotherapie
- Phytotherapie (Pflanzenheilkunde)

Diese klassischen NHV sind auch als sog. „Fünf Säulen der Naturheilkunde“ im Rahmen der Traditionellen Europäischen Medizin (TEM) seit den Zeiten Hildegard von Bingens bekannt, werden aber letztlich in allen traditionellen Medizinsystemen und *Whole Medical Systems* (WMS) erfolgreich angewandt [15-17]. Zu den sog. erweiterten NHV gehören die sog. ausleitenden Verfahren (z.B. Schröpfen, Blutegel, Aderlass), Manuelle Medizin, Neuraltherapie u.a.

Darüber hinaus sind zunehmend die weltweit vorhandenen TMS von Bedeutung. Am bekanntesten sind die Traditionelle Chinesische Medizin und die Traditionelle Indische Medizin (TIM)/Ayurveda.

In einem offiziellen Strategiepapier der WHO „Traditional Medicine 2014-2023“ fordert die WHO, diese Verfahren vermehrt in der primären Versorgung einzusetzen [13]. All diesen Verfahren gemeinsam ist das Ziel, die Selbstregulation der Betroffenen („Selbstheilungskräfte“) zu induzieren, wobei die individuelle Konstitution des Patienten und die biopsychosoziale Situation berücksichtigt werden [12].

NHK wird im deutschsprachigen Raum insbesondere in der Gesundheitsförderung und Prävention, Rehabilitation, diversen Privatkliniken, auf NHK spezialisierten stationären Einrichtungen und v.a. im ambulanten Sektor in der hausärztlichen Medizin angewandt. NHV sind seit 1988 Bestandteil der deutschen Approbationsordnung für Ärzte. In 2021 waren in Deutschland bei den Ärztekammern 12615 Ärzte mit der Zusatzbezeichnung

NHV registriert, davon waren nur 1242 Ärztinnen und Ärzte stationär im Bereich NHV tätig [18]. An deutschen Universitäten finden sich in 2022 10 (vorrangig Stiftungs-) Professuren – davon drei Professuren an der Charité – mit NHK-Schwerpunkt mit dem Ziel der Überprüfung der Wirksamkeit von NHK-Interventionen im Sinne der *Evidence-based Medicine* (EbM).

In Europa ist die Nachfrage bezüglich NHK seit Jahrzehnten hoch: Das sog. CAMbrella-Projekt zeigte, dass bis zu 50 Prozent der Europäer naturheilkundliche Interventionen anwenden, wobei die Nutzung innerhalb der EU zwischen 0,3 und 86 % erheblich variierte [8, 19]. In Deutschland werden NHV von ca. 50-70% der Bevölkerung in Anspruch genommen [20-25]. Mehrheitlich wünschen sich Europäer naturheilkundliche Interventionen als Teil der Gesundheitsversorgung, jedoch ist der Zugang in vielen Ländern erschwert, z.B. wegen fehlender Kostenübernahme durch gesetzliche Krankenversicherungen, durch fehlendes Angebot oder unzureichend geregelte Qualifikation der Anbieter u.a. [19]. Insgesamt wird NHK-Forschung kaum durch die öffentliche Hand gefördert – was im Widerspruch zur Nutzung durch die Bevölkerung und die hohe Popularität von NHK steht und deshalb für die Medizin in jedem Falle von maßgeblicher Relevanz sein sollte [8, 19].

1.2 Chronische Erkrankungen

Die sog. nichtübertragbaren Krankheiten (engl. *non-communicable diseases*, NCDs) stellen laut der *World Health Organization* (WHO) neben der Klimakrise und den Infektionserkrankungen mit mikrobiellen Resistenzentwicklungen eine der größten globalen Herausforderungen der Gegenwart dar [26]. NCDs sind seit mehreren Dekaden weltweit die häufigste Todesursache: Fast drei Viertel aller Menschen sterben an den Folgen von NCDs [27]. Zu den wichtigsten NCDs gehören chronische Erkrankungen wie Herz-Kreislauf-Erkrankungen, Krebserkrankungen, Atemwegserkrankungen, Diabetes mellitus Typ 2 u.a. [26]. Diese vier genannten Erkrankungsgruppen machen 80% der NCD-bedingten Mortalität aus [28].

Die Studie GEDA 2019/2020-EHIS zeigte in der deutschen Bevölkerung ab dem mittleren Erwachsenenalter (d.h. ab 45 Jahren) einen schrittweisen Anstieg der Prävalenz bei

chronischen Erkrankungen wie Herz-Kreislauf-Erkrankungen, Diabetes mellitus, Arthrose u.a. bis in das hohe Erwachsenenalter [29]. Knapp zwei Drittel der Personen im höheren Erwachsenenalter (d.h. ab 65 Jahren) gaben eine chronische Erkrankung oder eine seit mindestens 6 Monate andauernde gesundheitliche Beschwerde an – nur etwa die Hälfte berichtete von einer guten/sehr guten subjektiven Gesundheit [29]. Dies zeigt die hohe *Public Health* Relevanz chronischer Erkrankungen auch vor dem Hintergrund des demografischen Wandels [30].

Inzidenz und Prävalenz von NCDs nehmen in Wohlstandsgesellschaften also kontinuierlich zu und haben sowohl in Bezug auf gesundheitsökonomische Lasten wie auch sog. behinderungs- bzw. krankheitsbereinigte Lebensjahre (engl. *Disability-Adjusted Life Years*, DALYs) akute Erkrankungen in ihrer Bedeutung überholt [31]. In Deutschland verursachen NCDs bedeutende Therapiekosten und Sozialleistungen in Höhe von über 200 Milliarden Euro pro Jahr [32]. Da diese Erkrankungen zumeist einen chronischen Verlauf aufweisen und häufig mit Einschränkungen des alltäglichen Lebens verbunden sind, bedeuten sie für viele Menschen auch eine Einschränkung der Lebensqualität [31]. Nichtübertragbare Krankheiten spielen damit auch bei den DALYs die größte Rolle: Weltweit sind mehr als 60 % der DALYs auf NCDs zurückzuführen [33].
Für die meisten der aufgeführten chronischen Erkrankungen gilt, dass diese als überwiegend lebensstilverursacht/-assoziiert angesehen werden. Die drei Kernvariablen eines gesundheitsabträglichen Lebensstils sind dabei 1. Bewegungsmangel, 2. Fehl- und Überernährung sowie 3. Distress und psychische Belastungen [5]. Naheliegende, jedoch derzeit noch wenig genutzte bzw. umgesetzte Präventionsmöglichkeiten sind dementsprechend: 1. Bewegung und körperliche Aktivität, 2. eine vollwertige, pflanzenbasierte und Energie-adäquate Ernährung sowie Elemente des zeitbegrenzten Essens (sog. *Time-Restricted Eating*/Intermittierendes Fasten) und 3. Achtsamkeit, Entspannungsübungen, Stressreduktion und verbesserte Stressverarbeitung (Coping/Resilienz). Diese Präventionsansätze werden im Rahmen von CIM-Interventionen vermittelt [34]. Auf Basis des biopsychosozialen Modells fokussiert die CIM auf die Stärkung selbstverantwortlicher Menschen im Kontext von Gesundheitsförderung, Prävention und Therapie [12].

Die Verfahren der CIM sind jedoch im Gegensatz zur Vielfalt ihrer weltweiten Anwendungsvarianten, zum Ausmaß ihrer hohen Inanspruchnahme in Deutschland und ihrer globalen gesundheitspolitischen Bedeutung ein wissenschaftlich bisher unzureichend erschlossenes Feld mit gleichzeitig großem medizinischem Potenzial für die globale Gemeinschaft. Dabei gibt es zunehmend belastbare klinisch-wissenschaftliche Evidenz zur Prävention und Therapie chronischer Erkrankungen, bei denen CIM und NHK relevante Beiträge zur Lösung dieser bedeutsamen medizinischen Fragestellungen beitragen können [35-37].

1.3 Stand der Forschung

Klassische NHV werden von der konventionellen Medizin weitestgehend akzeptiert; dies liegt v.a. an der allgemeinen zunehmenden Evidenzgrundlage der Bereiche Ernährung, Bewegung und Mind-Body Medizin (MBM) [38-41]. In der Phytotherapie zeigen u.a. einzelne Heilpflanzen wie Johanniskraut, Weißdorn und diverse Kombinationspräparate (z.B. Iberogast) gute Evidenz in Bezug auf gesundheitsrelevante Outcomes, wenngleich methodologisch hochwertige (multizentrische) *randomized controlled trials* (RCTs) wie im Bereich der synthetischen Arzneimittel aus diversen Gründen ausstehen [42-44]. Im Bereich der Hydro-, Balneo- und Thermotherapie fehlen bislang robuste, v.a. langfristige klinische Wirksamkeitsnachweise [45, 46]. Im Folgenden wird die Evidenzlage für die in dieser Habilitationsschrift relevanten Bereiche der NHK Ernährungs-/Fastentherapie und MBM dargestellt.

1.3.1 Ernährungs- und Fastentherapie

Fasten, Kalorienrestriktion, vollwertige und pflanzenbasierte Ernährung sind im letzten Jahrzehnt zunehmend in den Mittelpunkt des wissenschaftlichen Interesses gerückt. Experimentelle und klinische Forschungsergebnisse weisen auf präventive und therapeutische Effekte verschiedener Formen des Fastens und der kalorischen Restriktion bei verschiedenen Indikationen hin [47-50]. Fasten führt in Organismen zu komplexen Aktivierungen und Hemmungen biologischer Steuerungssysteme, die Stoffwechsel und Zellalterung betreffen, mit vermutlich überwiegend gesundheitsfördernden Effekten. Ergebnisse aus Tiermodellen mit wiederholten Fastenzyklen deuten auf eine Reduktion der altersbedingten Morbidität hin [51]. Zudem

führt Fasten im Organismus zu einer Vielzahl an Signalkaskaden, z.B. in den Signalwegen von *Insulin-like growth factor 1* und *mammalian Target of Rapamycin* (mTor), sowie zu einer Induktion der Autophagie, Stammzellneubildung und Ketonkörperproduktion [51]. Die meisten dieser Effekte wurden in zahlreichen experimentellen Studien und inzwischen auch in ersten Humanstudien über längeres therapeutisches und intermittierendes Fasten sowie über das sog. „Scheinfasten“ (engl. *Fasting Mimicking Diet*) bestätigt [51-53].

Die Hauptindikationen für eine Fastentherapie sind Stoffwechsel- und entzündliche Krankheiten, v.a. metabolische Erkrankungen und Erkrankungen des rheumatischen Formenkreises [54-56]. Darüber hinaus wird die Fastentherapie auch zur Einleitung einer Lebensstiländerung und Verhaltensänderung mit dem Ziel eines gesünderen Lebensstils eingesetzt. Es gibt zunehmende Belege, dass Fasteninterventionen v.a. kardiovaskuläre Risikofaktoren reduzieren könnten [54, 55]. Während in den letzten Jahren v.a. Studien zum sog. intermittierenden Fasten (Fastenzeit: 14-48 Stunden) durchgeführt wurden, wurde das sog. prolongierte Fasten oder therapeutische Fasten über einen längeren Zeitraum (Fastenzeit: 3 bis 21 Tage oder in Einzelfällen 28 Tage) in Humanstudien bisher weniger untersucht [47, 57]. Fastentherapeutische Ansätze dieser Art haben jedoch in Europa, und insbesondere im deutschsprachigen Raum, eine lange Tradition, z.B. in Form des sog. Buchinger-Fastens [58]. Diese Art des therapeutischen Fastens wird als tägliche maximal Nahrungsenergiezufuhr von 200 bis 500 kcal über einen Zeitraum von bis zu vier Wochen – in Studien jedoch meistens über 5-10 Tage untersucht – definiert [58].

Auch eine vollwertige pflanzenbasierte Ernährung (*whole-food plant-based diet*, PBD) kann ein entscheidender Faktor zur Prävention und Therapie chronischer Erkrankungen sein [59-61]. In der Naturheilkunde werden grundsätzlich Kostformen der Vollwerternährung – mit hohen Anteilen unverarbeiteter Nahrung, reichlich Ballaststoffen und möglichst geringem/keinem Anteil tierischer Produkte – bevorzugt, z.B. die traditionelle Mittelmeerernährung, traditionelle asiatische Ernährungsweisen, die *Planetary Health Diet* und v.a. auch die pflanzenbasierten Ernährungsweisen (z.B. lacto-vegetarische, lacto-ovo-vegetarische, pescetarische, flexitarische oder vegane Ernährung).

Gesundheitsfördernde Effekte einer pflanzenbasierten Ernährung zeigten sich v.a. bei metabolischen Erkrankungen und Diabetes mellitus Typ 2 und sind dort auch mit günstigeren kardiovaskulären Risikoprofilen assoziiert, v.a. mit niedrigerem Blutdruck, Körpergewicht, Taillenumfang, *Low-Density-Lipoprotein* (LDL)-Cholesterin und Triglyceriden [62-67]. In diesem Zusammenhang wird die regelmäßige Zufuhr von hochwertigen ungesättigten Fettsäuren, Ballaststoffen, Nüssen, vollwertigen Kohlenhydraten mit niedrigem glykämischem Index sowie der reichliche Verzehr von Gemüse, Hülsenfrüchten, Obst, Kräutern und Gewürzen mit hohem Gehalt an sekundären Pflanzenstoffen als entscheidend für die günstigen Wirkungen solcher Ernährungsweisen erachtet [59, 60, 62, 63, 68]. Weiterhin reduziert eine pflanzenbasierte Ernährung die Gesamtenergieaufnahme durch den Verzehr von Lebensmitteln mit einer geringeren Energiedichte [69].

Tierische Produkte sowie industriell stark verarbeitete Nahrungsmittel werden im Rahmen solcher Ernährungsweisen nur selten oder gar nicht konsumiert [70, 71]. Epidemiologische Daten zeigen, dass ein Ersatz tierischen Proteins durch pflanzliches Protein mit reduzierter Sterblichkeit, v.a. durch eine reduzierte kardiovaskuläre Mortalität, und eine höhere Zufuhr von Gesamt- und tierischem Protein mit einem erhöhten Diabetes mellitus Typ 2-Risiko assoziiert ist [72, 73]. Ein rezenter Lancet-Artikel führte den neuen Begriff der „*Planetary Health Diet*“ (planetare Gesundheitsernährung) als ein nachhaltiges Ernährungssystem ein, das die globale Ernährung hin zu deutlich mehr pflanzlichen Lebensmitteln und erheblich weniger tierischen Lebensmitteln verlagern soll [38].

In der Ernährungsmedizin wird immer deutlicher, dass Ernährung auch einen Einfluss auf das psychische Wohlbefinden ausübt [74-76]. In einer 2019 veröffentlichten Übersichtsarbeit "*Feeding melancholic microbes: MyNewGut recommendations on diet and mood*" haben führende Ernährungs- und Mikrobiomforscher den Stand der aktuellen Empfehlungen im Kontext von Mikrobiom und Ernährung zusammengefasst: Das Konsortium empfiehlt Patienten mit Depressionen oder einer Veranlagung zu Depressionen eine pflanzliche Ernährung, die reich an Ballaststoffen, Vollkornprodukten und Polyphenolen ist, sowie Fisch oder Algen [77].

Zusammenfassend ergibt sich für chronische, insbesondere für kardiometabolische Erkrankungen, nach aktueller Datenlage experimenteller, klinischer und epidemiologischer Studien eine zunehmend solide Evidenz für gesundheitliche Vorteile pflanzenbasierter Vollwerternährungsweisen und der Fastentherapie [54, 55, 62-66].

1.3.2 Ordnungstherapie und Mind-Body Medizin

In der letzten Dekade hat sich der Schwerpunkt der angloamerikanischen CIM-Forschung stark in Richtung MBM und strukturierte Lebensstilmodifikation verlagert, die beide eine starke Überschneidung mit der sog. Ordnungstherapie der TEM aufweisen [34]. Der Begriff Ordnungstherapie geht u.a. auf Sebastian Kneipp (1821-1897) zurück und bezieht sich auf die Ordnung des menschlichen Lebens, d.h. die Gestaltung des persönlichen Alltags, v.a. bezüglich des Umgangs mit Stress- und Entspannungsphasen.

Nationale und internationale Erhebungen machen deutlich, dass Distress, neben Bewegungsmangel und Fehlernährung, inzwischen einer der maßgeblichen Risikofaktoren für eingeschränkte Lebensqualität und Gesundheitsgefährdung darstellt – so hat die WHO Stress zu einer der größten Gesundheitsrisiken des 21. Jahrhunderts erklärt [78-80].

Eine dauerhaft hohe und negative Stressbelastung ist einer der dramatisch ansteigenden Risikofaktoren für die meisten chronischen Erkrankungen der Industriegesellschaften [80-82]. Verdichtung von Arbeitsprozessen, erhöhte Mobilität und eine ständige Erreichbarkeit (*„always on“* kurz für *always online* – ständige Verbindung mit dem Internet) u.a. führen bei den meisten Menschen zu einer erhöhten subjektiv empfundenen Stressbelastung [80]. Während ein gewisses Maß an Stress (Eustress) vorteilhaft sein kann, z.B. als Entwicklungsanreiz, kann eine chronische als nicht kontrollierbar wahrgenommene Stressbelastung zu gesundheitsabträglichen Folgen führen (Distress). Kurz- und mittelfristig kommt es im Sinne der *fight-or-flight response* zu akuten Erhöhungen von Blutdruck und Atemfrequenz und zur Ausschüttung von Stresshormonen (Kortisol, Adrenalin, Dopamin) u.a. [83]. Mittel- und langfristig kann es zur Ausbildung eines gesundheitsabträglichen Lebensstils führen [80, 84].

Für zahlreiche Erkrankungen ist ein Anteil der Stressinduktion in der Pathogenese chronischer Krankheiten wissenschaftlich gesichert [81, 82]. Stress ist u.a. beteiligt an der Entstehung von Bluthochdruck, koronarer Herzkrankheit und dadurch eine Steigerung der kardiovaskulären Mortalität sowie psychischen Erkrankungen, insbesondere Depression, aber auch Erkältungen, Kopfschmerzen und Schlafstörungen [78, 79, 85-88].

Vielversprechende Behandlungsansätze der CIM ergeben sich im Bereich der Ordnungstherapie und MBM, die sich v.a. der strukturierten Stressreduktion und dem gesundheitsfördernden Umgang mit chronischen Stress- und Erkrankungssituationen widmet [89].

Innerhalb der Ordnungstherapie und MBM sind Meditation und Yoga die am meisten gewichtete und wissenschaftlich am besten untersuchtesten CIM-Therapieverfahren, darunter eine große Anzahl an Wirksamkeitsnachweisen auf dem Evidenzlevel 1A für die gesamte Bandbreite der medizinischen Indikationsfelder [34, 40, 41, 90-95]. Diese im wissenschaftlichen Kontext zumeist säkularisierten Interventionen als grundlegende Erfahrungen der inneren Einkehr, geistiger Sammlung und Stille können oftmals automatisierte Gedanken und Stresskreisläufe durchbrechen [34, 96]. Die Anzahl der Yoga- und Meditationstraditionen ist insgesamt groß und zudem von einer Vielzahl grundlegend unterschiedlichster Techniken geprägt [97]. In Studien am meisten untersucht wurden die sog. Achtsamkeitsmeditation – z.B. im Rahmen des säkularisierten 8-Wochen Programms „Achtsamkeitsbasierte Stressreduktion“, engl. *Mindfulness-Based Stress Reduction* (MBSR) – und das sog. Hatha Yoga [97].

Hauptsächlich getrieben durch wissenschaftliche Aktivitäten an verschiedenen US-amerikanischen Universitäten in den letzten Jahrzehnten, und in der letzten Dekade auch zunehmend in Europa, gibt es zahlreiche systematische Reviews und Metaanalysen zu MBM aus verschiedenen medizinischen Indikationsfeldern [40, 41, 90-95]. Besonders zahlreich sind die Studien zur Wirksamkeit von Meditationstechniken bezüglich der mentalen Gesundheit, aber auch bezüglich verschiedener internistischer Indikationen [40, 93-95]. Aufgrund der vorliegenden wissenschaftlichen Daten zu Meditation und Yoga stellt sich nicht mehr in erster Linie die Frage, ob diese Interventionen wirksam sind, sondern in welchem Ausmaß und wie effizient diese im Vergleich zu konventionellen Therapien

sind, auch unter Berücksichtigung der Compliance und Patientenpräferenz [40, 41, 90-95]. So nehmen Studien zunehmend differenziertere Fragestellungen in Fokus, indem sie z.B. verschiedene Meditations- bzw. Yogastile vergleichen oder Yoga als WMS und nicht nur als rein körperliche Übungsdisziplin untersuchen [98, 99]. Beide MBM-Verfahren etablieren sich zunehmend in der konventionellen Medizin und damit auch im Erstattungsrahmen der gesetzlichen Krankenversicherungen [100].

1.4 Zielstellungen der vorliegenden Originalarbeiten

Das Ziel der in dieser Schrift vorgestellten Originalarbeiten war es, CIM-Interventionen zum einen als ergänzende Therapieoption bei Patienten mit chronischen Erkrankungen und zum anderen in der Prävention chronischer Erkrankungen zu untersuchen. Dazu wurden zwei RCTs bei Patienten mit Metabolischen Syndrom durchgeführt, die ein Programm zur Lebensstilmodifikation mit Schwerpunkt Fasten-/Ernährungstherapie und MBM bzw. ein Programm zur Ernährungsmodifikation durchliefen, sowie eine RCT zur TIM bei Patienten mit Reizdarm. Weiterhin wurden MBM-Interventionen in einem RCT bei Probanden mit Distress und bereits eingetretenen Stress-assoziierten Beschwerden untersucht sowie in einer Kohortenstudie im Schulsetting.

2. Eigene Arbeiten

2.1 Effekte von Ernährungs-/Fastentherapie und Lebensstiländerung bei Patienten mit Metabolischem Syndrom – eine randomisierte kontrollierte Studie

In Deutschland, Europa und den USA sind als bevölkerungs- und gesundheitsökonomisch relevantesten Diagnosen die kardiometabolischen Erkrankungen an erster Stelle zu nennen [101]. Der wesentliche gemeinsame Risikofaktor für diese Erkrankungen (sowie zahlreiche weitere Erkrankungen) ist Übergewicht bzw. Adipositas. Zwei Drittel der Männer und die Hälfte der Frauen in Deutschland sind übergewichtig; ein Viertel der Erwachsenen ist adipös [102]. Das sog. metabolische Syndrom (die Kombination aus abdomineller Fettleibigkeit, Bluthochdruck, Fettstoffwechselstörung und Diabetes mellitus Typ 2) wird neben dem Rauchen als der entscheidende Risikofaktor für die koronare Herzkrankheit angesehen.
Die Evidenz im Bereich kalorischer Restriktion und Fasten hat in den letzten Jahren einen starken Aufschwung erfahren; viele hochrangig publizierte Studien zeigten sowohl im Zell- und Tiermodell als auch zunehmend in klinischen Studien am Menschen zahlreiche Beeinflussungen von Stoffwechselwegen mit vorwiegend günstigen gesundheitsrelevanten Aspekten, insbesondere bei kardiometabolischen Erkrankungen [103, 104]. Die Translation der in den Grundlagenwissenschaften gewonnenen Erkenntnisse in die klinische Forschung ist erst in den letzten Jahren erfolgt; so finden sich bisher nur wenige methodisch hochwertige klinische Fastenstudien zu dieser Indikation.

Um hier einen Beitrag zu leisten, führten wir bei 145 Patienten mit metabolischem Syndrom eine bizentrische RCT mit einer 5-tägigen Fastenintervention, gefolgt von einem 10-wöchigen Programm zur Lebensstiländerung (modifizierte *Dietary Approaches to Stop Hypertension* (DASH)-Diät, Bewegung, Achtsamkeit) im Vergleich zu einer Kontrollgruppe durch, die nur das 10-wöchige Programm zur Lebensstiländerung erhielt [105].

Auch wenn sich in den ko-primären Endpunkten ambulanter systolischer Blutdruck und Homeostasis Model Assessment (HOMA)-Index in Woche 12 keine signifikanten

Gruppenunterschiede darstellten, führte die Fastenintervention (Studienvisite in Woche 1) zu einer signifikanten Senkung des HOMA-Indexes, des diastolischen Blutdrucks, des BMI, des Gewichts, des Taillenumfangs, des Blutzuckerspiegels, des Insulinspiegels, des Hämoglobin A_{1c} (HbA1c), der Triglyzeride, des Interleukin 6 u.a. im Vergleich zu der Kontrollgruppe [105]. Die Effekte auf Gewicht, Body-Mass-Index (BMI), Glukose, High-Density-Lipoprotein (HDL) und C-reaktives Protein (CRP) waren in Woche 24 zwischen den Gruppen signifikant unterschiedlich zu Gunsten der Fastengruppe.

In den separat publizierten *Patient-Reported Outcomes* zeigten sich in Woche 1 direkt nach dem Fasten signifikante Gruppenunterschiede in Depressivität und Müdigkeit zu Gunsten der Fastenintervention [106]. Fasten kann nach diesen Daten kurzfristig zu psychisch stimmungsaufhellenden Wirkungen führen. Das anschließende 10-wöchige Programm zur Lebensstilmodifikation hatte insbesondere positive Effekte auf die Lebensqualität bei den Patienten mit metabolischem Syndrom, in Woche 12 verbesserten sich die meisten *Patient-Reported Outcomes* in beiden Gruppen. Die meisten günstigen Effekte innerhalb der Gruppen blieben auch in Woche 24 bestehen. Das Fasten und die Ernährungsmodifikation bediente schwerpunktmäßig die ernährungs-/ fastentherapeutische Säule der NHK, das nachfolgende MBM-Programm zur Lebensstilmodifikation v.a. die Ordnungstherapie.

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Effects of Fasting and Lifestyle Modification in Patients with Metabolic Syndrome: A Randomized Controlled Trial

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Abstract: Background: Lifestyle interventions, such as fasting, diet, and exercise, are increasingly used as a treatment option for patients with metabolic syndrome (MS). This study assesses the efficacy and safety of fasting followed by lifestyle modification in patients with MS compared to lifestyle modification only. Methods: Single-blind, multicenter, parallel, randomized controlled trial in two German tertiary referral hospitals in metropolitan areas. Interventions: (a) 5-day fasting followed by 10 weeks of lifestyle modification (modified DASH diet, exercise, mindfulness; $n = 73$); (b) 10 weeks of lifestyle modification only ($n = 72$). Main outcomes and measures: Co-primary outcomes were ambulatory systolic blood pressure and the homeostasis model assessment (HOMA) index at week 12. Further outcomes included anthropometric, laboratory parameters, and the PROCAM score at weeks 1, 12, and 24. Results: A total of 145 patients with metabolic syndrome (62.8% women; 59.7 ± 9.3 years) were included. No significant group differences occurred for the co-primary outcomes at week 12. However, compared to lifestyle modification only, fasting significantly reduced HOMA index (Δ = −0.8; 95% confidence interval [CI] = −1.7, −0.1), diastolic blood pressure (Δ = −4.8; 95% CI = −5.5, −4.1), BMI (Δ = −1.7; 95% CI = −2.0, −1.4), weight (Δ = −1.7; 95% CI = −2.0, −1.4), waist circumference (Δ = −2.6; 95% CI = −5.0, −0.2), glucose (Δ = −10.3; 95% CI = −19.0, −1.6), insulin (Δ = −2.9; 95% CI = −5.3, −0.4), HbA1c (Δ = −0.2; 95% CI = −0.4, −0.05;), triglycerides (Δ = −48.9; 95% CI = −81.0, −16.9), IL−6 (Δ = −1.2; 95% CI = −2.5, −0.005), and the 10-year risk of acute coronary events (Δ = −4.9; 95% CI = −9.5, −0.4) after week 1. Fasting increased uric acid levels (Δ = 1.0; 95% CI = 0.1, 1.9) and slightly reduced eGRF (Δ = −11.9; 95% CI = −21.8, −2.0). Group differences at week 24 were found for weight (Δ = −2, 7; 95% CI = −4.8, −0.5), BMI (Δ = −1.0; 95% CI = −1.8, −0.3), glucose (Δ = −7.7; 95% CI = −13.5, −1.8), HDL (Δ = 5.1; 95% CI = 1.5, 8.8), and CRP (Δ = 0.2; 95% CI = 0.03, 0.4). No serious adverse events occurred. Conclusions: A beneficial effect at week 24 was found on weight; fasting also induced various positive short-term effects in patients with MS. Fasting can thus be considered a treatment for initializing lifestyle modification for this patient group; however, it remains to be investigated whether and how the multilayered effects of fasting can be maintained in the medium and longer term.

Keywords: fasting; metabolic syndrome; modified DASH diet; Mediterranean diet; lifestyle; relaxation; MICOM (mind–body medicine in integrative and complementary medicine)

1. Introduction

Modern lifestyle leads to an increasing prevalence of type 2 diabetes, metabolic syndrome, and cardiovascular risk constellations [1]. Most risk factors for cardiovascular disease can be influenced by patients' behavior; this applies above all to poor nutrition, being overweight, lack of exercise, and psychological distress [1]. Epidemiological studies also underline the role of psychological risk factors, such as psychosocial distress, depression, and anxiety, in cardiac health [2,3]. Most coronary patients do not achieve their blood pressure, low-density lipoprotein (LDL) cholesterol, and glucose targets [4]. Moreover, cardiovascular prevention requires advanced preventive cardiological programs delivered by interdisciplinary teams of healthcare professionals, which address all aspects of lifestyle and risk factor management [4].

Lifestyle modification targeting physical inactivity, diet, and psychosocial stress have thus been associated with significant reductions in blood pressure and improvements of other cardiovascular risk factors in risk groups [5–10]. There also are hints that combinations of multiple lifestyle modifications might be superior to interventions only targeting a single health behavior [11–13]. There is increasing interest and evidence that fasting might substantially reduce cardiovascular risk factors [14–16].

There is an increasing number of randomized studies on intermittent fasting in cardiometabolic endpoints, generally lasting 16 to 48 h [16]. Adults who practiced TRE typically lost 1% to 4% of their body weight within several weeks [17–20]. Furthermore, TRE can improve cardiometabolic endpoints, such as insulin sensitivity and blood pressure [16,21]. Fasting over a longer period, normally from 3 to 21 or more days, has been less studied in humans, although it has a long-standing history in Europe [20]. Fasting is commonly defined as the daily nutritional energy intake of 200 to 500 kcal for up to four weeks [22]. It has been shown to lower blood pressure, blood lipid levels, and other cardiovascular risk factors at least in the short term and appears to be associated with only few adverse events even in diseased populations [22,23]. Animal models of repeated cycles of fasting suggest reductions in mortality and age-associated morbidity, altered signaling, e.g., in signaling pathways of insulin, IGF-1, AMPK, or mTor, as well as enhanced autophagy and ketone body production [24]. Most of these effects have been confirmed in the first human studies on prolonged, periodic, and intermittent fasting as well as fasting-mimicking diets in the meantime [16,24–26].

This study aimed to assess the effects of fasting in patients with metabolic syndrome, followed by a multimodal lifestyle modification intervention named MICOM (mind–body medicine in integrative and complementary medicine), compared to lifestyle modification intervention only. We hypothesized a priori that a 5-day fast followed by 10 weeks of lifestyle modification would be more effective for reducing ambulatory systolic blood pressure and the homeostasis model assessment (HOMA) index than lifestyle modification alone.

2. Materials and Methods

2.1. Design

This single-blind, multicenter, parallel, randomized controlled trial was conducted at the Department of Internal and Integrative Medicine, Evang. Kliniken Essen-Mitte, Essen, Germany and the Department of Internal and Integrative Medicine, Immanuel Hospital Berlin and Charité Outpatient Center for Complementary and Integrative Medicine, Berlin, Germany. The study had been approved by the ethics committees of the Charité-Universitätsmedizin Berlin (approval number: EA4/141/13) and the University of Duisburg-Essen (approval number: 14-5733 BO) and registered at ClinicalTrials.gov (registration

number: NCT02099968) prior to patient recruitment. The study was conducted and reported in accordance with the CONSORT (CONsolidated Standards of Reporting Trials) 2010 guidelines [27]. No important changes were made to the study protocol after trial commencement.

2.2. Participants

Patients were recruited from study centers and through local newspaper announcements, screened by a research assistant to assess eligibility, and, if apparently eligible, assessed by a study physician. If patients met all inclusion criteria and did not meet any exclusion criteria, informed consent was obtained, and they were included in the trial.

Patients (male/female) with a metabolic syndrome according to the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) criteria were included. Patients were further required to be diagnosed with systolic hypertension and/or with an additional subclinical atherosclerosis (<50% coronary artery stenosis, <50% carotid artery stenosis, or peripheral artery disease stage 1).

Exclusion criteria included: (i) diabetes mellitus type 1 or insulin bolus therapy (c-peptide < 1.2 ng/mL), (ii) coronary artery disease, myocardial infarction, pulmonary embolism, or stroke within the past 3 months, (iii) heart failure $\geq$ stage I NYHA, (iv) peripheral artery disease $\geq$ stage 2, (v) chronic kidney disease > stage 2 (GFR < 60 mL/min), (vi) eating disorder, dementia, or psychosis, or (vii) other severe internal diseases.

2.3. Interventions

Both interventions were group-based and conducted by a multidisciplinary team of healthcare professionals (nutritional counselors, mind–body therapists, or sport therapists) with board certified education. They incorporated aspects of the mind–body program, which was originally developed by the Benson-Henry Mind/Body Medical Institute at Harvard Medical School and further developed and adapted to the German needs, as described in the MICOM (mind–body medicine in integrative and complementary medicine) program [28]. This program focuses on mindfulness and specific group training that are rooted in psychoneuroendocrinology and use formal meditation and gentle yoga exercises. Nutritional education included counseling, comprehensive lectures, and cooking classes.

2.3.1. Fasting and Lifestyle Modification (F + LM)

Patients in this group started with two calorie-restricted vegan days (max 1200 kcal/day), followed by a 5-day modified fasting intervention (intake of 300–350 kcal/day, obtained from vegetable juices and vegetable broth). Thereafter, a stepwise reintroduction of food according to published guidelines of fasting was performed, followed by a group dietary and lifestyle modification intervention [29] (weekly 6-h multimodal sessions for a total of 10 weeks). This included lectures and teaching kitchens on a vegetarian whole-food diet with a focus on a plant-based Mediterranean diet and a modified DASH diet [30–32], intermittent fasting (rice only days once/week) [33], and recommendations for specific cardioprotective foods, such as beetroot, nuts, and olive oil.

Each session started with 20–30 min of activating exercises, and moderate aerobic exercise, i.e., walking, was introduced in a 45-min supervised training at one of the first sessions. Each session closed with a supervised training in stress reduction using progressive muscle relaxation, mindfulness meditation, or yoga. Mindfulness was further incorporated in a 90-min supervised training at one of the first sessions. The mindfulness session included a theoretical introduction into the concept of mindfulness combined with practical exercises of meditation, yoga, qigong, body scan, etc. Mindfulness in everyday life was specifically targeted during homework, where participants are taught to be mindful during routine activities, such as eating, talking, or working.

Home practice outside the session was encouraged for both aerobic exercise and relaxation/mindfulness training.

After the end of the program, in weeks 13 to 24, monthly group sessions were offered to ensure adherence.

2.3.2. Lifestyle Modification (LM)

The lifestyle intervention was similar to the one performed for the fasting and lifestyle modification group, without the fasting intervention. The program consisted of 55 h of group intervention over a period of 10 weeks. After the end of the program, in months 13 to 24, monthly group sessions were offered to ensure adherence.

2.4. Randomization

Patients were randomly allocated 1:1 to F + LM or LM by block-randomization with randomly varying block lengths, stratified by (a) study center and (b) the intake/nonintake of antihypertensive medication. The randomization list was created by a biometrician not involved in patient recruitment or assessment, using the Random Allocation Software [34]. The list was password-secured, and no person other than the biometrician was able to access it. Based on these results, the sealed, sequentially numbered opaque envelopes containing the treatment assignments were prepared. After obtaining written informed consent and baseline assessment, the study physician opened the lowest numbered envelope to reveal that patient's assignment.

2.5. Outcome Measures

Outcomes were assessed at baseline and at 1, 12, and 24 weeks after randomization by a blinded outcome assessor who was not involved in patient recruitment, allocation, or treatment. Two primary outcome measures were defined: ambulatory systolic blood pressure and the homeostasis model assessment (HOMA) index at week 12. Herein, primary outcomes and further clinical parameters are reported. Further explorative experimental variables (immune function, microbiome) are reported elsewhere [35]. Further psychometric parameters will be reported elsewhere.

2.5.1. Physician-Assessed Outcomes

Twenty-four-hour ambulatory systolic and diastolic blood pressure were measured using an validated digital blood pressure monitor (Mobil-O-Graph® PWA, I.E.M., Stolberg, Germany) [36]. Measurements at week 0 were made within a week before the start, those at week 12 within a week after the end of the intervention at the same time of day at each of the three measurement time points. The monitoring software automatically removed incorrect measurements using built-in algorithms. Clinical blood pressure was measured in the hospital by a sphygmomanometer, using the average of three consecutive measurements. Clinical blood pressure was measured at each time point and ambulatory blood pressure only at baseline at weeks 12 and 24.

Body weight was measured using the Omron BF 511 bioelectrical impedance device [37]. BMI was calculated as the weight in kilograms divided by the square of height in meters. Waist circumference was measured by two research assistants using a measuring tape in the horizontal plane exactly midway between the iliac crest and the costal arch. Measures were repeated twice, and the mean of both measures was used; if the two measures differed by more than 1 cm, both measurements were repeated. Hip circumference was measured in the horizontal plain at the maximal circumference of the hips or buttock region above the gluteal fold, whichever is larger, using the same approach as for waist circumference. Waist–hip ratio was calculated as the quotient of waist circumference and hip circumference [38]. Body fat percentage and muscle mass percentage were measured by bioelectrical impedance analysis using the Omron BF 511 bioelectrical impedance device [37].

2.5.2. Laboratory Measures

Blood samples were collected from the antecubital vein into vacutainer tubes and analyzed using the Modular P analyzer (Roche, Mannheim, Germany). Metabolic parameters included blood glucose levels, blood insulin levels, and HbA1c, and were analyzed using standard procedures. HOMA index was calculated as blood insulin level (µU/mL) × blood glucose level (mmol/L)/22.5 [39]. Further laboratory parameters included blood lipid levels (total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), uric acid, blood creatinine level, estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), insulin-like growth factor 1 (IGF-1), and interleukin 6 (IL-6).

2.5.3. PROCAM Score

Cardiovascular risk was calculated by the PROCAM (Prospective Cardiovascular Münster Study) score considering clinical (age, smoking status, diagnosis of diabetes mellitus type 2, systolic blood pressure, intake of antihypertensive medication, myocardial infarction, and/or stroke within the close family) and laboratory parameters (HDL, LDL, triglyceride, and fasting glucose level) [40]. Based on this score, the 10-year risk of an acute coronary event was calculated [40].

2.6. Safety

All adverse events occurring during the study period were recorded. Patients experiencing such adverse events were asked to see the study physician to assess their import and initiate any necessary response. Open-ended questions were used at week 1, 12, and week 24 to assess any adverse events not previously mentioned by the patients. Patients were asked to indicate any adverse events during the study period regardless of their severity or potential relationship to the study intervention.

2.7. Sample Size Calculation and Statistical Analysis

The required sample size was calculated a priori using G*Power software [41]. Based on prior research on multimodal lifestyle interventions [6,7], such as yoga [42], mindfulness [43], and Mediterranean diet [44], a between-group effect size of d = 0.5 was expected. A level 2.5% *t*-test requires a total of 64 patients per group to detect a respective group difference with a statistical power of 80%. Accounting for a potential loss in power because of a maximum of 10% dropouts, it was planned to include at least 142 patients in this trial.

All analyses were based on an intention-to-treat basis, including all participants being randomized, regardless of whether they provided a full set of data or adhered to the study protocol. Missing data were imputed by multiple means using Markov chain Monte Carlo methods [45,46], yielding a total of 50 complete datasets.

Group differences were analyzed by univariate analyses of covariance (ANCOVA), which modeled the outcome at week 1, 12, or 24 as a function of the treatment group (classified factor), the stratification factors study center (classified covariate), baseline antihypertensive medication intake (classified covariate), and the respective baseline value (linear covariate). Afterward, the 50 estimates of group differences were combined to produce overall effect size estimates, 95% confidence intervals, and *p*-values.

Thus, the analysis accounted for potential baseline differences in medication and in the respective outcomes. Inferential statistical tests for baseline differences between groups were not conducted because the CONSORT statement explicitly discourages such tests, given that baseline differences in a randomized trial are generally considered to be random.

For the primary and secondary outcomes, p-values ≤ 0.025 and ≤ 0.050, respectively, were considered significant.

All analyses were performed using the Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, release 22.0, IBM Group, Armonk, NY, USA).

3. Results

3.1. Patients

A total of 452 patients were telephone screened, and 258 were excluded because they did not meet the inclusion criteria (Figure 1). A total of 49 patients were excluded after medical assessment. A total of 145 patients were enrolled after providing informed consent and were randomized to the F + LM group (n = 73) or the LM group (n = 72). During the study period, 15 patients each were omitted during follow-up in the F + LM and LM groups (Figure 1). Participants' mean age was 59.7 ± 9.3 in the whole study population (Table 1) and about two-thirds of the participants were female, one-third of those having a university degree. Baseline characteristics were balanced between groups. Patients had a BMI of 33.3 ± 4.5 kg/m^2 (Table 1). Patients in the F + LM group attended a mean of 8.2 ± 2.3 (82.0%) out of 10 possible intervention sessions; patients in the LM group attended 7.1 ± 3.5 (71%) sessions (p = 0.124).

3.2. Primary Outcome Measures

The two primary outcome measures, 24-h ambulatory systolic blood pressure and the HOMA index at week 12, showed reductions in both groups and were not significantly different between the groups (Tables 2 and 3).

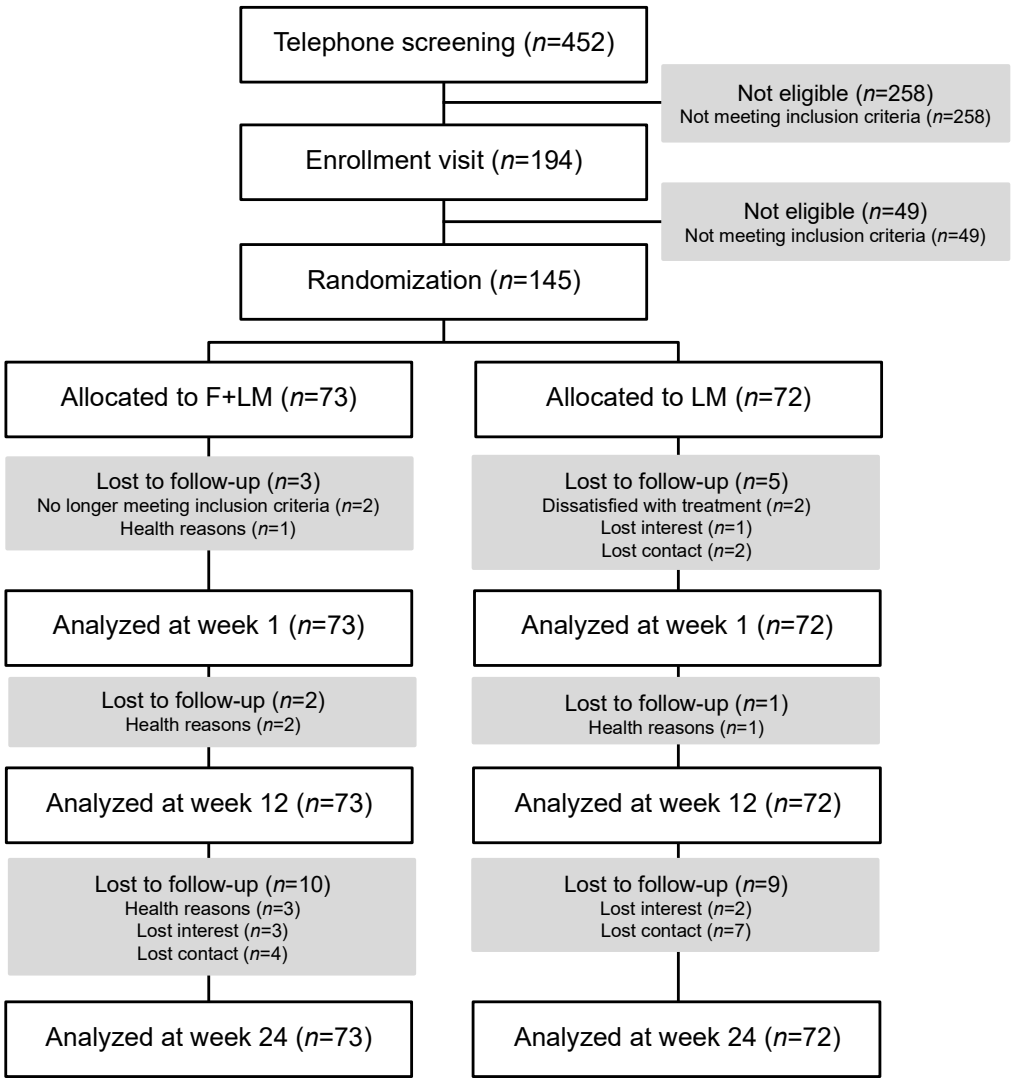

Figure 1. Study flow chart. Abbreviations: F + LM, fasting and lifestyle modification; LM, lifestyle modification.

Table 1. Baseline sociodemographic and clinical characteristics. If not otherwise denoted, values are reported as mean ± standard deviation. Abbreviations: F + LM, fasting and lifestyle modification; LM, lifestyle modification.

	Total (*n* = 145)	**F + LM (*n* = 73)**	**LM (*n* = 72)**
Sociodemographic characteristics			
Gender female *n* (%)	91 (62.8%)	48 (65.8%)	43 (59.7%)
Age years	59.7 ± 9.3	58.6 ± 10.8	60.8 ± 7.5
Marital status *n* (%)			
Single	15 (10.3%)	6 (8.2%)	9 (12.5%)
Married	98 (67.6%)	49 (67.1%)	49 (68.1%)
Divorced	21 (14.5%)	12 (16.4%)	9 (12.5%)
Widowed	5 (3.4%)	3 (4.1%)	2 (2.8%)
Education *n* (%)			
Secondary modern school ("Hauptschule") qualification	25 (17.2%)	9 (12.3%)	16 (22.2%)
High school ("Realschule") qualification	41 (28.3%)	19 (26.0%)	22 (30.6%)
A level ("Abitur")	18 (12.4%)	12 (16.4%)	6 (8.3%)
University degree	53 (36.6%)	28 (38.3%)	25 (34.7%)
Employment *n* (%)			
Employed full-time	41 (28.3%)	20 (27.4%)	21 (29.2%)
Employed part-time	19 (13.1%)	11 (15.1%)	8 (11.1%)
Occasionally	5 (3.4%)	3 (4.1%)	2 (2.8%)
On sick leave	3 (2.1%)	2 (2.7%)	1 (1.4%)
Unemployed	3 (2.1%)	2 (2.7%)	1 (1.4%)
Retired age-related	44 (30.3%)	20 (27.4%)	24 (33.3%)
Retired health-related	15 (10.3%)	7 (9.6%)	8 (11.1%)
Homekeeper	10 (6.9%)	6 (8.2%)	4 (5.6%)
Clinical characteristics			
Weight kg	97.0 ± 15.8	98.1 ± 16.1	95.9 ± 15.5
Body Mass Index kg/m^2	33.3 ± 4.5	33.7 ± 4.5	32.84.5
Diagnosis of obesity since months	65.0 ± 123.6	73.3 ± 140.7	56.5 ± 103.8
Diagnosis of hypertension since months	119.5 ± 112.4	119.3 ± 113.8	119.7 ± 111.8
Antihypertensive drugs since months	106.0 ± 108.6	98.7 ± 101.7	113.4 ± 115.4
Diagnosis of coronary artery disease *n* (%)	5 (3.4%)	2 (2.7%)	3 (4.2%)
Diagnosis of peripheral artery disease *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diagnosis of hyperlipidemia since months	62.2 ± 83.1	63.7 ± 91.9	60.7 ± 73.9
Lipid-lowering drugs since months	30.4 ± 59.0	28.3 ± 56.9	32.6 ± 61.4
Diagnosis of hyperglycemia since months	11.5 ± 39.0	10.2 ± 32.6	12.7 ± 44.8
Anti-hyperglycemic drugs since months	17.2 ± 36.1	9.0 ± 24.8	25.6 ± 43.3
Bariatric surgery *n* (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2. Effects of the study interventions on physician-assessed outcomes, the PROCAM score, and the 10-year risk of acute coronary events based on the PROCAM score. Values are expressed as mean ± standard deviation. Bold *p*-values indicate significant group differences ($p < 0.05$). Abbreviations: BP, blood pressure; CI, confidence interval; F + LM, fasting and lifestyle modification; LM, lifestyle modification; NA, not assessed.

Outcome	Group	Week 0	Week 1	Week 1		Week 12	Week 12		Week 24	Week 24	
				Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*
Ambulatory systolic BP	F + LM	131.1 ± 9.1	NA	NA	NA	126.9 ± 8.9	−0.5 (−5.0, 3.9)	0.813	130.0 ± 9.0	−1.2 (−5.6, 2.1)	0.366
	LM	132.5 ± 11.0	NA			129.3 ± 10.8			130.7 ± 9.7		
Ambulatory diastolic BP	F + LM	80.1 ± 8.2	NA	NA	NA	78.4 ± 8.2	−1.3 (−4.8, 2.1)	0.450	79.1 ± 7.6	−1.0 (−4.2, 2.3)	0.501
	LM	82.0 ± 8.3	NA			80.2 ± 8.7			80.6 ± 8.5		
Clinical systolic BP	F + LM	138.9 ± 14.4	130.9 ± 16.1	−4.1 (−11.3, 3.2)	0.270	133.7 ± 13.5	1.6 (−4.4, 7.5)	0.609	138.3 ± 14.4	2.5 (−3.6, 8.5)	0.417
	LM	141.2 ± 19.0	136.2 ± 14.5			134.5 ± 12.3			135.2 ± 10.8		
Clinical diastolic BP	F + LM	88.3 ± 10.6	81.5 ± 9.7	−4.8 (−9.6, −0.06)	0.047	86.5 ± 11.2	3.4 (−0.7, 7.5)	0.106	88.7 ± 10.3	−2.7 (−6.8, 1.4)	0.200
	LM	89.5 ± 11.2	87.0 ± 11.1			86.7 ± 8.7			87.7 ± 8.8		
Weight	F + LM	98.1 ± 16.1	93.2 ± 15.2	−4.8 (−5.5, −4.1)	<0.001	92.8 ± 15.4	−3.5 (−5.1, −1.8)	<0.001	93.3 ± 15.5	−2.7 (−4.8, −0.5)	0.014
	LM	95.9 ± 15.5	95.8 ± 15.3			94.3 ± 15.1			93.8 ± 15.1		
Body Mass Index	F + LM	33.7 ± 4.5	32.1 ± 4.3	−1.7 (−2.0, −1.4)	<0.001	31.9 ± 4.3	−1.3 (−1.9, −0.7)	<0.001	32.1 ± 4.4	−1.0 (−1.8, −0.3)	0.007
	LM	32.8 ± 4.5	32.8 ± 4.4			32.3 ± 4.4			32.1 ± 4.3		
Waist circumference	F + LM	114.1 ± 10.5	110.7 ± 11.2	−2.6 (−5.0, −0.2)	0.035	108.2 ± 11.5	−3.5 (−5.8, −1.1)	0.004	108.9 ± 10.9	−1.2 (−6.3, 3.9)	0.633
	LM	112.1 ± 11.1	111.3 ± 11.1			109.4 ± 10.9			107.2 ± 16.5		
Waist/hip Ratio	F + LM	1.0 ± 0.5	1.0 ± 0.1	−0.01 (−0.05, 0.03)	0.486	1.0 ± 0.1	−0.03 (−0.06, 0.01)	0.192	1.0 ± 0.1	−0.01 (−0.06, 9.04)	0.658
	LM	1.0 ± 0.2	1.0 ± 0.1			1.0 ± 0.1			1.0 ± 0.1		

Table 2. *Cont.*

Outcome	Group	Week 0	Week 1	Week 1		Week 12	Week 12		Week 24	Week 24	
				Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*
Body fat percentage	F + LM	41.5 ± 8.9	42.0 ± 9.1	0.6 (−0.8, 1.9)	0.420	39.4 ± 8.9	−2.2 (−3.4, 0.9)	0.001	40.1 ± 9.2	−1.0 (−2.6, 0.6)	0.214
	LM	39.4 ± 8.6	39.9 ± 8.6			39.2 ± 8.7			39.1 ± 8.8		
PROCAM Score	F + LM	48.4 ± 13.6	45.4 ± 13.2	−2.4 (−5.6, 0.8)	0.139	45.8 ± 13.4	−3.4 (−6.7, −0.2)	0.048	47.3 ± 12.7	−2.0 (−5.5, 1.4)	0.242
	LM	50.1 ± 11.8	50.9 ± 13.2			49.7 ± 12.9			50.0 ± 11.6		
10-year coronary risk	F + LM	14.9 ± 12.6	12.1 ± 11.2	−4.9 (−9.5, −0.4)	0.033	12.6 ± 11.8	−6.2 (−10.3, −2.0)	0.004	13.7 ± 12.0	−3.8 (−8.2, 0.5)	0.080
	LM	16.0 ± 13.6	17.4 ± 15.2			15.5 ± 12.9			15.8 ± 12.5		

Table 3. Effects of the study interventions on laboratory parameters. Values are expressed as mean ± standard deviation. Bold *p*-values indicate significant group differences ($p < 0.05$). Abbreviations: BP, blood pressure; CI, confidence interval; CRP, C-reactive Protein; eGFR, estimated glomerular filtration rate; F + LM, fasting and lifestyle modification; HbA1c, glycated hemoglobin; HOMA, homeostasis model assessment; IGF, insulin-like growth factors; IL, interleukin; LM, lifestyle modification.

Outcome	Group	Week 0	Week 1	Week 1		Week 12	Week 12		Week 24	Week 24	
				Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*
HOMA index	F + LM	3.5 ± 2.5	2.0 ± 1.6	−0.8 (−1.7, −0.1)	0.046	3.2 ± 2.2	0.2 (−0.7, 1.1)	0.676	3.0 ± 1.9	−0.2 (−0.9, 0.6)	0.639
	LM	3.7 ± 2.4	3.4 ± 2.3			3.4 ± 2.2			3.6 ± 2.0		
Blood glucose	F + LM	113.3 ± 18.9	107.0 ± 18.3	−10.3 (−19.0, −1.6)	0.022	106.2 ± 13.4	−7.7 (−17.2, 1.9)	0.113	110.5 ± 12.8	−7.7 (−13.5, −1.8)	0.011
	LM	110.1 ± 22.0	114.4 ± 26.9			109.3 ± 24.4			111.5 ± 20.3		
Blood insulin	F + LM	12.4 ± 7.3	8.0 ± 5.4	−2.9 (−5.3, −0.4)	0.024	11.6 ± 6.6	0.9 (−1.4, 3.3)	0.428	10.9 ± 5.9	−0.5 (−2.7, 1.7)	0.641
	LM	13.0 ± 7.5	12.4 ± 7.0			11.9 ± 5.9			12.4 ± 5.7		
HbA1c	F + LM	5.9 ± 0.5	5.8 ± 0.5	−0.2 (−0.4, −0.05)	0.010	5.8 ± 0.5	−0.08 (−0.3, 0.1)	0.485	5.9 ± 0.4	−0.2 (−0.4, 0.04)	0.122
	LM	5.9 ± 0.7	6.0 ± 0.7			5.9 ± 0.7			6.0 ± 0.7		

Table 3. *Cont.*

Outcome	Group	Week 0	Week 1	Week 1		Week 12	Week 12		Week 24	Week 24	
				Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*		Group Difference (95% CI)	*p*
Total cholesterol	F + LM	224.4 ± 50.0	208.4 ± 47.6	−6.9 (−25.3, 11.5)	0.458	214.3 ± 40.6	−4.0 (−19.7, 11.7)	0.616	227.7 ± 39.9	9.5 (−9.7, 27.9)	0.339
	LM	224.3 ± 48.3	224.9 ± 47.5			212.8 ± 42.2			216.8 ± 42.0		
HDL cholesterol	F + LM	53.4 ± 16.0	49.2 ± 12.0	−1.1 (−4.4, 2.3)	0.531	53.4 ± 14.7	3.3 (−1.0, 7.7)	0.134	55.3 ± 13.3	5.1 (1.5, 8.8)	0.007
	LM	56.6 ± 19.0	54.1 ± 16.0			53.1 ± 15.7			53.5 ± 15.1		
LDL cholesterol	F + LM	140.2 ± 37.3	134.1 ± 40.3	−0.9 (−16.3, 14.5)	0.904	135.2 ± 34.5	−3.6 (−17.1, 9.9)	0.598	144.9 ± 32.1	7.1 (−7.7, 21.9)	0.344
	LM	139.6 ± 43.5	142.3 ± 42.6			132.8 ± 37.4			137.8 ± 37.5		
Triglyceride	F + LM	188.0 ± 210.6	116.4 ± 53.9	−48.9 (−81.0, −16.9)	0.003	157.4 ± 89.5	−23.0 (−58.2, 12.1)	0.197	157.3 ± 93.9	−21.9 (−59.4, 15.6)	0.250
	LM	175.5 ± 111.1	169.9 ± 93.4			175.3 ± 101.9			161.0 ± 78.4		
Uric acid	F + LM	6.3 ± 1.7	8.0 ± 2.2	1.0 (0.1, 1.9)	0.026	6.3 ± 1.6	−0.1 (−0.9, 0.6)	0.710	6.2 ± 1.6	0.1 (−0.5, 0.7)	0.650
	LM	6.6 ± 1.5	6.7 ± 1.7			6.2 ± 1.5			6.2 ± 1.2		
Creatinine	F + LM	0.9 ± 0.2	1.0 ± 0.2	0.04 (−0.05, 0.1)	0.383	0.9 ± 0.2	−0.03 (−0.1, 0.04)	0.354	0.8 ± 0.2	−0.04 (−0.1, 0.02)	0.187
	LM	0.9 ± 0.2	0.9 ± 0.2			0.9 ± 0.2			0.9 ± 0.2		
eGFR	F + LM	83.5 ± 15.7	73.4 ± 17.5	−11.9 (−21.8, −2.0)	0.019	85.8 ± 13.6	1.4 (−6.4, 9.1)	0.728	86.6 ± 14.6	2.4 (−6.1, 11.0)	0.577
	LM	82.4 ± 14.5	81.5 ± 14.5			82.9 ± 13.6			82.1 ± 12.2		
CRP	F + LM	0.4 ± 0.4	0.5 ± 0.4	0.03 (−0.1, 0.2)	0.677	0.4 ± 0.5	0.04 (−0.1, 0.2)	0.628	0.4 ± 0.5	0.2 (0.03, 0.4)	0.024
	LM	0.3 ± 0.3	0.4 ± 0.3			0.3 ± 0.3			0.4 ± 0.3		
IGF-1	F + LM	119.9 ± 38.1	104.1 ± 40.6	−13.6 (−28.8, 1.5)	0.077	123.7 ± 38.6	−7.6 (−20.2, 5.0)	0.235	126.5 ± 40.6	2.4 (−11.7, 16.6)	0.736
	LM	126.2 ± 48.2	120.0 ± 44.2			129.9 ± 43.7			128.4 ± 43.7		
IL-6	F + LM	3.1 ± 2.0	2.8 ± 2.7	−1.2 (−2.5, −0.005)	0.049	3.4 ± 4.7	−1.5 (−3.5, 0.5)	0.149	2.9 ± 1.7	−0.5 (−1.5, 0.6)	0.358
	LM	2.8 ± 2.2	3.1 ± 2.8			3.7 ± 4.2			3.2 ± 1.6		

3.3. Physician-Assessed Outcomes and PROCAM Score

At week 1, after the fasting week, the clinical diastolic blood pressure, weight, BMI, waist circumference, and the 10-year risk of acute coronary events (based on the PROCAM score) were significantly lower in the F + LM group than in the LM group (Table 2, Figure 2). While these effects were maintained at week 12, along with further effects on body fat percentage and the PROCAM score, only weight and BMI were lower in the F + LM group at week 24 (Table 2).

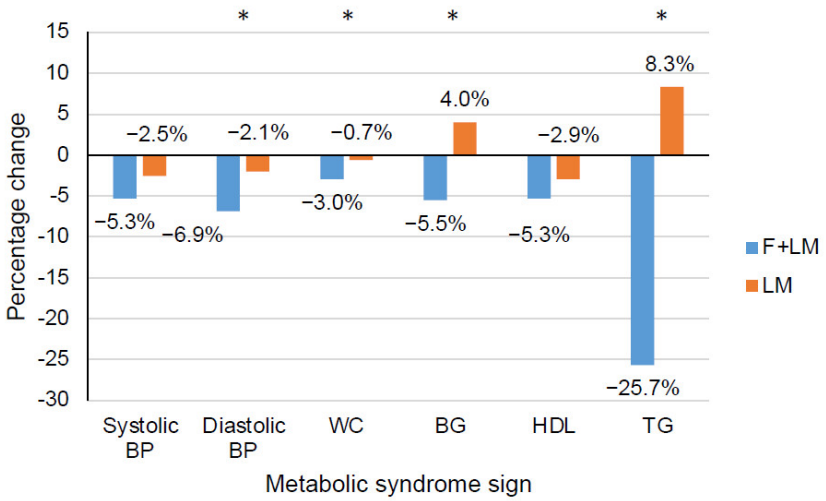

Figure 2. Percentage change in diagnostic signs of the metabolic syndrome after the 5-day fasting period (F + LM) or 5-day waiting period (LM). Abbreviations: BG, blood glucose level; BP, blood pressure; F + LM, fasting and lifestyle modification; HDL, high-density lipoprotein cholesterol; LM, lifestyle modification; TG, triglycerides; WC, waist circumference; *, $p < 0.05$.

3.4. Laboratory Parameters

Group differences favoring the F + LM group over the LM group were found after the fasting week for HOMA index, blood glucose level, blood insulin level, HbA1c, triglyceride levels, and IL-6 (Table 3, Figure 2). Uric acid and eGFR significantly worsened in the F + LM group compared to the LM group after the fasting week. None of these group differences persisted at week 12. However, further positive effects favoring F + LM over LM at week 24 were found for blood glucose level and HDL cholesterol (Table 2). CRP was higher in F + LM compared to LM at week 24.

3.5. Safety

One serious adverse event each occurred in both groups. In the F + LM group, an acute diverticulitis occurred in a patient with a known diverticulosis; a causal relationship to the study intervention was rated as unlikely. The patient completely recovered after sigmoid resection and stationary treatment. In the LM group, a patient had suffered a "trauma" (physical and psychological), resulting in a hospitalization; further details could not be elicited as the patient did not want to give further information. A total of 73 minor adverse events occurred in 43 patients in the F + LM group, and a total of 51 minor adverse events occurred in 32 patients in the LM group (Table S1 in the Supplementary Material).

4. Discussion

No significant between-group differences were found in the two primary outcomes, 24-h systolic blood pressure and HOMA index, at week 12 in patients with metabolic syndrome. However, there were interesting exploratory findings suggesting benefits from fasting in this patient population. In patients initially fasting for 5 days, lower body weight and BMI values were found at all three assessment points compared to the non-fasting group along with further, mainly short-term, anthropometric and laboratory differences.

Markedly, all parameters of the metabolic syndrome except for HDL cholesterol showed significant improvement after the fasting period compared to the non-fasting period. Both interventions were safe.

Trial participants were demographically heterogeneous. More than 60% were women. The distributions of educational attainment were broad but slightly skewed toward persons with higher education. The inclusion criteria of the study included a large proportion of patients who were German adults with metabolic syndrome. These aspects of the study suggest that the study results should be applicable to a large proportion of the German population.

The beneficial augmenting cardiometabolic effects of fasting are in line with previous studies [22,23,26]. Calorie restriction and fasting have been argued to reduce cardiovascular risk; however, this was predominantly demonstrated in animal models [47,48], uncontrolled studies [23], and studies including time-restricted eating, intermittent fasting, and fasting-mimicking diets [26]. In a large observational study [23], weight loss increased and abdominal circumference decreased with the length of the fasting period. Beneficial effects on blood pressure, blood lipids, and glycaemia were also shown.

At least in the short-term, the 6% absolute risk reduction in cardiovascular events in this study corroborates these findings. Proposed mechanisms for risk reduction include reductions in age-associated changes in the heart and vessels as well as reduced levels of apoptosis, insulin and IGF-1 signaling, enhanced autophagy, and ischemic preconditioning [24,47].

Minor reduction in calculated glomerular filtration was not persistent and might be attributed to mild protein catabolism [23]. Likewise, increased uric acid levels during fasting are known in the literature but have not been associated with symptomatic gout [22,23]. On the one hand, the increased concentration of uric acid is probably due to a slight initial increase in protein catabolism. On the other hand, once the levels of ketone bodies rise in the serum, uric acid is being retained in the kidneys due to both substances competing for tubular secretion and ketone bodies being preferentially secreted during fasting [49]. Prior studies found no deterioration of renal function [23]. Nevertheless, the effect of fasting on kidney function must be further investigated.

Our study has some important limitations. First, the main limitation is the lack of effects at week 24. Since the primary assessment time point was the end of the lifestyle modification programs, the short-term effects of fasting can be regarded as preliminary only. While the interventions included dietary advice, fasting was used only once and no approaches to maintain the effects of fasting in the medium and longer term, such as regular intermittent fasting or repeated cycles of fasting or fasting-mimicking diets, as recently suggested, were used [15,26]. It seems likely that the mean difference between groups expected in the sample size calculation was chosen too optimistically in view of the relatively strong control group. Accordingly, the lack of effects at week 24 could also be attributed to a lack of power. Second, adherence to the (dietary) interventions was not assessed in detail (e.g., via nutritional protocols). Third, the time intensity of the two programs was slightly different, as more elements were implemented in the F + LM group due to the fasting component.

Against the background of the above-mentioned limitations, future studies should undertake efforts to maintain the fasting effect by repeating fasting cycles or the additive use of intermittent fasting. Hereby, relevant and delineated mechanisms behind the metabolic switch of fasting, such as endocrine and neurobiological effects, autophagy and microbiome-related effects should be considered and translated to clinical protocols [47,50]. Future studies will likely require substantially larger sample sizes to detect group differences in e.g., coronary risk scores, if such effects do exist.

Most health insurance companies do not cover multimodal lifestyle modification interventions for the prevention and treatment of metabolic syndrome. Given the substantial health benefits of lifestyle modification interventions to improve cardiovascular parameters, it is time to consider how such programs might be implemented, particularly for patients

at increased cardiovascular risk. The costs of such programs should be weighed against the benefits of preventing heart disease, hypertension, diabetes, and other conditions, thereby avoiding the need for potentially costly medical treatments.

5. Conclusions

While the beneficial effects of fasting were not preserved in week 24, fasting induced relevant short-term effects in patients with metabolic syndrome. Fasting can thus be considered as a starting point for treating metabolic syndrome. However, it remains to be investigated how the effects of fasting can be maintained in the medium and longer term. Ultimately, a population-wide adoption of a healthy lifestyle as implemented in the study interventions may reduce the societal burden of cardiovascular diseases.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11164751/s1, Table S1: Type and number of adverse events in the two intervention groups.

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2.2 Pflanzenbasierte Ernährung für die Herzgesundheit – Daten zu Nährstoffprofilen aus einer randomisierten kontrollierten Studie

Eine PBD kann für Patienten mit kardiovaskulären Risikofaktoren günstige Effekte haben [107-112]. Jedoch kann eine unzureichend geplante PBD auch Mangelzustände an bestimmten Makro- und Mikronährstoffen induzieren [113, 114]. Patienten mit erhöhten kardiovaskulären Risikofaktoren wurden in der sog. CardioVeg-Studie randomisiert entweder einer PBD-Intervention (n = 36; acht 90-minütige Gruppensitzungen innerhalb von 8 Wochen, einschließlich zwei 120-minütiger Kocheinheiten) oder einer Warteliste-Kontrollgruppe zugewiesen, deren Teilnehmer acht Wochen lang eine omnivore Ernährung beibehalten sollten (n = 34). Die Nährstoffprofile der Patienten wurden mit dreitägigen Wiegeprotokollen zu Baseline und nach acht Wochen erfasst und ernährungswissenschaftlich ausgewertet. Außerdem wurden die Ergebnisse mit den aktuellen Ernährungsempfehlungen der Fachgesellschaften für Ernährung in Deutschland, Österreich und der Schweiz verglichen. Darüber hinaus wurden auch klinische Parameter (anthropometrische Daten/Labordaten u.a.) erhoben.

Auch wenn – SARS-CoV-2-Pandemie bedingt – nur Daten einer Teilstichprobe ausgewertet werden konnten (n = 18 in der PBD-Gruppe und n = 19 in der Kontrollgruppe, bei denen vollständige Ernährungsprotokolle vorlagen) führte die Arbeit doch zu interessanten Erkenntnissen: Eine PBD zeigte günstige Effekte für die kardiometabolische Gesundheit, z.B. konnte eine geringere Energiedichte der Nahrung, ein höherer Verzehr von Ballaststoffen, eine geringere Aufnahme von Cholesterin und gesättigten Fettsäuren und eine geringere Aufnahme von Salz gezeigt werden. Die empfohlene Zufuhr der meisten Vitamine und Mineralstoffe wurde erfüllt, mit Ausnahme von Vitamin B12 in der PBD-Gruppe. Bei zwei kritischen Nährstoffen (Vitamin D, Jod) lag die Zufuhr in beiden Gruppen unter den empfohlenen Werten. Im Vergleich zur Kontrollgruppe führte die PBD-Intervention nach 8 Wochen zu einem signifikanten Rückgang von Körpergewicht, BMI, Taillenumfang, HbA1c und Nüchternblutzucker. Zusammenfassend konnte gezeigt werden, dass die PBD ein günstigeres Nährstoffprofil für die kardiovaskuläre Gesundheit aufwies als die omnivore Ernährungsweise der Kontrollgruppe.

nutrients

MDPI

Article

Does a Plant-Based Diet Stand Out for Its Favorable Composition for Heart Health? Dietary Intake Data from a Randomized Controlled Trial

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Abstract: A plant-based diet (PBD) can provide numerous health benefits for patients with cardiovascular risk factors. However, an inadequately planned PBD also bear the potential for deficiencies in certain macro- and micronutrients. The present study analyzed nutrient profiles of individuals who adopted a PBD as part of the CardioVeg study. Participants with cardiovascular risk factors were randomly assigned to either a whole-food PBD intervention (n = 36; eight 90 min group meetings including two 120 min cooking sessions) or a control group asked to maintain an omnivorous diet (n = 34) for eight weeks. Food intake data were collected using three-day weighed food records and analyzed with NutriGuide software, including the German Nutrient Data Base (German: Bundeslebensmittelschlüssel). Nutrient intake was compared before and after eight weeks as well as between the groups. The results for both groups were then contrasted to the current dietary recommendations published by the societies for nutrition in Germany, Austria, and Switzerland. Moreover, anthropometric/laboratory data and ambulatory blood pressure monitoring were determined at baseline and after 8 weeks. Data of a subsample (n = 18 in the PBD group and n = 19 in the control group) were used for the present analyses of the dietary intake data. A PBD yielded several benefits including (but not limited to) a lower energy density, a lower intake of cholesterol and saturated fat, an increased consumption of fiber, and a lower intake of salt. Recommended intakes of most vitamins and minerals were generally met, except for vitamin B12 in the PBD group. A low intake of several other critical nutrients (vitamin D, iodine) was observed in both groups. Compared with the control group, PBD resulted in a significant decrease in body weight, body mass index, waist circumference, HbA1c, and fasting blood glucose after 8 weeks. Overall, it can be concluded that a PBD had a more favorable nutrient composition for cardiovascular health than the omnivorous dietary pattern of the control group.

Keywords: plant-based diet; nutrient supply; cardiovascular risk; dietary intake; vegan; vegetarian; micronutrients; macronutrients

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1. Introduction

Plant-based diets (PBD) are becoming increasingly popular for their many health benefits, both in the prevention and treatment of disease. PBD have been shown to convey protective effects against obesity, diabetes, and other metabolic disorders [1–3]. In addition, there is mounting evidence that a plant-based diet is beneficial for heart health [4–9].

PBDs maximize the consumption of nutrient-dense plant foods while minimizing (or eliminating) processed foods, oils, and animal products [10,11]. Thus, PBD are abundant in vegetables, fruits, legumes, and other unprocessed plant products. Systematic reviews

and meta-analyses have demonstrated that the intake of fruits and vegetables [12–16], legumes [17], dietary fiber [18], nuts [19], and unsaturated fatty acids [20] provide multiple health benefits and are associated with a reduced frequency of cardiovascular events. The consumption of animal products (including red and processed meats) on the other hand is associated with an increased cardiovascular risk [21].

Results from the Adventist cohort study showed that people who eat a PBD reduced their risk of developing hypertension by almost 75% [22]. Vegetarian diets were also associated with significantly lower medical care expenditure in patients with cardiovascular disease and were suggested as an effective strategy to alleviate the medical-economic burden in selected populations [23].

Although PBD may offer numerous health benefits, it is often claimed that inadequately planned and non-diversified PBDs bear the potential of macro- and micronutrient deficiencies [24,25]. According to the Deutsche Gesellschaft für Ernährung (DGE, German Nutrition Society), it is "difficult or impossible to achieve an adequate supply of some nutrients with a purely plant-based diet" [26]. Vitamin B12, among others, is the most critical nutrient [26]. Further potentially critical nutrients are protein, long-chain n-3 fatty acids, as well as other vitamins (riboflavin, vitamin D) and minerals (calcium, iron, iodine, zinc, and selenium) [26].

We conducted a randomized controlled trial (the "CardioVeg" study) to investigate the effects of a PBD on cardiovascular risk factors. The aim of this dietary intake data analysis was to evaluate the macro- and micronutrient intake before and after an eight-week PBD intervention in patients with cardiometabolic risk factors. The results were contrasted with the current dietary recommendations published by the Societies for Nutrition in Germany (DGE), Austria (Österreichische Gesellschaft für Ernährung, ÖGE) and Switzerland (Schweizerische Gesellschaft für Ernährung, SGE)—the so-called D-A-CH (D—Deutschland, Germany), A—Austria, CH—Confoederatio Helvetica, Switzerland) recommendations [27]. We hypothesized that a properly composed PBD diet could meet all D-A-CH recommendations for macro- and micronutrient (except for vitamin B12) and may even excel with a beneficial dietary composition for cardiovascular health.

2. Materials and Methods

The CardioVeg study was a randomized controlled trial that examined the effects of PBD on health outcomes in relation to cardiovascular risk factors. Participants with an increased cardiometabolic risk (see Table 1) were randomized to follow a PBD (plant-based group, PBG) or to continue an omnivorous diet (waiting list control group, CG).

The CardioVeg study had been approved by the ethics committee of the Charité-Universitätsmedizin Berlin (approval number: EA4/025/19). Written, informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (NCT03901183) prior to patient recruitment. The present analysis is limited to a subsample of participants in the CardioVeg study. Only individuals that submitted a complete and plausible dietary protocol were considered. Further clinical parameters will be reported elsewhere. The allocation was based on a computer-generated randomization protocol and was supervised by a certified biostatistician. Due to an obvious lifestyle intervention, the assignment could not be blinded for participants.

2.1. Dietary Intervention

Participants in the PBG were asked to follow an ad libitum whole-food PBD, consisting of vegetables, grains, legumes, and fruits. We instructed participants to avoid animal products to the greatest extent possible [11,28]. The term PBD is frequently used as an umbrella term comprising various dietary patterns: veganism (complete avoidance of animal products), pescetarianism (including seafood), ovo-vegetarianism (including eggs), lacto-vegetarianism (including dairy products), ovo-lacto-vegetarianism (including eggs and dairy products) [28–30]. In our study, participants were free to choose their dietary pattern from the above-mentioned selection. All participants received nutritional

counseling to establish a healthy whole-food PBD. The sessions were held by certified dietitians and nutrition scientists within eight group sessions of 90 min over a total period of 8 weeks in Berlin. During the counseling sessions, the nutritionists illustrated a whole-food plant-based diet. The sessions were structured into themes such as healthy plant-based proteins, fats, complex carbohydrates, vitamins, etc. Food recipes were handed out and substitutes for animal foods were recommended. At the weekly meetings, progress was shared initially, and participants exchanged their experience with the nutritionist. The consultation included 2 cooking sessions (120 min each) focusing on practical suggestions to implement a well-balanced PBD. Due to the COVID-19 pandemic, external regulations forced us to conduct the nutrition course online after inclusion of half of the subjects. An 8-week intervention period represents a time frame that is considered acceptable, and not too long to commit to weekly counseling sessions, and at the same time long enough to develop healthy habits [31].

Table 1. Inclusion and exclusion criteria for the CardioVeg study.

Inclusion Criteria	Exclusion Criteria
Men and women aged 25 to 75 and diagnosed with: • hypertension (from >140 mmHg systolic and/or >90 mmHg diastolic), • central obesity (waist circumference > 94 cm for men, >80 cm for women), • A non-vegetarian diet in the past 6 months (at least 4× meat and/or meat products per week, at least 5× dairy products per week) • No fasting, no specific diet or change of diet in the last 2 months • Weight stable over the last two months (±3 kg) • Medication unchanged for at least one month	• a poor general condition • diagnosed coronary heart disease • diabetes mellitus type I • cerebrovascular disease • severe mental illness • severe acute or chronic comorbidity • pregnancy and lactation or planned pregnancy in the next 6 months • eating disorder • alcohol consumption more than 2 beers 0.5l or 2 wines 0.2l per day • no alcohol abstinence 48 h before blood samples possible • over 5 cigarettes/day • medication that affect weight • antibiotics within the last 6 months • major surgery <6 months prior to randomization • BMI over 40 kg/m^2 • existing vegetarian or plant-based diet • bariatric surgery • simultaneous participation in another clinical trial • participation in a clinical trial within the last 3 months prior to inclusion in the study • lack of consent to participate in the study

The waiting list CG was instructed to maintain their current omnivorous diet but was offered to participate in the nutritional counseling program after completion of the last study visit.

Participants received no remuneration.

2.2. Dietary Intake and Monitoring

Dietary intake was assessed using 3-day weighed food records (3 consecutive days, with 2 weekdays and one weekend day). Participants were instructed and given templates to accurately protocol food intake (portion sizes of various foods and beverages consumed). These records were logged by all participants at baseline and after 8 weeks at the same time of the study visits, when also laboratory and anthropometric measurements were assessed (see Section 2.3).

Dietary intake data were collected and digitalized by a nutrition scientist, using the Software NutriGuide 4.7 Plus (Nutri-Science GmbH, Hausach, Germany). NutriGuide performs its analysis based on the nutritional charts of the German Nutrient Data Base (German: Bundeslebensmittelschlüssel, BLS 3.02), containing about 14.800 food items split by their nutrients. Three-day average values for energy, carbohydrate, protein, fat, and micronutrient intake were calculated. Absolute values and percentage values in relation to the Daily Recommended Intake (DRI) of the D-A-CH were used for further analysis. The D-A-CH reference values for nutrient intake are published collaboratively by the Societies for Nutrition in Germany (DGE), Austria (ÖGE) and Switzerland (SGE) [27].

The daily recommended intake was individually adjusted to gender, age, and estimated to the physical activity level (PAL) of 1.6 indicating a sedentary lifestyle (with occasionally additional energy expenditure for walking and standing activity). The gender- and age-specific DRI for a PAL of 1.6 can be obtained from the Supplementary Materials, Table S1 [27].

2.3. Anthropometric/Laboratory Data and Blood Pressure

Anthropometric and laboratory data as well as ambulatory blood pressure monitoring (ABPM) were determined at baseline and after 8 weeks. Blood tests assessed blood sugar, insulin resistance (Homeostasis Model Assessment, HOMA-Index), hemoglobin A1c (HbA1c), triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol levels. Blood samples were collected after a 10 h overnight fast from the antecubital vein into vacutainer tubes and analyzed using the Modular P analyzer (Roche, Mannheim, Germany).

Trained staff measured participants' weight and height, which was used to calculate body mass index (BMI). Abdominal obesity was determined by waist circumference, which was measured by the study nurse at midpoint between the last rib and the iliac crest. Twenty-four-hour ambulatory systolic and diastolic blood pressure were measured using a digital blood pressure monitor validated for clinical studies (Spacelabs 90217A). The monitoring software automatically removed incorrect measurements using build-in algorithms.

2.4. Statistical Analysis

SPSS Version 27.0 and Microsoft Excel were used to complete all statistical analyses. A p-value of <0.05 was used to determine statistical significance.

- Data are presented as means ± standard deviations and 95% confidence interval
- For laboratory data the Shapiro–Wilk test was used to determine normality.
- When normality was confirmed, participants characteristics and biochemistry was analyzed with a two samples t-test to assess differences between groups.
- Dietary nutrient intake was compared within the groups with the related-samples Wilcoxon signed rank test.
- Treatment effect and p-value between groups was determined using the Mann–Whitney-U test, comparing the difference of nutrient intake (Δ = intake at baseline vs. intake after 8 weeks). The difference is depicted as mean and 95% confidence interval (CI).

3. Results

3.1. Randomization/Participants

Participants (n = 70) with increased cardiometabolic risk factors were randomized to follow a plant-based (n = 36) or to continue an omnivorous diet (n = 34). Patients were recruited between May 2019 and February 2021. From initially 70 participants recruited to complete the CardioVeg study, 7 participants withdrew. Twenty-two participants did not return their dietary records for nutritional analyses and were thus excluded from the present analysis. We removed four participants due to noncompliance with the study protocol. A total sample size of 37 (n = 18 in the PBG and n = 19 in the CG) was used for the present analyses of the dietary intake data. Figure 1 shows the participant inclusion flow chart for the present analysis.

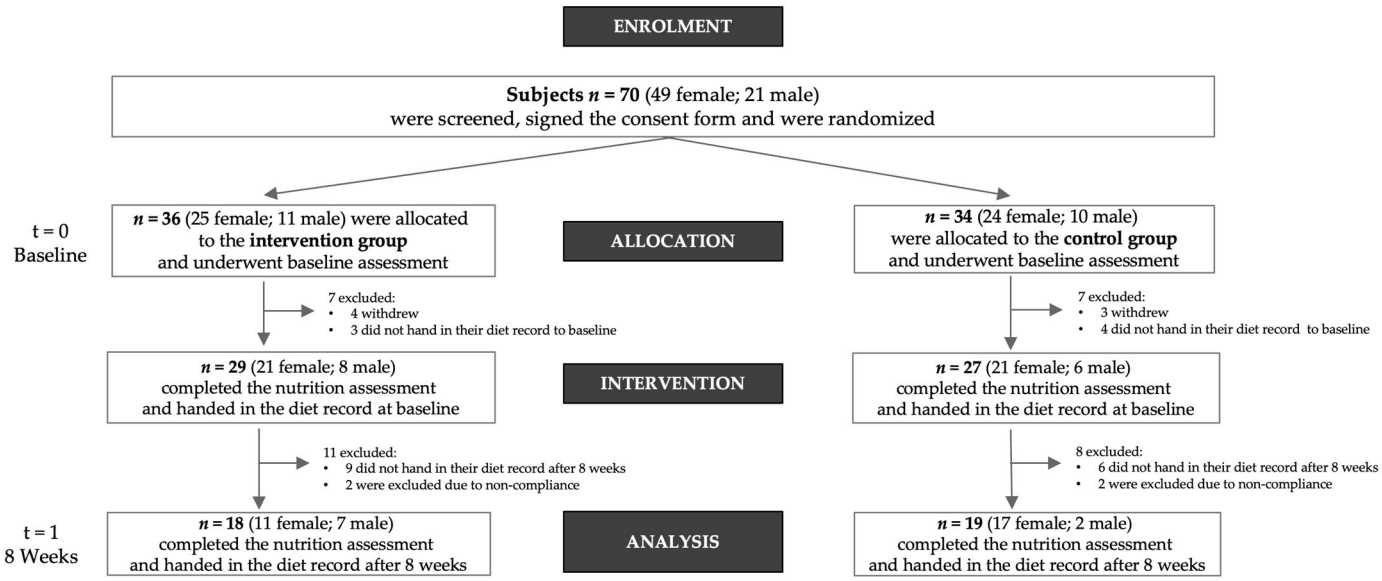

Figure 1. Flowchart of the study population.

The majority of participants of this subgroup were women: 61.1% in the PBG (n = 18) and 89.5% in the CG (n = 19). The mean age of participants in the PBG was 61.1 ± 7.0 years and 62.8 ± 7.0 years in the CG.

3.2. Anthropometric/Laboratory Data and Blood Pressure

Table 2 shows anthropometric and laboratory data at baseline and after 8 weeks. The PBD resulted in a significant decrease in body weight after 8 weeks (mean difference [95% CI] = −3.5 kg [−5.3–−1.7]), BMI (−1.2 kg/m^2 [−1.8–−0.6]), and waist circumference (−3.2 cm [−5.1–−1.3]), see Table 2. In addition to that, we observed a significant reduction in HbA1c (−1.7 mmol/mol [−2.8–−0.6]) and fasting blood glucose levels (−5.8 mg/dl [−9.1–−2.6]) in the PBG. Compared to the CG, all above values were significant (Table 2). HOMA Index, triglycerides, cholesterol (LDL, HDL) as well as ABPM were not significant between the groups, although PBG showed more favorable effects.

Table 2. Characteristics of the study population before and after 8 weeks.

	Plant-Based Group (n = 18)			Control Group (n = 19)			
	Baseline	**Week 8**	**Δ [95% CI]**	**Baseline**	**Week 8**	**Δ [95% CI]**	***p*-Value ***
Anthropometrics							
Weight [kg]	93.0 ± 16.6	89.5 ± 15.5	−3.5 [−5.3–−1.7]	80.7 ± 11.9	80.4 ± 12.1	−0.3 [−1.1–0.5]	0.002
Body mass index [kg/m^2]	31.7 ± 4.6	30.5 ± 4.1	−1.2 [−1.8–−0.6]	29.5 ± 4.5	29.4 ± 4.8	−0.1 [−0.4–0.3]	0.002
Waist circumference [cm]	109.9 ± 11.1	106.7 ± 9.4	−3.2 [−5.1–−1.3]	101.2 ± 7.0	101.5 ± 7.1	0.2 [−0.9–1.4]	0.004
Laboratory data							
Fasting blood glucose [mg/dl]	99.7 ± 15.5	93.9 ± 12.9	−5.8 [−9.1–−2.6]	93.1 ± 16.2	92.5 ± 15.1	−0.6 [−3.9–2.8]	0.042
HbA1c [mmol/mol]	40.1 ± 6.5	38.4 ± 5.4	−1.7 [−2.8–−0.6]	36.5 ± 3.1	36.8 ± 3.8	0.3 [−0.5–1.2]	0.009
HOMA Index	3.7 ± 2.7	2.9 ± 1.8	−0.8 [−1.4–−0.1]	2.6 ± 1.9	2.4 ± 1.7	−0.2 [−0.6–0.3]	0.170
Triglycerides [mg/dl]	112.1 ± 36.5	126.6 ± 48.5	14.6 [−2.5–31.6]	120.1 ± 58.1	135.6 ± 76.7	15.6 [−1.0–32.2]	0.936
Cholesterol [mg/dl]	214.1 ± 26.8	198.7 ± 28.1	−15.4 [−27.4–−3.5]	227.4 ± 46.1	223.9 ± 53.7	−3.5 [−15.5–8.4]	0.191
LDL [mg/dl]	137.3 ± 26.0	125.0 ± 27.6	−12.3 [−23.9–−0.7]	147.4 ± 44.8	147.0 ± 52.7	−0.4 [−11.6–10.8]	0.171
HDL [mg/dl]	63.6 ± 15.9	56.3 ± 13.4	−7.4 [−10.1–−4.7]	66.3 ± 21.1	62.4 ± 20.2	−3.9 [−6.9–−0.9]	0.117
Ambulatory blood pressure monitoring							
ABPM SBP [mm Hg]	135.9 ± 11.0	130.3 ± 14.7	−5.6 [−10.6–−0.5]	130.6 ± 13.3	131.9 ± 13.1	1.3 [−3.5–6.1]	0.088
ABPM DBP [mm Hg]	83.3 ± 8.8	80.1 ± 9.3	−3.2 [−6.2–−0.3]	76.9 ± 5.8	78.0 ± 6.8	1.1 [−1.8–3.9]	0.069

Data is presented as mean ± SD; the difference is depicted as mean and 95% Confidence Interval; * p-value between groups was determined using a two samples t-test.

3.3. Results of the Dietary Intake Data

All 37 participants of this subgroup analysis followed an omnivorous diet before the intervention. According to the food records, 19 participants of the CG remained their omnivorous diet for the course of the study. Participants of the PBG adjusted their diet as follows: Eleven participants adopted a strict vegan diet. Four participants adopted a lacto-vegetarian diet, two adopted a lacto-ovo-vegetarian and one participant switched to a pesco-vegetarian diet.

Ultimately, we examined the effects of the plant-based intervention on diet quality. Mean daily intakes of the major nutrient components and the percentage of adequate nutrient intake (adjusted to gender, age and physical activity) in relation to the D-A-CH recommendations are shown in Table 3 and in detail in Table S2 in the Supplementary Materials. Figure 2 shows nutrient intakes in relation to D-A-CH reference values: Potentially beneficial nutrients in a PBD are shown in section A. Potentially critical nutrients in a PBD are plotted in section B.

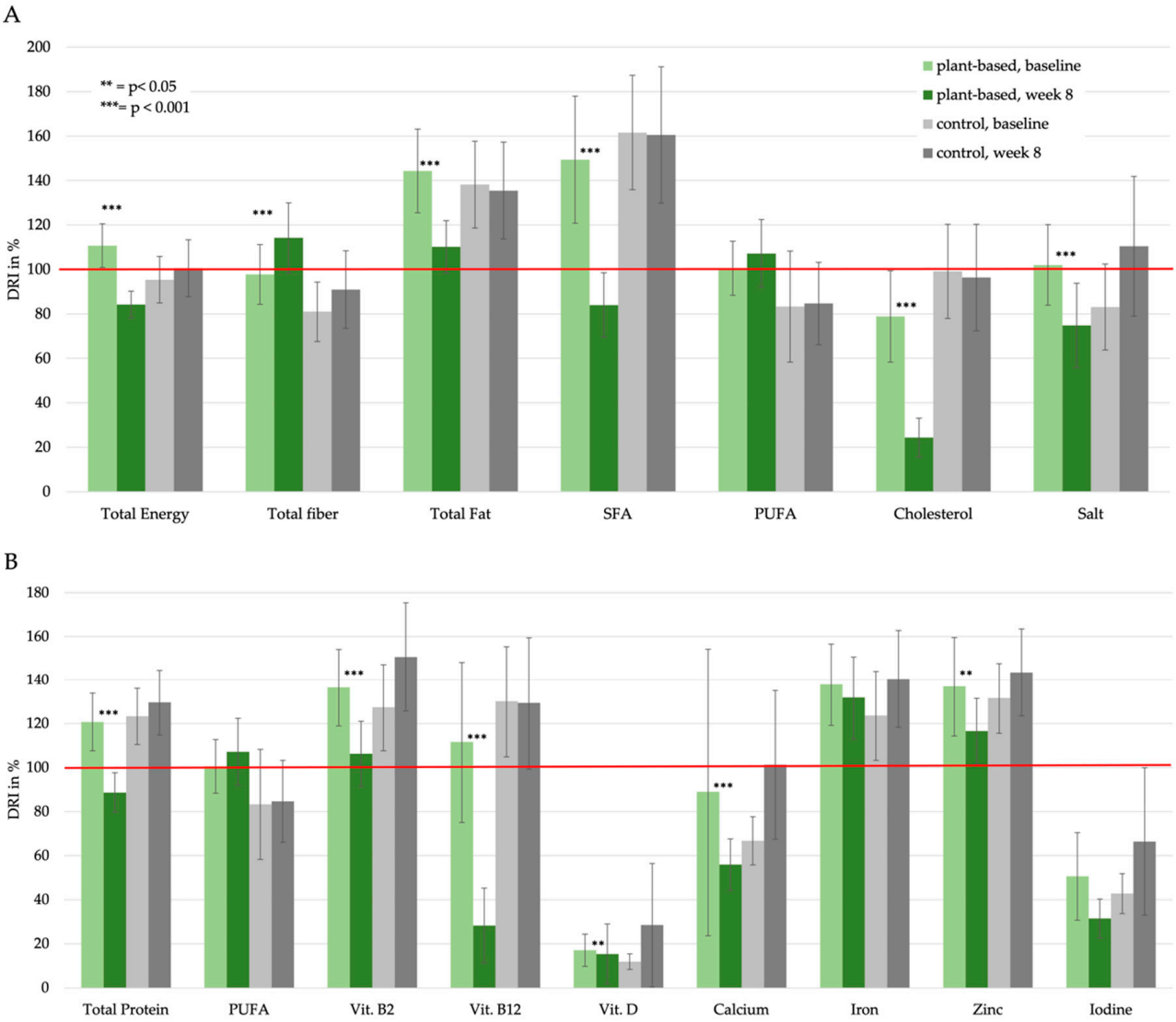

Figure 2. Nutrient intake in relation to the D-A-CH reference values: (**A**) potential beneficial nutrients in a PBD; (**B**) potential critical nutrients in a PBD. The error bars represent the 95% Confidence Interval of the average daily nutrient intake. *p*-value is based on the comparison of absolute values within the group and assessed by related-samples Wilcoxon signed rank test (absolute values are listed in Table S2).

Table 3. Absolute and relative daily nutrient intake before and after 8 weeks and comparison between the groups (extract from Table S2 in the Supplementary Materials).

	Plant-Based Group (n = 18)				Control Group (n = 19)				p-Value [b]
	Baseline		Week 8		Baseline		Week 8		
	Intake [a]	% of DRI [c]	Intake	% of DRI	Intake	% of DRI	Intake	% of DRI	
Macronutrients									
Energy [kcal]	2392.2 ± 382.6	111 [101;121]	1798.1 ± 315.1	84 [78;90]	1955.4 ± 452.0	95 [85;106]	1955.1 ± 477.1	101 [88;113]	<0.001
Total carbohydrates [g]	217.2 ± 58.9	74 [65;82]	189.7 ± 41.6	69 [62;75]	178.8 ± 52.7	64 [54;73]	187.9 ± 47.2	74 [60;89]	0.078
Total dietary fiber [g]	24.2 ± 8.7	98 [84;111]	31.3 ± 8.6	114 [98;130]	24.9 ± 8.3	81 [68;94]	24.5 ± 8.1	91 [74;108]	0.002
Total Protein [g]	90.3 ± 15.0	121 [108;134]	56.2 ± 10.1	89 [80;98]	74.4 ± 15.5	123 [110;136]	75.8 ± 18.4	123 [110;136]	<0.001
Total Fat [g]	112.6 ± 22.3	144 ± 41 [125;163]	78.1 ± 18.3	110 [98;122]	91.3 ± 29.5	138 [119;158]	87.5 ± 30.8	135 [114;157]	0.005
SFA [g]	45.3 ± 12.7	149 [121;178]	21.3 ± 9.0	84 [70;98]	35.6 ± 12.8	162 [136;187]	34.7 ± 14.7	161 [130;191]	<0.001
MUFA [g]	41.1 ± 9.1	157 [134;180]	28.3 ± 8.2	123 [105;141]	31.2 ± 10.5	143 [122;164]	29.5 ± 10.6	136 [113;158]	0.001
PUFA [g]	18.3 ± 5.3	101 [88;113]	23.7 ± 8.4	107 [92;122]	18.4 ± 12.1	83 [58;108]	17.6 ± 8.4	85 [66;103]	0.129
LA [g]	14.4 ± 5.2	290 [246;333]	19.1 ± 7.4	300 [244;357]	14.0 ± 9.4	253 [177;330]	14.1 ± 7.6	250 [181;318]	0.191
ALA [g]	2.5 ± 1.8	351 [280;421]	4.1 ± 3.3	375 [231;519]	3.2 ± 3.8	293 [133;453]	2.3 ± 2.1	224 [139;309]	0.013
Cholesterol [mg]	383.7 ± 133.1	79 [58;99]	76.7 ± 58.8	24 [16;33]	301.9 ± 142.6	99 [78;120]	294.7 ± 163.8	96 [72;120]	<0.001
Salt [g]	6.5 ± 2.0	102 [84;120]	3.7 ± 2.1	75 [56;94]	4.3 ± 2.0	83 [64;102]	5.0 ± 1.8	110 [79;142]	<0.001
Vitamins									
Retinol equivalent [µg]	1660.6 ± 865.3	169 [119;219]	1230.4 ± 771.3	140 [95;184]	1575.9 ± 8401	173 [141;206]	1578.3 ± 632.6	193 [155;230]	0.202
Vitamine B1 [mg]	1.4 ± 0.3	133 [118;148]	1.4 ± 0.4	128 [110;145]	1.2 ± 0.3	111 [98;125]	1.3 ± 0.4	130 [110;150]	0.136
Vitamine B2 [mg]	1.7 ± 0.4	136 [119;154]	1.1 ± 0.3	106 [92;121]	1.4 ± 0.4	127 [108;147]	1.5 ± 0.5	151 [126;175]	0.242
Vitamine B3, Niacin equivalent [mg]	38.3 ± 8.1	268 [229;307]	24.7 ± 5.5	195 [166;224]	31.1 ± 7.8	269 [235;304]	30.1 ± 8.2	258 [224;292]	<0.001
Vitamine B5 [mg]	5.0 ± 1.2	80 [71;90]	4.0 ± 1.6	69 [56;81]	4.5 ± 1.2	71 [62;81]	4.7 ± 1.7	85 [67;103]	0.068
Vitamine B6 [mg]	1.8 ± 0.4	132 [117;146]	1.5 ± 0.4	117 [102;132]	1.6 ± 0.3	127 [113;141]	1.6 ± 0.4	131 [116;145]	0.005
Vitamine B7, Biotin [µg]	52.3 ± 16.3	118 [102;135]	48.5 ± 14.8	109 [93;125]	46.3 ± 11.7	97 [84;110]	49.5 ± 15.2	116 [98;134]	0.288
Vitamine B9, Folate [µg]	350.9 ± 109.1	115 [98;131]	310.9 ± 70.6	109 [99;118]	291.6 ± 94.3	94 [79;109]	292.1 ± 75.9	103 [88;118]	0.236
Vitamine B12 [µg]	5.7 ± 2.4	112 [75;148]	1.0 ± 1.2	28 [11;45]	3.9 ± 1.7	130 [105;155]	4.0 ± 2.0	129 [99;159]	<0.001
Vitamine C [mg]	125.5 ± 54.3	144 [120;167]	144.1 ± 84.6	160 [121;200]	157.1 ± 80.1	175 [135;214]	126.4 ± 47.3	127 [104;150]	0.121
Vitamine D [µg]	3.8 ± 3.2	17 [10;24]	1.7 ± 1.5	15 [2;29]	3.9 ± 6.3	12 [8;15]	2.7 ± 1.5	28 [−1;58]	0.136
Vitamine E [mg]	16.8 ± 6.0	155 [134;177]	19.8 ± 5.4	163 [141;184]	16.1 ± 7.7	142 [111;172]	18.0 ± 8.0	152 [119;185]	0.574
Vitamine K [µg]	195.6 ± 193.3	254 [143;366]	152.2 ± 131.3	214 [117;310]	161.4 ± 108.5	246 [172;320]	190.2 ± 152.7	269 [162;376]	0.316
Minerals									
Sodium [mg]	2753.5 ± 822.2	109 [90;128]	1620.7 ± 870.7	81 [60;101]	1861.1 ± 863.5	90 [69;110]	2147.6 ± 820.4	119 [88;149]	<0.001
Chloride [mg]	4170.7 ± 1222.8	113 [94;132]	2563.5 ± 1298.8	86 [66;106]	2814.6 ± 1189.6	91 [72;110]	3291.0 ± 1150.5	117 [93;141]	<0.001
Potassium [mg]	3402.8 ± 651.3	160 [145;175]	2970.9 ± 655.5	144 [126;162]	3001.4 ± 627.3	144 [126;161]	3046.4 ± 581.7	149 [134;164]	0.021
Magnesium [mg]	498.1 ± 401.7	145 [83;208]	428.3 ± 107.4	131 [111;152]	348.4 ± 117.6	110 [91;129]	362.4 ± 99.6	127 [108;145]	0.715
Zinc [mg]	11.9 ± 2.6	137 [114;160]	8.9 ± 2.2	117 [102;131]	9.6 ± 2.5	132 [116;148]	10.6 ± 3.6	143 [123;164]	0.001
Copper [µg]	2260.1 ± 720.2	181 [154;207]	2372.7 ± 603.8	180 [152;208]	1896.4 ± 658.7	146 [119;173]	1931.5 ± 613.2	163 [136;189]	0.738
Phosphorus [mg]	1453.4 ± 258.4	187 [170;204]	1127.2 ± 303.5	156 [133;179]	1210.0 ± 246.9	165 [146;185]	1289.6 ± 331.4	187 [166;209]	<0.001
Fluoride [µg]	2004.3 ± 4179.9	45 [−17;108]	953.0 ± 501.6	31 [22;41]	789.0 ± 377.2	24 [18;30]	872.4 ± 435.6	58 [−1;116]	0.136
Calcium [µg]	1174.5 ± 1412.9	89 [24;154]	551.4 ± 188.7	56 [44;68]	708.4 ± 203.7	67 [56;78]	849.8 ± 260.5	101 [68;135]	<0.001
Iron [mg]	14.3 ± 3.8	138 [119;157]	13.8 ± 3.7	132 [113;151]	13.5 ± 4.0	124 [103;144]	13.6 ± 4.1	141 [118;163]	0.727
Iodine [µg]	121.9 ± 77.2	51 [31;71]	54.7 ± 25.5	32 [23;40]	91.9 ± 55.1	43 [34;52]	92.3 ± 28.0	66 [33;100]	<0.001
Manganese [µg]	5402.7 ± 2411.8	194 [162;226]	8038.3 ± 3563.5	243 [200;287]	5630.7 ± 2979.4	155 [114;196]	6324.4 ± 3642.3	218 [142;293]	0.019

Data results from three-day weighed food records analyzed with NutriGuide software, including the German Nutrient Data Base (German: Bundeslebensmittelschlüssel). [a] Nutrient intake is presented as mean ± SD and compared within the groups with the Wilcoxon signed rank test for paired samples. [b] Treatment effect and p-value between groups was determined using the Mann–Whitney U test, comparing the delta of the nutrient intake (=intake at baseline vs. intake after 8 weeks). [c] The adequate nutrient supply is depicted as mean [95% confidence interval]. It was calculated as a percentage of the daily recommended intake (DRI) and adjusted to gender and age and under the assumption of moderate movement (Physical Activity Level, PAL 1,6). D-A-CH Reference values are defined by the German (D), Austrian (A), and Swiss (CH) nutrition societies.

3.4. Macronutrient Intake

In terms of macronutrient intake, there were following significant between-group differences after 8 weeks: total daily intakes of energy, total protein, total fat, and cholesterol were significantly lower in the PBG (all $p < 0.001$ between the groups). The PBG consumed significantly less saturated fatty acids (SFA, $p < 0.001$) and less monounsaturated fatty acids (MUFA) ($p = 0.001$). Polyunsaturated fatty acid (PUFA) intake increased slightly, but the difference was not significant between the groups ($p = 0.129$). PBG participants consumed significantly more dietary fiber ($p = 0.002$) and Alpha-Linolenic Acid (ALA) ($p = 0.013$) than participants in the CG.

3.5. Micronutrient Intake/Vitamins

We observed a significant decrease in the intake of essential vitamins (vitamins B2, B3, B5, B6, B12, and vitamin D) within the PBG. Retinol equivalent, vitamin B1, biotin and folate were all slightly reduced but the decrease was not statistically significant within the PBG. Concerning vitamin C and vitamin E there was a modest but not significant increase within the PBG. Glancing at potential between-group differences, only vitamin B3, B6, and B12 differed significantly.

3.6. Micronutrient Intake/Minerals

Compared to the CG, intake of certain minerals significantly decreased in the PBG: Sodium intake decreased by more than 1.1 g in the intervention group ($p < 0.001$). Additionally lower chloride ($p < 0.001$), potassium ($p = 0.021$), zinc ($p < 0.001$), sulfur ($p < 0.001$), phosphorus ($p < 0.001$), calcium ($p < 0.001$), and iodine ($p < 0.001$) were present in the PBG compared to the CG.

4. Discussion

The primary aim of the present dietary data analysis was to contrast the nutritional quality of a PBD to an omnivorous diet. Moreover, we sought to examine whether a properly composed whole-food PBD could meet all D-A-CH recommendations. We put a major focus on nutrients of potential public health concern [26,32]. Our data suggest that the PBD had various beneficial components including but not limited to a lower energy density, a lower intake of cholesterol and saturated fat, an increased consumption of dietary fiber. and a lower intake of salt. It is worth mentioning that most participants voluntarily chose a purely "vegan diet".

4.1. Potential Beneficial Nutrient Intake in a PBD

4.1.1. Energy Intake

Excess weight, as shown by a higher BMI or waist circumference, is one of the strongest risk factors for cardiovascular disease [33]. Plant-based foods are characterized by lower energy density and a higher nutrient density. Thus, they tend to promote weight loss [28]. Consistent with our results, the PBG consumed significantly fewer calories compared to the CG although neither group had any quantity restrictions. It is conceivable that the reduced energy density contributed to weight loss in the PBG [34].

4.1.2. Dietary Fiber Intake

Other nutrient-related benefits of the PBD intervention included a high intake of dietary fiber. Dietary fiber is a component of plant foods that cannot be broken down by enzymes in the human gastrointestinal tract. Its consumption reduces the risk of obesity in adults, as well as the risk of hypertension and coronary heart disease [35,36]. By lowering total and LDL cholesterol concentrations, dietary fiber also diminishes the risk of dyslipidemia [37–40]. As a guideline, D-A-CH recommends a dietary fiber intake of at least 30 g/day. Participants in the PBG achieved this recommendation, while the CG failed.

4.1.3. Saturated Fatty Acids (SFA) and Cholesterol Intake

Participants allocated to the PBG consumed less SFA and less MUFA while their intake of PUFA increased slightly but not significantly. SFA content is particularly low in a PBD [41,42], which has been linked to coronary heart disease prevention by improving lipid profiles and lowering blood pressure [43–45]. Notably, the between-group differences were also significant: While CG substantially exceeded the recommended daily intake of SFA, the PBG was able to successfully reduce its consumption below the limit.

Throughout the study the intake of PUFAs increased slightly in the PBG but not significantly. There was no insufficient intake before and after the intervention in the PBG. Differently, the intake of PUFAs in the CG was already low at the beginning of the study and remained low during the 8 weeks of the study. Plant foods contain just small amounts of MUFA and PUFA, mainly α-linolenic acid (ALA). ALA is a short-chain n-3 PUFA that occurs in plant derived sources such as vegetable oils, walnuts, rapeseed, linseed, and hemp. ALA can be converted to a limited extent to essential omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) that are known to be cardioprotective [29,44,46,47].

A high intake of saturated fat has been shown to adversely affect serum LDL concentrations [48]. Moreover, several studies suggested an association between dietary cholesterol and serum cholesterol [49,50]. While some international dietary associations have removed the target values for dietary cholesterol, D-A-CH maintains its recommendation and still advises limiting cholesterol intake to about 300 mg per day. Both study groups did not exceed this recommendation. However, it is evident that subjects in the PBG group consumed significantly less dietary cholesterol than subjects in the CG group and were able to reduce this consumption during the intervention.

Despite a close relationship between SFA, cholesterol intake and blood lipid levels, our analysis did not show significant results regarding lipid panels. One potential reason is the short intervention duration. Non-statistical differences may also be a result of under-powering (see Section 5).

4.1.4. Salt Intake

Sodium and chloride are essential for various metabolic pathways and fluid regulation, however, a high consumption of salt is a major cause of hypertension and an independent risk factor for coronary heart disease and stroke [51]. There is consistent evidence that a moderate reduction in salt intake (i.e., a reduction of 3 to 5 g) can lead to a decrease in blood pressure [52,53]. Although the physiological requirement is only 2 to 3 g per day, the D-A-CH recommends a maximum of 5 g per day. The PBG group managed to significantly lower their salt intake from 6.5 ± 2.0 g to 3.7 ± 2.1 g, while the CG did not show any decrease.

4.2. Potential Critical Nutrients in a PBD

Our data suggest that participants allocated to the PBG consumed adequate amounts of macronutrients and essential vitamins and met the D-A-CH recommendations in most cases.

4.2.1. Protein Intake

The adequacy of protein intake in PBDs is controversial. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs, and each protein has unique functions. Although protein-rich plant foods such as traditional legumes, nuts, and seeds may be sufficient to achieve complete protein intake in adults following a PBD, our dietary data analysis showed otherwise. The PBG consumed only 89% [95% CI: 89;98] protein, which is 11% less than recommended by D-A-CH.

4.2.2. Critical Micronutrients

According to the German Nutrition Society, a strict PBD does not provide an adequate supply of some nutrients or provides them only with difficulty. Potentially critical nutrients in a vegan diet include vitamins (vitamin B12, riboflavin/vitamin B2 and vitamin D) as

well as certain minerals (calcium, iron, iodine, zinc, selenium) [26]. The most critical nutrient is certainly vitamin B12 [26]. As expected, vitamin B12 intake in the PBG decreased significantly below the DRI. Since vitamin B12 is an important component of various metabolic pathways, it is strongly recommended to supplement this essential nutrient when adopting a PBD.

In our analysis riboflavin, also known as vitamin B2, also declined slightly in the PBG, yet it remained above the recommended daily intake. As for vitamin D and pantothenic acid (vitamin B5), both groups showed inadequate intakes, suggesting that these nutrients are not only critical for vegans, but nutrients of public health concern.

Pantothenic acid is a water-soluble vitamin and a precursor for the synthesis of coenzyme A. In fact, coenzyme A is essential for many biochemical reactions that maintain life [54].

Vitamin D is essential for maintaining bone mineralization by regulating calcium and phosphorus homeostasis. However, a deficiency has not only negative effects on the human skeletal system but also facilitates the development and progression of numerous common diseases, including cardiovascular disease, diabetes, autoimmune diseases, and cancer [55].

The intake of the trace element iodine was also insufficient in both groups. Iodine is an essential component of thyroid hormones, which are needed throughout life for normal growth, neurological development and metabolism. Insufficient iodine intake impairs the production of thyroid hormones and leads to a condition called hypothyroidism. This leads to a range of health impairments of varying severity [56].

Calcium intakes decreased in the PBG and did not meet the D-A-CH guideline. As a major component of bones and teeth, calcium also plays an important role as a second messenger in cell signaling pathways [57].

Other critical nutrients such as iron, and zinc decreased in PBG, but levels were still above recommended values.

5. Limitations

The present study has several strengths and limitations that warrant further discussion. We conducted most of the study under pandemic conditions—external regulations and lockdowns forced us to switch from face-to-face training to online sessions. Despite these difficulties, we managed to recruit a total of 70 people. The main limitation of this subsample analysis is that not all participants provided plausible and complete food records. Therefore, the current analysis is limited to 37 participants. Our study may thus be underpowered and unable to detect smaller group differences.

Adopting a PBD may be difficult in the first weeks and requires external support. It is conceivable that online education sessions are less effective and do not allow for the same personal interaction that is possible during in-person events. Whether this affected adherence in the PBG, however, remains a subject to speculations.

Another limitation of this study results from the dietary protocols: The direct form of a dietary survey by keeping protocols causes a higher awareness among the participants. This may lead to a more conscious perception of their own diet. Foods that are assumed to be positively evaluated by the investigator (e.g., vegetables, fruits) are usually overestimated in quantity or even consumed more frequently during the protocol days. In contrast, other foods that are considered undesirable (e.g., sweets, alcoholic beverages) tend to be underestimated or consumed less. This effect, which is desirable in nutrition education, is a potential source of error in the analysis of our nutrition data.

Although three-day weighed food records are the gold standard in nutritional monitoring, they are also susceptible to various bias, including reporting bias. More solid results on nutrient absorption and acquired deficiencies can be obtained by blood analysis. In our study, we focused on dietary intake and omitted blood tests regarding micro-/macronutrients; however, we would recommend and perform them in future studies. Concerning our study, it would be particularly interesting to determine in the blood whether the critical nutrients were too low in the intake but possibly still sufficiently present in the organism. Furthermore, these parameters could be complemented by microbiome and

multi-omics data, since our microbiota produces vitamins, among other substances, and thus contributes to a healthy diet [58].

6. Conclusions

The present analysis of dietary intake showed that the nutrient composition of participants in the whole-food PBG was more favorable for cardiovascular health compared with participants to the omnivorous CG. Beneficial features of the PBD included a lower energy density, a lower intake of SFA and cholesterol, an increased consumption of dietary fiber, and a lower intake of salt. The recommended intake for most vitamins and minerals were met. As expected, participants in the PBG did not meet the recommendations for vitamin B12, and supplementation may thus be warranted. A low intake of several critical nutrients (vitamin D, pantothenic acid, and iodine) was observed in both groups, suggesting that these are nutrients of public health concern. Targeted supplementation with the previously mentioned micronutrients could improve the nutritional quality of the PBD and prevent the development of nutritional deficiencies. Overall, however, the benefits and the preventive effect that PBD offers for heart health are so valuable that we recommend PBD as adjunct therapy to the patient's medication and usual diet.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/nu14214597/s1, Table S1. D-A-CH reference values: Gender- and age-specific DRI for a PAL of 1.6; Table S2. Absolute and relative daily nutrient intake before and after the intervention and comparison between the groups.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Charité-Universitätsmedizin Berlin (EA4/025/19).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data from the study are available upon reasonable request.

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Abbreviations

ALA	α-Linolenic Acid
ABPM	Ambulatory blood pressure monitoring
BMI	Body Mass Index
BLS	German Nutrient Data Base; german: Bundeslebensmittelschlüssel
CI	Confidence Interval
CG	Control Group
CVD	Cardiovascular Disease
D-A-CH	Association of nutritional societies of Germany (D), Austria (A) and Switzerland (CH)

DBP	24 h Diastolic Blood Pressure
DGE	Society for Nutrition in Germany (Deutsche Gesellschaft für Ernährung)
DRI	Daily Recommended Intake
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
HOMA	Homeostasis Model Assessment
LDL	Low Density Lipoprotein
MUFA	Monounsaturated Fatty Acids
ÖGE	Society for Nutrition in Austria
PAL	Physical Activity Level
PBD	Plant-Based Diet
PBG	Plant-Based Group
PUFA	Polyunsaturated atty Acids
SBP	24 h Systolic Blood Pressure
SD	Standard Deviation
SFA	Saturated Fatty Acids
SGE	Society for Nutrition in Switzerland

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2.3 Ernährung nach Traditionell Indischer Medizin vs. Ernährung nach der Deutschen Gesellschaft für Ernährung bei Patienten mit Reizdarmsyndrom – eine randomisierte kontrollierte Studie

Mit dieser bizentrischen RCT liegt eine erste Studie zur Wirksamkeit einer individualisierten Ernährungsberatung im Sinne der Traditionell Indischen Medizin (TIM)/Ayurveda im Vergleich zu den konventionellen Ernährungsempfehlungen der Deutschen Gesellschaft für Ernährung (DGE) bei Patienten mit Reizdarmsyndrom vor.

In Südostasien stellt der Ayurveda das größte TMS dar – insbesondere in Indien kann die TIM als eine Volksmedizin bezeichnet werden. Auch in Europa und den Vereinigten Staaten hat der Ayurveda in den letzten Jahren an Popularität gewonnen, insbesondere bei der Behandlung chronischer und psychosomatischer Erkrankungen [115].

Hauptargumente für die Wahl der Diagnose Reizdarmsyndrom für diese Studie war die hohe Prävalenz und die gesundheitsökonomische Relevanz des Reizdarmsyndroms, aber auch die gute Therapierbarkeit aus Sicht der TIM. Die Ergebnisse dieses RCTs zeigten, dass eine Ernährungsumstellung nach TIM-Prinzipien der konventionellen Ernährungstherapie nicht unterlegen sein könnte. Zudem war die Reduktion auf dem primären Endpunkt *Irritable bowel syndrome – Severity Scoring System* (IBS-SSS) in der Ayurveda-Gruppe signifikant höher als in der konventionellen Therapiegruppe und klinisch bedeutsam. In weiterführenden statistischen Modellen wurde der Einfluss verschiedener Variablen analysiert. Das Haupt-Modell zeigte, dass 68% der Varianz in der IBS-SSS-Reduktion nach 3 Monaten durch die Therapie erklärt werden konnte, 6,5% durch die Erwartungen der Patienten an ihre Therapien und 23,4% durch die Veränderung des IBS-SSS zu Baseline. Den Großteil des Gesamteffektes haben also therapeutische Effekte ausgemacht. Beide Therapien trugen in gleichem Maße zur Varianz der Ergebnisse bei. Je höher der IBS-SSS-Wert vor der Intervention und je größer die Erwartungen der Patienten waren, desto größer war die Reduktion des IBS-SSS.

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Ayurvedic vs. Conventional Nutritional Therapy Including Low-FODMAP Diet for Patients With Irritable Bowel Syndrome—A Randomized Controlled Trial

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Aims: To compare the effects of Ayurvedic and conventional nutritional therapy in patients with irritable bowel syndrome (IBS).

Methods: Sixty-nine patients with IBS were randomized to Ayurvedic ($n = 35$) or conventional nutritional therapy according to the recommendations of the German Nutrition Society including the low-FODMAP diet ($n = 34$). Study visits took place at baseline and after 1, 3, and 6 months. The primary outcome was IBS symptom severity (IBS-SSS) after 3 months; secondary outcomes included stress (CPSS), anxiety and depression (HADS), well-being (WHO-5) and IBS-specific quality of life (IBS-QOL). A repeated measures general linear model (GLM) for intent-to-treat-analyses was applied in this explorative study.

Results: After 3 months, estimated marginal means for IBS-SSS reductions were 123.8 [95% confidence interval (95% CI) = 92.8–154.9; $p < 0.001$] in the Ayurvedic and 72.7 (95% CI = 38.8–106.7; $p < 0.001$) in the conventional group. The IBS-SSS reduction was significantly higher in the Ayurveda group compared to the conventional therapy group (estimated marginal mean = 51.1; 95% CI = 3.8–98.5; $p = 0.035$) and clinically meaningful. Sixty-eight percentage of the variance in IBS-SSS reduction after 3 months can be explained by treatment, 6.5% by patients' expectations for their therapies and 23.4% by IBS-SSS at pre-intervention. Both therapies are equivalent in their contribution to the outcome variance. The higher the IBS-SSS score at pre-intervention and the larger the patients' expectations, the greater the IBS-SSS reduction. There were no significant group differences in any secondary outcome measures. No serious adverse events occurred in either group.

Conclusion: Patients with IBS seem to benefit significantly from Ayurvedic or conventional nutritional therapy. The results warrant further studies with longer-term follow-ups and larger sample sizes.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT03019861, identifier: NCT03019861.

Keywords: nutrition – clinical, Traditional Indian Medicine, irritable bowel syndrome, Ayurveda, clinical trials, complementary medicine, integrative medicine

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders with a prevalence between 5 and 10% for many European countries and the USA (1). Both the individual burden of typical clinical symptoms and the discussed pathophysiological mechanisms may differ from patient to patient and IBS subtypes (2). A coherent link between certain pathologies and the symptoms of IBS is still unclear. In addition, IBS is often associated with other somatic comorbidities and mental disorders (3). IBS has considerable consequences in terms of quality of life, work productivity and burden on health-care systems (4).

Dietary changes are one of the most commonly used interventions in patients with IBS (5), especially the low fermentable oligo-, di-, monosaccharides and polyols (FODMAP)-diet, which showed clinically meaningful responses in 50–86% of patients (6).

Some patients with IBS report dissatisfaction with conventional medical therapies and seek other forms of treatment especially Complementary and Integrative Medicine (CIM) (2). Of the various CIM interventions, the Traditional Indian Medicine Ayurveda, a Whole Medical System, is increasingly used worldwide and is recognized by the World Health Organization as a medical science (7). In Europe and the United States, Ayurveda has become increasingly popular in recent years, especially in the treatment of chronic and psychosomatic disorders (8).

Ayurvedic IBS-treatment is based on diagnosing the condition from an Ayurvedic perspective, which takes into consideration inter-person variablity of digestive functions, physio-psychological personality type and variations in the presenting symptoms (9). The treatment approach in Ayurveda is thereby a customized nutritional therapy tailored to the individual constellation of various factors of the patient including their symptoms, constitution, digestive capacity, bowel sensitivity, composition of the *milieu intérieur*, individual food habits assessed during the diagnostic processes and the like (10, 11). Ayurvedic diets are fairly easy to implement by patients in their daily lives and generally are comparatively inexpensive methods of self-care. In Ayurveda, customized nutritional therapy is most often used to treat patients with IBS. Additionally, oral herbal preparations and/or specific types of Ayurvedic enema therapies are used in case of therapeutic resistance to nutritional therapy (11). However, to date, little systematic data is available on the effectiveness of Ayurvedic nutritional therapy in comparison to conventional nutritional therapy for IBS patients and the feasibility of such an approach in western settings.

Therefore, the primary objective of this non-inferiority study was to test whether an Ayurvedic nutritional therapy provides at least comparable benefits to the patients as a conventional nutritional therapy according to the recommendations of the German Nutrition Society (DGE) including the low-FODMAP diet on IBS symptom severity in patients with IBS (in mathematical terms: Ayurvedic nutritional therapy $\geq$ conventional nutritional therapy). This includes that Ayurvedic nutritional therapy can also be better than conventional nutritional therapy. The hypotheses as in most clinical trials, were stated in terms of differences in the mean response of an outcome of interest, here IBS-SSS reduction (IBS-SSS at pre-intervention – after 3 months) and adjusted for various covariates.

METHODS

Study Design

In a two-armed multicenter randomized controlled clinical trial, IBS patients were allocated 1:1 to two treatment groups: (1) Ayurvedic nutritional therapy and (2) conventional nutritional therapy according to the recommendations of the DGE including low-FODMAP diet. The study protocol was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (EA4/115/16) and the University Hospital Essen (16-7254-BO) and all participants gave their informed consent. The trial was registered at ClinicalTrials.gov prior to patient recruitment (NCT03019861). Trained study personnel performed collection of data at Immanuel Hospital Berlin, Department of Internal and Integrative Medicine, Berlin, Germany and at Evang. Kliniken Essen-Mitte, Department of Internal and Integrative Medicine, Essen, Germany.

Participants

Volunteers, who lived in the region of Berlin and Essen, were recruited by local newspaper advertisements and flyers. Subjects were included if they (1) were aged 18–70 years of all sexes, and (2) had the diagnosis IBS according to the the German S3 IBS guideline (12, 13), diagnosed by an external physician. Subjects were excluded if they (1) had a generally poor overall state of health, (2) had a serious acute or chronic co-morbidity, (3) were pregnant or breast feeding, (4) had a pre-diagnosed eating disorder, (5) were in recognition procedure for early retirement or disability, and/or (6) participated in another clinical trial.

Outcome Measures

All participants were asked to complete standardized validated questionnaires at the beginning of the study, at 1 month, at 3 months and at 6 months follow-up. The primary outcome was change of the mean score of the German version of Irritable Bowel Syndrome – Severity Scoring System (IBS-SSS) questionnaire at 3 months (14). We modified the visual analog scales in the original IBS-SSS version to 4 (question no. 3 and 4), respectively, 5-point (question no. 1b and 2b) Likert scales, since all questionnaires were filled out online in Limesurvey. Pre-specified secondary outcomes included the following validated questionnaires in German:

- Irritable Bowel Syndrome – Quality Of Life (IBS-QOL), a 34-item scale designed for the assessment of quality of life in patients with IBS (15).
- Quality of life and well-being were assessed by the 5-item WHO-Five Well-being index (WHO-5) (16).
- Cohen Perceived Stress Scale (CPSS), a 10-item scale for measuring personal levels of experienced and perceived stress (17).
- Hospital Anxiety and Depression Scale (HADS), a 14-item scale designed for the assessment of anxiety and depression symptoms in general populations (18).

Additional Parameters

Adverse events were systematically ascertained. Moreover, additional questions on 5-point Likert scales at month 3 (1: agree fully to 5: disagree fully) and evaluation questions at month 6 were asked, using Numeric Rating Scale (NRS) questions regarding adherence to diet and health (0: not at all to 10: very). Adherence to diet was assessed by the patients themselves and through an external assessment by dieticians based on dietary protocols and records made during the consultations (NRS 0: not at all to 10: very).

Furthermore, microbiome analysis and qualitative focus group interviews were conducted, results of which will be published elsewhere.

Randomization and Masking

After completing the baseline questionnaires, the participants were randomly assigned to one of the study arms. Block randomization (block-size 4) was used. The randomization list was created by the biometrician not involved in patient recruitment or assessment based on the Blockrand-package (Version 1.3) in R. The list was password-secured and no other person than the biometrician was able to access it. The subjects were randomly allocated by opening of a sealed envelope prepared by a study nurse not involved in the study. As with all therapy trials, the participants, therapists and research assistants who assisted in the therapy arrangements could not be blinded regarding the treatment allocation. Also the study directors and statisticians conducting outcome analysis were not masked.

Interventions

With each participant, patient history was taken, and all participants received a 45 ± 10 min. personal nutritional therapy session (baseline consultation), followed by two further 30 ± 10 min. nutritional therapy sessions 3 and 8 weeks after the baseline consultation. The study was conducted in comparable German outpatient clinic settings in Berlin and Essen. The basic principles for the interventions were defined by a consensus process prior to enrolment of the study participants.

The Ayurvedic approach included individualized nutritional recommendations for a diet based on Ayurvedic concepts, predominantly on the concept of strength of digestion and metabolism ("digestive fire," Sanskrit: = *agni*), which is further referred to in this paper as "general nutritional therapy of Ayurveda" (11, 19). Customized advice was dependent on individual symptoms and circumstances ("specific nutritional therapy of Ayurveda") (9, 20). The main content of both therapeutic aspects are summarized in the **Supplementary Material** *General and Specific Nutritional Therapy of Ayurveda*. Specific suggestions and details for food items, recipes, food preparation, timings, spices etc. were given to each participant and the list of food was adapted to local availability in order to maximize practicability and participants' adherence to the intervention. Two experienced Ayurveda nutritional experts and registered German naturopaths (German: "*Heilpraktiker*") with each more than 500 h of academic training in Ayurveda and more than 10 years of continuous clinical experience with Ayurveda in Germany performed the counseling sessions in both study centers.

Conventional treatment consisted of nutritional therapy in accordance with the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE) with specific suggestions for foods and recipes (21). Two experienced German dieticians with more than 3 years of continuous clinical experience in treating patients performed the nutritional therapy. Participants also received a brochure with nutritional recommendations for IBS patients, which was prepared by the DGE (21). This brochure explained the principles of a balanced diet and the essence of a low-FODMAP diet. In particular, participants were informed that foods rich in fructans and galacto-oligosaccharides (e.g., wheat, rye, onions, and legumes), as well as items containing lactose, foods with an excess of fructose (e.g., apples, mangoes, and honey), and foods rich in sorbitol, mannitol, maltitol, and xylitol (e.g., apricots, peaches) should be avoided. To help participants select suitable foods, they were also given a series of low-FODMAP recipes, a list of foods they should avoid, and another list of foods they could eat instead. After the 12-week intervention period of the study (elimination phase), participants re-examined a different FODMAP group each week for 2–3 days per week to test individual tolerance to each of the FODMAP groups (reintroduction phase).

All participants were asked to maintain their routine activities and not to begin any other treatment during the study.

Statistical Analysis

Group sample sizes of 36 and 36 achieve 80% power to detect non-inferiority using a one-sided, two-sample *t*-test in

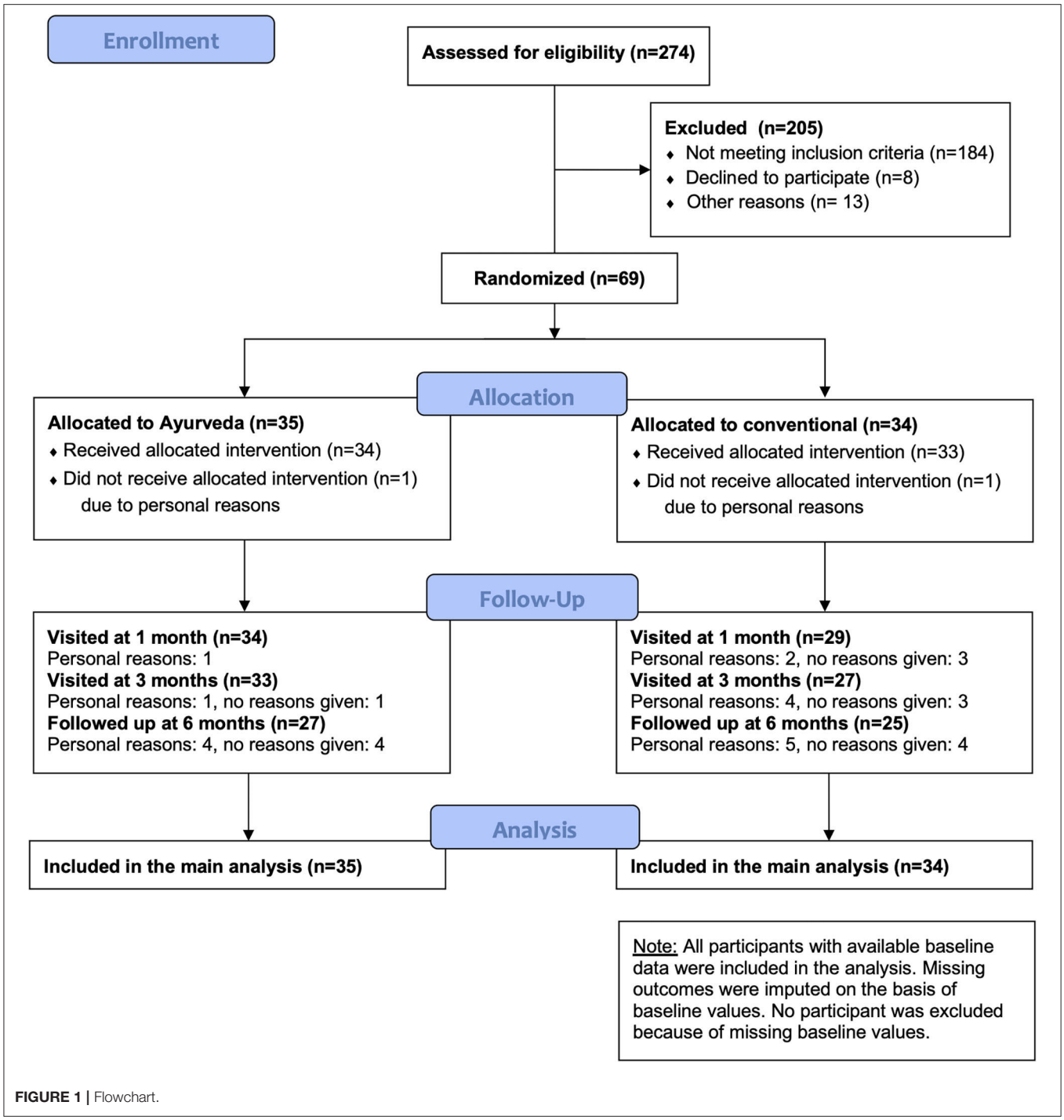

FIGURE 1 | Flowchart.

the present explorative study. The primary objective was to estimate the therapeutic quality and difference of both therapies. The significance level (alpha) of the test is 0.05. The margin of equivalence is 50 points, which is the minimally clinically important difference (MID), i.e., that "patients perceive as important, either beneficial or harmful, and that would lead the clinician to consider a change in the patient's management" (22). The null and the alternative hypothesis of this non-inferiority clinical trial are H_0: $\mu_1 - \mu_0 \leq -\delta$ vs. H_1: $\mu_1 - \mu_0 > -\delta$, where $\delta \geq 0$. δ is called the margin of clinical significance which is in our case 50 (=MID). The true difference between the Ayurveda mean and the conventional nutritional therapy mean is assumed to be 35 points. The estimates of the standard deviations are assumed to be 25 points for both groups (22).

This intention-to-treat (ITT) randomized study was designed to test whether or not the mean effectiveness [as measured

TABLE 1 | Baseline characteristics.

		Treatment groups		Sig.*
	Total	**Conventional nutritional therapy**	**Ayurvedic nutritional therapy**	
	(*n* = 69)	**(*n* = 34)**	**(*n* = 35)**	
Age	46.4 ± 13.9	41.8 ± 14.4	50.8 ± 12.0	0.006
	Median: 50	Median: 38	Median: 52	
Sex (women)	75.4%	70.6%	80.0%	0.364
Body mass index	24.1 ± 3.7	23.3 ± 3.5	25.9 ± 3.7	0.052
Duration of IBS diagnosis (years)	8.0 ± 8.8	6.7 ± 7.3	9.2 ± 10.0	0.264
Patients' expectations for conventional nutritional therapy	5.7 ± 2.3	5.7 ± 2.1	5.6 ± 2.4	0.171
Patients' expectations for Ayurvedic nutritional therapy	7.4 ± 2.0	7.5 ± 1.6	7.4 ± 2.3	0.072
Previous drug therapy for IBS				
Analgetics	3 (4.4%)	1 (3.0%)	2 (5.7%)	0.59
Antispasmodics	5 (7.4%)	1 (3.0%)	4 (11.4%)	0.19
Laxatives	2 (2.9%)	1 (3.0%)	1 (2.9%)	0.97
Antidiarrheal drugs	4 (5.9%)	1 (3.0%)	3 (8.6%)	0.33
Probiotics	28 (41.2%)	14 (42.4%)	14 (40.0%)	0.84
Phytotherapeutic agents	27 (39.7%)	14 (42.4%)	13 (37.1%)	0.66
Concomitant and previous illnesses				
Cardiovascular diseases	16 (23.5%)	6 (18.2%)	10 (28.6%)	0.42
Renal diseases	4 (5.9%)	3 (9.1%)	1 (2.9%)	0.24
Metabolic diseases	8 (11.8%)	1 (3.0%)	7 (20.0%)	0.40
Skin diseases	5 (7.4%)	3 (9.1%)	2 (5.7%)	0.17
Irritable Bowel Syndrome – Severity Scoring System (IBS-SSS)	275.9 ± 77.1	279 ± 78.2	272.7 ± 77.1	0.731
Quality Of Life (IBS-QOL)	53.0 ± 20.7	52.6 ± 21.8	53.4 ± 19.9	0.862
Cohen Perceived Stress Scale (CPSS)	19.7 ± 7.0	19.4 ± 7.7	19.9 ± 6.3	0.767
Hospital Anxiety and Depression Scale (HADS-Total)	14.1 ± 6.0	13.7 ± 6.2	14.6 ± 5.8	0.524
Hospital Anxiety Scale (HADS-A)	8.3 ± 3.7	7.9 ± 3.9	8.6 ± 3.6	0.447
Hospital Depression Scale (HADS-D)	5.8 ± 3.3	5.7 ± 3.6	5.9 ± 3.0	0.767
WHO-5 Well-Being Index	43.7 ± 20.5	45.1 ± 20.2	42.4 ± 20.9	0.594

**Statistical tests to compare baseline data in randomized controlled trials have remained questionable since 1990 (Ahn, 2019). Tests of baseline differences are not necessarily wrong, just illogical (Senn, 1994).*

by the primary outcome parameter IBS-SSS reduction (IBS-SSS at pre-intervention – after 3 months) and adjusted for various covariates] of the Ayurvedic nutritional therapy is non-inferior to the mean effectiveness of the conventional nutritional therapy. Missing data were handled by maximum likelihood multiple imputation. Additional parameters (section Additional Parameters) were not imputed. Generalized Linear Models (GLM) were primarily used to reduce within-group error variance and to eliminate confounding factors. For checking the assumptions for GLMs we carried out Levene's test, for homogeneity of variances, Shapiro-Wilk's resp. Kolmogorov's test for normality with Lilliefors significance correction and the test for homogeneity of regression slopes. The estimated marginal means section of the output gives the adjusted means (controlling for the covariates) for each diet group. For *post-hoc* comparisons of the main effects we used a Sidak correction for confidence interval adjustment. We included study centers as a random effect, treatment group as a fixed factor, IBS-SSS at pre-intervention and for sensitivity analysis participants' expectations for their individual therapy at pre-intervention as covariates. All statistical analyses were done within the statistical programming language R (Version 3.5.2), SPSS (Version 26; IBM) and NCSS (Version 10). All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

A total of 274 patients were screened for eligibility (**Figure 1**). Most patients were excluded because of other gastrointestinal diagnoses and consequently did not have a diagnosis of IBS. Sixty-nine patients fulfilled the eligibility criteria and were enrolled into the study (34 in the conventional group and 35 in the Ayurveda group). The first patient was enrolled in January 2017; follow-up visits for the last patient were completed by February 2019. Overall, 60 participants (87%) completed the visit at 3 months, 52 (75%) completed the follow up at 6 months. Sixty-nine data sets were included in the final analysis.

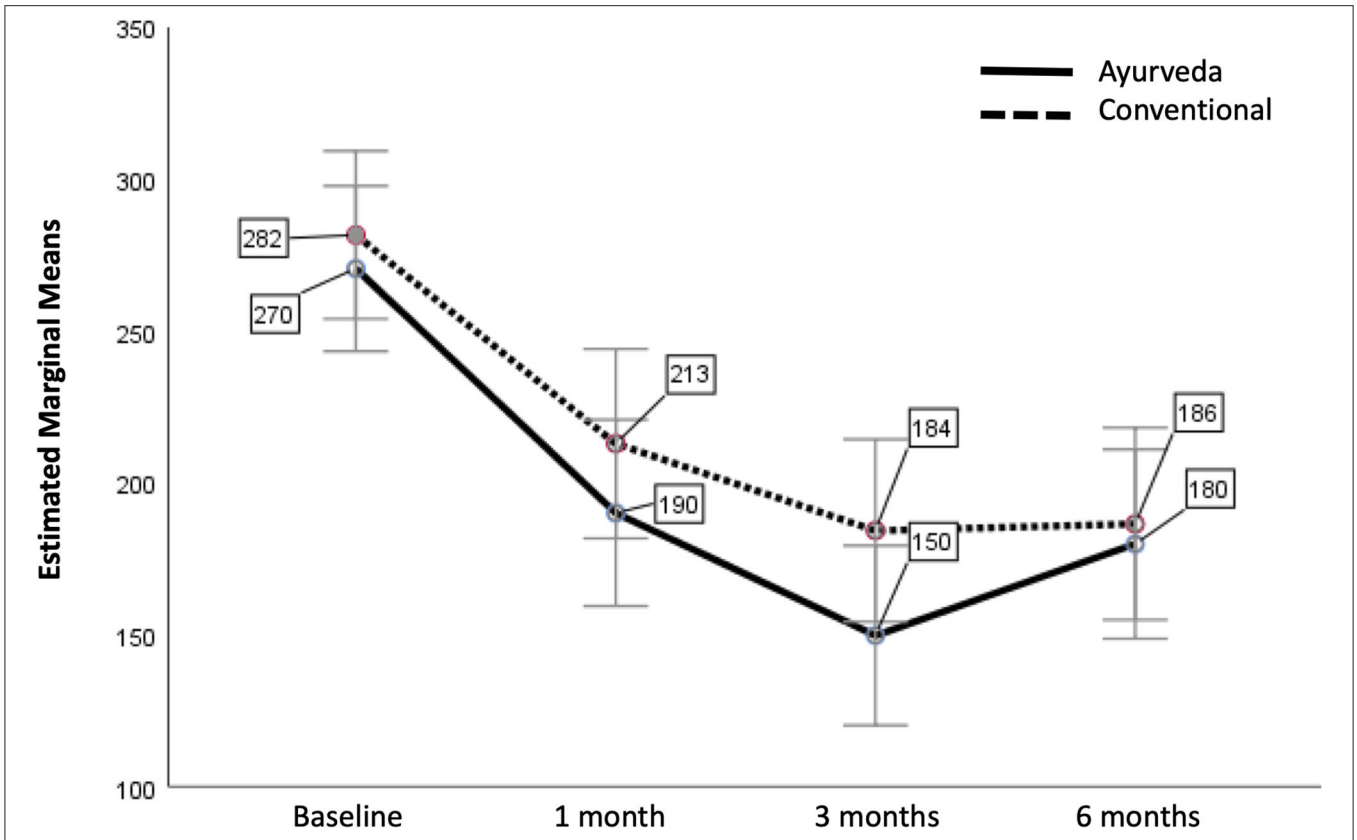

FIGURE 2 | Estimated Marginal Means of IBS-SSS with patients' expectations as covariate (with error bars 95% confidence interval). The covariate patients' expectations is evaluated at the value 6.57 (adjusted mean).

Baseline Characteristics

Mean patients age in the Ayurveda group ($n = 35$) was 50.8 ± 12.0 years, in the conventional group ($n = 34$) 41.8 ± 14.4 years. Eighty percent of the patients in the Ayurveda group and 71% in the conventional group were women (**Table 1**). The difference of IBS-SSS at pre-intervention between both therapy groups was 6.5 ± 18.7 points. Duration of IBS diagnosis was 9.2 ± 10.0 years in the Ayurveda group and 6.7 ± 7.3 years in the conventional group. Patients' expectations for Ayurvedic therapy as well as for conventional therapy did not significantly differ between both therapy groups (**Table 1**). Overall patients with Ayurvedic nutritional treatment had a significantly ($p = 0.003$) higher mean expectation at pre-intervention for the benefit of their treatment (7.4 ± 2.4) compared to the corresponding patients with conventional therapy (5.7 ± 2.1). We could not find random imbalances in prognostic factors which may otherwise bias intention-to-treat effect.

Primary Outcome

After 3 months, the mean values of IBS-SSS were reduced from 272.7 ± 77.1 to 166.9 ± 92.0 in the Ayurveda group and from 279.2 ± 78.2 to 199.7 ± 98.3 in the conventional group. The means of the paired differences between IBS-SSS at baseline and after 3 months were 105.9 ± 83.8 [95% confidence interval (95% CI) = 77.1–134.7; $p < 0.001$] for Ayurvedic nutritional therapy and 79.5 ± 126.0 (95% CI = 35.6–123.5; $p = 0.001$) for conventional therapy.

The assumptions of equality of error variances for IBS-SSS reduction after 3 months was not violated (Levene's test $p = 0.152$). The estimated marginal means (also known as adjusted means or predicted means) for IBS-SSS reduction after 3 months (controlled for patients' expectations for their therapies and IBS-SSS at pre-intervention as covariates and centers as random factor) were 123.8 ± 15.5 (95% CI = 92.8–154.9) in the Ayurveda group and 72.7 ± 17.0 (95% CI = 38.8–106.7) in the conventional group. The mean difference of the IBS-SSS reductions between both therapy groups based on the estimated marginal means was statistically significant in favor of the Ayurveda group (mean difference 51.1 ± 23.7; 95% CI = 3.8–98.5; $p = 0.035$). The mean difference of 51.1 was above the minimally clinically important difference (MID) of IBS-SSS (MID = 50) (23) and thus beside statistically significant also clinically significant.

Tests of "between-subjects effects" showed that the effect size of the treatment was large (partial $\eta^2 = 0.68$; Cohen's f = 1.46). Sixty-eight percentage of the variance in IBS-SSS reduction after 3 months can be explained by the variable treatment. Furthermore, we found in this model no significant difference in IBS-SSS reduction after 3 months between both treatments ($p = 0.343$). In contrast to this result, patients' expectations for their therapies and IBS-SSS at pre-intervention both had a significant influence

TABLE 2 | Pairwise comparison based on estimated marginal means.

(I) IBS-SSS	(J) IBS-SSS	Mean difference (I-J)	Std. error	Sig.[a]	95% confidence interval for difference[a]	
					Lower bound	Upper bound
Baseline	1 month	74.6*	9.5	0.000	48.7	100.5
	3 months	109.1*	10.5	0.000	80.6	137.6
	6 months	92.9*	11.9	0.000	60.5	125.3

*The mean difference is significant at the 0.05 level.
[a]Adjustment for multiple comparisons: Sidak.

on outcome [expectations: $p = 0.041$; $F_{(df1,error63)} = 4.4$; partial $\eta^2 = 0.065$; IBS-SSS at pre-intervention: $p < 0.001$; $F_{(df1,error1.02)} = 19.3$; partial $\eta^2 = 0.234$]. The variable centers was not significant ($p = 0.454$). 23.4% of the variance in IBS-SSS reduction after 3 months can be explained by IBS-SSS at pre-intervention and 6.5% by patients' expectations for their therapies at pre-intervention.

Next we analyzed IBS-SSS at the various time points as within-subjects variable, with treatment as between-subjects factor and patients' expectations for their therapies as covariate (**Figure 2**). The assumptions for this repeated measure test are fulfilled (Box's test of equality of covariance matrices: $p = 0.103$; Levene's test of equality of error variances across treatment groups: $p > 0.05$ for all 4 time points).

A test for within-subjects effects showed, that there was no significant difference between Ayurveda and conventional nutritional therapy over time how they affected IBS-SSS [$p = 0.281$; $F_{(df1,error66)} = 1.2$; partial $\eta^2 = 0.018$]. There was also no significant difference between patients' expectations of their therapy over time how they affected IBS-SSS ($p = 0.130$; $F = 2.3$; partial $\eta^2 = 0.034$]. We had a nearly significant change in IBS-SSS over time (Wilks' lambda $p = 0.050$). There was the same change in mean IBS-SSS over time for both therapies (Wilks' lambda $p = 0.548$, i.e., there is no significant interaction).

Combining both treatments with patients' expectations for their therapies as covariate we obtain the following differences of estimated marginal means for IBS-SSS (**Table 2**).

Pairwise comparisons based on estimated marginal showed a clinically [mean difference (I-J) > MID (50)] and statistically significant improvement for all 3 time points compared to baseline ($p < 0.001$). In particular after 6 months there is still a significant positive effect for both treatments.

The 3D-surface plot of IBS-SSS reduction (**Figure 3**) shows that the reduction increases with IBS-SSS at pre-intervention and with patients' expectations regarding treatment. Patients with expectations ≤ 4 had a mean IBS-SSS reduction of 38.8 ± 74.9, a value below the minimally clinically important difference (MID) of IBS-SSS (MID = 50).

Fifty percent of the participants with severe IBS changed to moderate and 30% to mild (**Table 3**).

Secondary Outcomes

After 3 months, the mean values of the quality of life scores IBS-QOL were significantly ($p < 0.001$) improved from 53.4 ± 19.9 to 70.9 ± 20.9 in the Ayurveda group as well as significantly ($p = 0.002$) improved from 52.6 ± 21.8 to 64.5 ± 18.9 in the conventional group. The estimated marginal means adjusted for IBS-QOL at baseline and for participants' expectations at baseline as well as for study centers as a random effect were 15.8 ± 3.2 (95% CI = 9.4–22.3) for Ayurveda and 10.2 ± 3.5 (95% CI = 3.2–17.2) for conventional therapy. The mean difference of the improvement of IBS-QOL between baseline and 3 months based on estimated marginal means between both therapy groups was 5.5 ± 4.3 (95% CI = −3.1–14.1; $p = 0.206$). Sixty-three percent of the variance in IBS-QOL improvement after 3 months can be explained by the study treatments, 23.7% by IBS-QOL at pre-intervention and 3.2% by participants' expectations for their therapies at pre-intervention.

Table 4 is a summary of the most important results for the various outcomes. There were significant outcome improvements for most secondary outcomes treated with Ayurveda except for HADS-D ($p = 0.070$) and CPSS ($p = 0.093$) in contrast to conventional therapy, where all secondary outcome improvements were not significant except for the IBS-QOL score ($p = 0.002$) and the WHO-5 well-being index ($p = 0.042$).

Evaluation and Additional Questions

Ayurvedic intervention was rated slightly better than conventional intervention by the patients in several additional questions at the 3 months visit and the evaluation questions at the 6 months follow-up (Supplementary Tables in the **Supplementary Material**).

Safety

There were 20 adverse events (12 in the Ayurveda group and 8 in the conventional group) throughout the intervention period in 19 participants ($n = 11$ in the Ayurveda group and $n = 8$ in the conventional group). No serious adverse event occurred. Adverse events were especially common cold ($n = 8$). Four events were possibly related to change of diet [2 in conventional group (obstipation; diarrhea) and 2 Ayurveda group (pyrosis; obstipation)].

Adherence

The dieticians rated the adherence (external assessment based on dietary protocols and records made during the consultations) in the conventional group 8.0 ± 1.3 and in Ayurveda 7.0 ± 1.9 on NRS (0: not at all adherent to 10: very adherent). Self-rated compliance among the participants at the 3 months visit in the conventional therapy was 7.4 ± 1.5 and in Ayurveda 8.1 ± 1.5 and at the 6 months follow-up in the conventional therapy 6.5

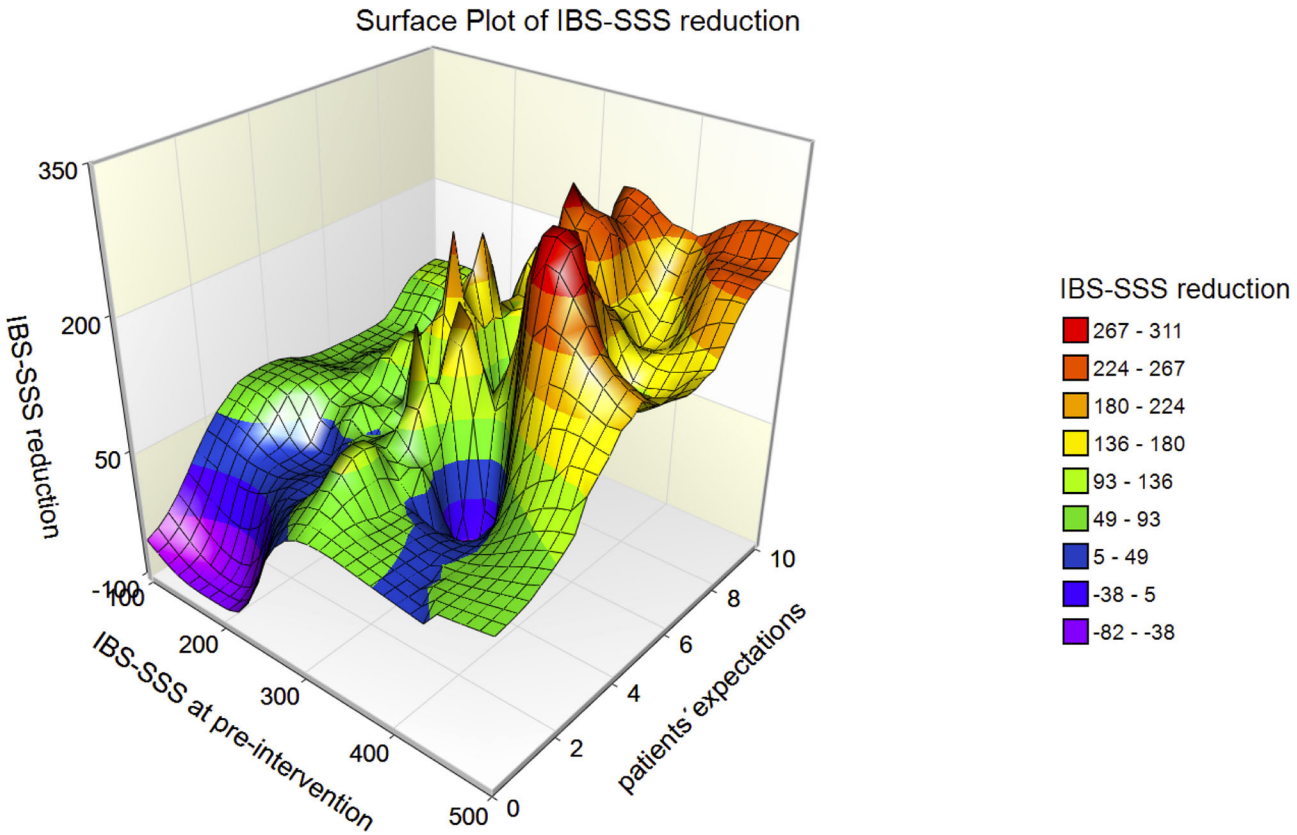

FIGURE 3 | 3D-surface plot of IBS-SSS reduction with respect to IBS-SSS at pre-intervention and patients' expectations. The higher IBS-SSS at pre-intervention and the larger the patients' expectations, the greater the IBS-SSS reduction.

TABLE 3 | Crosstabulation of IBS severity classes by IBS severity classes after 3 months.

		IBS-SSS after 3 months		
		Mild	**Moderate**	**Severe**
IBS-SSS at pre-intervention	Mild	100.0%		
	Moderate	56.4%	41.0%	2.6%
	Severe	30.0%	50.0%	20.0%
Total		49.2%	42.6%	8.2%

IBS-SSS, Irritable Bowel Syndrome-Severity Scoring System.

± 1.9 and in Ayurveda 6.2 ± 2.3 (0: not at all adherent to 10: very adherent).

DISCUSSION

The aim of this open-label multicenter randomized controlled clinical study with IBS patients was to investigate potential effects of Ayurvedic nutritional IBS therapy compared to conventional IBS therapy according to the recommendations of the German Nutrition Society including the low-FODMAP diet. The main findings of this study are:

- Both Ayurvedic and conventional therapy significantly reduced the primary outcome IBS-SSS at all 3 time points.
- The mean difference (51.1 ± 23.7) of the IBS-SSS reductions after 3 months between both therapy groups based on the estimated marginal means was statistically and clinically significant in favor of the Ayurveda group.
- Both therapies are equivalent in their contribution to the outcome variance.
- 68% of the variance in IBS-SSS reduction after 3 months can be explained by treatment, 6.5% by patients' expectations for their therapies and 23.4% by IBS-SSS at pre-intervention.
- Both patients' expectations of their therapies and the IBS-SSS at pre-intervention have a significant impact on the outcome. Notably, the higher the IBS-SSS score at pre-intervention and the larger the patients' expectations, the greater the IBS-SSS reduction.
- There were significant outcome improvements for all secondary outcomes in the Ayurveda group except for HADS-D, notably in contrast to conventional therapy where all secondary outcome improvements were not significant except for the IBS-QOL score and WHO-5.
- The compliance (both self-rated and externally assessed by dieticians) to the nutritional advices was high in both groups and deteriorated at the 6 months follow-up.

TABLE 4 | The means of the paired differences between outcome at baseline and after 3 months (paired samples test) and the effect of treatment (test of between-subjects effects).

Outcome	Ayurveda		Conventional		Tests of between-subjects effects (treatment)	
	Mean of the paired differences ± std	Sig	Mean of the paired differences ± std	Sig	Sig	Partial η^2
IBS - Severity Scoring System (IBS-SSS)	130.8 ± 81.2	<0.001	87.1 ± 99.5	<0.001	0.34	0.681
IBS - Quality Of Life (IBS-QOL)	17.5 ± 15.2	<0.001	11.9 ± 20.4	0.002	0.27	0.631
Cohen Perceived Stress Scale (CPSS)	1.9 ± 6.5	0.093	1.0 ± 5.6	0.289	0.62	0.281
Hospital Anxiety and Depression Scale (HADS-Total)	2.8 ± 6.1	0.01	−0.1 ± 5.2	0.947	0.41	0.582
Hospital Anxiety Scale (HADS-A)	1.8 ± 3.9	0.01	−0.3 ± 3.3	0.647	0.23	0.705
Hospital Depression Scale (HADS-D)	1.0 ± 3.3	0.07	0.2 ± 2.7	0.66	0.54	0.407
WHO-5 Well-Being Index	10.5 ± 21.3	0.006	6.7 ± 18.5	0.042	0.67	0.235

Ayurveda was rated slightly better in the participant evaluation and additional questions. No serious adverse event occurred.

Preconceived expectations of treatment may cause IBS patients to perceive and record the results of their symptoms differently, a particular problem with IBS, where treatment results are subjective, very sensitive to individual behavior and a considerable placebo/unspecific effect (24). Among IBS study patients, the placebo response rate is high (25, 26). A meta-analysis showed a pooled estimate of the placebo response rate of 42.6% (95% CI = 38.0, 46.5) in CIM trials (25). Therefore, recent placebo-controlled trials provide robust evidence of clinical efficacy vs. placebo, and the first meta-analysis of low-FODMAP RCTs reported a greater likelihood of reducing abdominal pain (OR 1.81), abdominal bloating (OR 1.75), and general gastrointestinal symptoms (OR 1.81) compared to controls (27). In line with these findings, the German Nutrition Society (as well as nutritional societies of several other countries) now recommend a low-FODMAP diet to be considered if basic nutritional advices have been unsuccessful for the dietary management of IBS (21, 28).

Over the past decade, numerous studies have been published on the effectiveness of the low-FODMAP diet for reducing IBS symptoms. A 2017 review found that at least 10 randomized clinical trials had examined the effectiveness of the low-FODMAP diet during the short-term food-elimination phase, with 50–80% of participants reporting an improvement in IBS symptoms (29). In a systematic review and meta-analysis published in 2018, 9 studies with a total of 596 participants were examined in which a low-FODMAP diet was compared with various control diets. The low-FODMAP diet improved the symptoms of IBS compared with other diets with regard to gastrointestinal symptoms, abdominal pain, and health-related quality of life (30). In comparison to other low-FODMAP studies our conventional nutritional diet intervention including the low-FODMAP diet had lower improvement on the IBS-SSS.

The authors are not aware of other studies assessing Ayurveda nutrition therapy for IBS patients to date when this manuscript was written. Studies on Ayurvedic therapy modalities for IBS patients thus far have analyzed herbal interventions only and do not investigate the dietary aspects of Ayurvedic treatment approach in IBS (31, 32). The striking lack of scientific evidence here is in marked contrast to the central importance of nutrition in Traditional Indian Medicine Ayurveda in general, but especially in relation to nutrition-associated diseases.

In conjunction with the positive clinical effects, recent studies have also shown that the low-FODMAP diet, which is not easy to adhere to for many patients due to its restrictive choices of foods (6), can lead to profound and possibly detrimental changes in the microbiota and metabolome, the duration and clinical relevance of which are not yet known (29). Looking at comparable effects in both groups in the adjusted model for the main outcome, the Ayurvedic nutritional concept for IBS, which was well-tolerated and evaluated by most patients, might be an effective and comparatively "easy-to-adhere-to" alternative (or add-on) to the low-FODMAP concept. Subsequent studies are warranted particularly in this area to further illuminate the potential role of Ayurvedic nutrition for IBS patients and in other diseases of digestive dysfunction. Since Ayurveda is one of the two largest traditional medicine systems globally, along with TCM, and is increasingly being offered and used outside of its countries of origin, there is an obvious research gap (33). This gap should be filled by robust clinical studies using Whole Systems and Mixed-Methods research, among others, to find out whether such Ayurvedic concepts are effective, safe and implementable under Western conditions (34, 35). According to our interpretation of the Ayurvedic principles, IBS symptoms can be understood as an expression of "over-burdening" of the "digestive fire" agni. And our main hypothesis in this study was that any factor, which reduces the workload of agni and stabilizes its function, is helpful to reduce IBS symptoms. This approach we framed as general nutritional therapy of Ayurveda. In addition, symptom specific advice was given to each patient (specific nutritional therapy). The general therapeutic

approaches could be comparable with a foundation, on which specific nutritional interventions can exert their action more effectively. The main general measures selected in this study in order to "deburden" agni were 1. warm food, 2. regular timings of meals which correlate with Ayurveda concepts of biorhythm, and 3. food articles which are generally light in digestion, but still satisfying and nourishing. The **Supplementary Material** *General and Specific Nutritional Therapy of Ayurveda* provides more details. According to the patients' life circumstance and their grade of motivation these ideals were individually adjusted during the nutrition consultations, which could lead to a partially reduced therapeutic effect.

The strengths of our study include the use of recommended and validated assessment tools and outcome parameters, clearly defined inclusion/exclusion criteria and consensual interventions in a multicentric setting. The implementation of an Ayurvedic nutritional approach that was both consequently based on traditional Ayurvedic paradigms and was adapted to a Western setting is also a strength of this study. Notably, only few minor adverse events occurred, suggesting that both interventions can be considered as safe and well tolerable which is of particular interest regarding the Ayurvedic concept since it had not been analyzed in a comparable setting before.

This study also has a number of limitations. First, the extent to which the observed effects were non-specific, particularly due to the attention of nutritional therapists, the influence of the specific settings and individual participants' beliefs and preconceptions about potential health effects of Ayurveda and meaning-responses cannot be estimated (25, 36). Second, this study did not have a minimal treatment or waiting list control group, thus the absolute effects of both of the interventions could not be calculated. Studies with a waiting control group or a participant preference trial are necessary to estimate non-specific effects (37, 38). Also, treatment effects might be linked to the natural course of the disease and/or patients might have variable symptoms. Third, a possible selection bias could not be excluded, as the majority of study participants was recruited via the Charité outpatient department for Complementary and Integrative Medicine. Fourth, the external physician could be a medical doctor of any specialty, so that a highly reliable IBS diagnosis such as one made by a board-certified gastroenterologist may not be guaranteed. Also, we used the national German S3 guidelines, which slightly differs from the IBS definition of the Rome III and IV consensus. Fifth, the drop-out rate in the conventional group was higher than anticipated and this poses another limitation to this study. The high attrition rate may introduce a bias into the results as we cannot rule out that participants dropped out due to dissatisfaction with or perceived ineffectiveness of the study intervention. Other reasons for drop-out may be related to the randomization to the different study interventions and the associated dissatisfaction of some participants. Also, a number of participants may have expected a faster relief through the interventions and thus may have experienced a loss of motivation when a relief of IBS symptoms did not emerge within the first weeks. Sixth, possible long-term effects remain unclear, as the study did not have long-term follow-ups. Seventh, this trial analysis was not analyzed by blinded statisticians. Eighth, this trial used the IBS-SSS as primary outcome. Alternatively, an 11-point NRS assessing worst abdominal pain in the past 24 h may also be adequate as a primary end point (39).

The conventional nutritional diet intervention including the low-FODMAP diet had lower improvement on the IBS-SSS in comparison to other low-FODMAP studies. This may indicate that our conventional nutritional counseling may not have provided advice strictly according to the low-FODMAP guidelines. The intervention was designed to explain the principles of a balanced diet for IBS patients in accordance with the German Nutrition Society and the essence of a low-FODMAP diet. We used dietary protocols as quality control and had them assessed by the consultants. However, we did not evaluate them from a nutritional point of view, so we do not know in detail if and to what extent the participants reduced the FODMAP content.

Another question to be addressed could be the feasibility and communicability of Ayurvedic dietary recommendations for IBS by conventional healthcare professionals without prior Ayurvedic knowledge. For example, as shown in the **Supplementary Material** of this publication, Ayurvedic dietary recommendations do not differ significantly in complexity from most other dietary recommendations for IBS, so that most likely no disproportionate effort would be required on the part of the relevant professionals to acquire the appropriate training and expertise. However, further transdisciplinary research would be desirable in this area as well.

CONCLUSION

Patients with IBS seem to benefit significantly from both Ayurvedic and conventional nutritional counseling. The expectations regarding interventions influenced the outcome parameters. Based on these results, Ayurvedic nutrition therapy could be a useful part of IBS treatment. Multicenter confirmatory studies with higher patient numbers, longer-term follow-ups and patient preference designs are indicated to confirm the results of this study, also to clarify whether such a therapy might not be even more effective than established conventional nutritional therapies for the treatment of IBS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MJ: guarantor of article, conceptualization, methodology, investigation, data curation, writing—original draft preparation, and project administration. TW: investigation, data curation, and writing—review and editing. DS, MM, DK-L, HC, and VM: writing—review and editing. LP: data curation, writing—review and editing. AM: conceptualization, supervision, and project administration writing—review and editing. NS: data curation and writing—review and editing. ES: writing—original draft preparation and review and editing. MW: formal analysis, data curation, data analysis, supervision, writing—original draft preparation, and review and editing. CK: conceptualization, methodology, supervision, project administration, and writing—review and editing. All authors approved the final version of the article.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.622029/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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2.4 Effekte von Yoga und Achtsamkeitsmeditation bei Distress – eine dreiarmige randomisiert kontrollierte Studie

Stress ist ein wachsendes Problem in industrialisierten Gesellschaften [78-80]. In dieser dreiarmigen randomisiert kontrollierten *Mixed-Methods* Studie wurden Probanden mit Distress und stress-assoziierten Symptomen in drei Gruppen randomisiert:

(1) "integrative" Yogakurse, die körperliche Übungen, Achtsamkeitstraining und ethische/philosophische Aspekte des traditionellen Yoga, säkularisiert im Gruppensetting vermittelt, kombinierten,

(2) körperorientierte Yogakurse, die v.a. körperliche Übungen beinhalteten, oder

(3) Achtsamkeitstraining ohne körperliches Training zugewiesen [98].

Mit dieser Studie sollte untersucht werden, inwieweit sich die o.g. MBM-Interventionen (jeweils 8 Termine á 90 Min.) in ihrer stressreduzierenden Wirkung voneinander unterscheiden. Von besonderem Interesse war, ob es Hinweise auf synergistische Effekte gibt, wenn körperliche Yogaübungen mit (mentalen) Achtsamkeitsübungen wie in Gruppe 1 kombiniert werden.

Als primärer Endpunkt wurde der Gruppenunterschied auf der *Cohen's Perceived Stress Scale* (PSS) nach 12 Wochen untersucht. Zu den sekundären Endpunkten gehörten Burnout, Lebensqualität, Depression, Achtsamkeit u.a. erhoben mit validierten Fragebogeninventaren. Alle Endpunkte wurden zu Beginn der Studie, nach 12 Wochen und nach 24 Wochen erhoben. Eine Stressreduktion im Bereich großer Effektstärken wurde in allen Gruppen beobachtet. Jedoch konnten keine signifikanten Gruppenunterschiede oder Hinweise auf relevante Synergieeffekte durch die Kombination von Achtsamkeit und körperlichen Yogaübungen identifiziert werden. In den sekundären Endpunkten konnten mittlere bis große Effekte mit marginalen Unterschieden zwischen den drei Interventionen in verschiedenen sekundären Endpunkten dargestellt werden. Die durchgeführten qualitativen Interviews zeigten, dass nur die Teilnehmer der Achtsamkeits- und der integrativen Intervention das Gefühl hatten, praktischere Fähigkeiten für den Umgang mit Stress im Alltag erworben zu haben. Alle Befragten

hatten sich vorgenommen, weiterhin möglichst regelmäßig Yoga oder Achtsamkeit zu praktizieren.

Zusammenfassend erwiesen sich die drei MBM-Interventionen als gleichermaßen wirksame Methoden zur Stressreduktion. Ihr Einsatz in der Praxis sollte von der generellen Verfügbarkeit und der Patientenpräferenz abhängen.

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Stress Reduction by Yoga versus Mindfulness Training in Adults Suffering from Distress: A Three-Armed Randomized Controlled Trial including Qualitative Interviews (RELAX Study)

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Abstract: Distress is a growing public health concern. In this three-armed randomized controlled trial, n = 102 adults with elevated stress levels and stress-related symptoms were randomly assigned to (1) "integrative" yoga classes which combined physical exercises, mindfulness training, and ethical/philosophical aspects of traditional yoga; to (2) Iyengar yoga classes which entailed primarily physical exercises; or to (3) mindfulness training without physical training. We hypothesized the synergistic effects of physical yoga exercises, mindfulness, and ethical/philosophical aspects. The primary outcome was the group difference on Cohen's Perceived Stress Scale (PSS) after 12 weeks. Secondary outcomes included burnout, quality of life, physical complaints, depression, anxiety, mindfulness, interoceptive awareness, self-regulation, spirituality, mysticism, and posttraumatic stress. All outcomes were evaluated at baseline (V0), after 12 weeks (V1), and after 24 weeks (V2). A subset of participants took part in qualitative interviews. A lasting and clinically relevant stress reduction was observed within all groups (PSS $\Delta V0–V1_{\text{Integrative Yoga}} = -6.69 \pm 6.19$; $\Delta V0–V1_{\text{Iyengar Yoga}} = -6.00 \pm 7.37$; $\Delta V0–V1_{\text{Mindfulness}} = -9.74 \pm 7.80$; all $p < 0.00$). Effect sizes were also statistically large at the end of the follow-up period (Cohen's $d_{\text{Integrative Yoga}} = 1.41$; $d_{\text{Iyengar Yoga}} = 1.37$; $d_{\text{Mindfulness}} = 1.23$). There were no significant group differences or evidence of relevant synergistic effects from combining mindfulness and physical yoga exercises. All three interventions were found to be equally effective methods of stress reduction. Their use in practice should be based on availability and patient preference.

Keywords: yoga; iyengar yoga; mindfulness; meditation; stress reduction; mixed methods

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1. Introduction

Stress has been defined as a real or anticipated disruption of the homeodynamic balance or an anticipated threat to well-being [1]. It can be caused by a wide range of intrinsic or extrinsic stimuli or stressors. Stressors can be real or perceived; thus, stress can be physical, but also purely psychological [2].

Two of the major physiological systems of stress response include the hypothalamic–pituitary–adrenocortical (HPA) axis and the autonomic nervous system (ANS). In contrast to repeated, ephemeral, and motivating stress, inadequate, aversive, excessive, or prolonged stress may exceed the regulatory capacity and adjustive resources of the organism. Chronic stress can, thus, cause sensitization, as well as habituation, of the HPA axis and

ANS responses [1]. In consequence, maladaptive responses are produced, as well as chronically altered homeodynamic capacities, associated with negatively affected mental health, physical health, and life expectancy [2–4].

Consequently, increased stress is a significant risk factor for the most common chronic diseases [5,6]. Acute and chronic stress is implicated in the development of hypertension, coronary heart disease, general cardiovascular mortality, infectious diseases, chronic inflammation, chronic pain, fatigue syndrome, obesity, diabetes type II, metabolic syndrome, osteopenia/osteoporosis, headache, and cancer, among others [7–15]. Furthermore, it is linked to a broad range of psychiatric disorders, including anxiety, depression, eating disorders, post-traumatic stress disorder, and sleep disorder [12–18]. Stress, therefore, results in estimated annual costs of more than 1% of the gross domestic products of Western countries [19–21].

It has been shown that relaxation techniques can interrupt a chronic stress load, and, thus, help avert its negative consequences [22,23]. Moreover, they can enable changes in cognition, thus reducing perceived stress [22–26]. Various techniques have been shown to be effective and are routinely applied in prevention, therapy, and rehabilitation [27,28]. Particularly prevalent is the use of mindfulness-based methods such as mindfulness meditation and yoga [29–31].

Mindfulness describes focusing on the present moment. Body perceptions, thoughts, and emotions are met with a non-judgmental and accepting attitude [32,33]. Its psychological mechanisms of action are well researched. By training the ability to focus on the present, it helps to disrupt dysfunctional mental processes [22,25,26,34,35]. On a neuropsychological level, areas of the brain involved in emotion regulation are activated and trained [36]. Ultimately, improved attention regulation can lead to the ability to control thoughts, feelings, and behavior better [24,25,37]. The dysfunctional experience and management of stress, which is associated with poor emotion regulation, negative cognitions, and impulsive behavior, can be changed [24,32,38–43]. Subjectively perceived stress then decreases, allowing for increases in physical and mental health and in quality of life [42,44–48].

Yoga originated in South Asia more than 2000 years ago. It traditionally integrates religious, spiritual, physiological, and psychological methods into a "Whole Medical System" [49]. There are different styles of yoga that emphasize certain sub-aspects. This diversity makes it difficult to standardize its mechanisms of action, and to study yoga in general [50]. Most research on yoga as a medical tool focuses on less complex "body-oriented" forms of yoga such as Iyengar yoga. More complex forms are poorly studied in terms of medical outcomes, including stress reduction. The results of the few available studies examining integrated yoga show positive effects regarding stress experience, anxiety, depression, quality of life, and physical illness [51,52]. Practitioners may benefit from the synergistic effects of different aspects of yoga [53,54]. In this study, an attempt is made to reflect a complex kind of yoga in the sense of a Whole Medical System under the name "integrative yoga", including physical yoga exercises, mindfulness, and ethical/philosophical aspects [55].

Iyengar yoga is a widely recognized and well researched style of yoga. In its initial stages, Iyengar yoga focuses largely on the physical practice of yoga postures, and can, therefore, be described as "body-oriented". It was established from 1937 on by its founder, B.K.S Iyengar. He systematically studied the benefits of various yoga exercises, and introduced assistive devices so that people with different physical conditions could perform the exercises [56]. His scientific approach contributed significantly to the researchability of yoga [57]. In our own studies with women suffering from stress, pronounced beneficial effects on quality of life, anxiety, stress, and depression were found after 12 weeks of intensified Iyengar yoga practice [57,58]. Another study showed evidence of anxiolytic and antidepressant effects of Iyengar yoga [59]. In the context of this study, Iyengar yoga exercises were taught without meditation and philosophical content to reflect only the physical aspect of yoga.

Mindfulness training, integrative yoga, and Iyengar yoga differ significantly in terms of content and physical engagement. This leads, in turn, to differences in clinical applicability and, possibly, efficacy. In integrative yoga, meditation, physical movement, and ethical/philosophical aspects are combined with the principles of mindfulness, possibly enhancing efficacy [60,61]. Mindfulness training, in comparison, has very low physical requirements for the practitioner [38]. Although the psychological mechanisms of action of mindfulness are well researched, it is unclear whether mindfulness-based relaxation techniques develop their effect solely through an improved capacity for mindfulness [39].

Against this background, the present study investigates the extent to which the above-mentioned relaxation methods differ from one another in their effects. Of particular interest is whether there are indications of a special effectiveness when physical exercises are combined with mental mindfulness exercises.

Hypothesis 1. *Stress reduction by integrative yoga > stress reduction by Iyengar yoga > stress reduction by mindfulness training.*

We also examine whether stress reduction, along with any other effects, differentially affects quality of life. In doing so, we assume an increased effectiveness depending on the number of potential effect factors of each method.

Hypothesis 2. *Quality of life by integrative yoga > quality of life by Iyengar yoga > quality of life by mindfulness training.*

To adequately map the broader, multifaceted effects of integrative yoga, Iyengar yoga, and mindfulness training, we also conducted qualitative interviews. These were intended to provide a more accurate understanding of how study participants experienced each intervention. Moreover, they were to provide information on how the interventions may have changed the participants' perception of stress in daily life. The findings are intended to further elucidate the mechanisms of stress reduction, and might allow for a more targeted use of yoga and/or mindfulness training in clinical psychological practice.

2. Materials and Methods

2.1. Study Design

We conducted a single-center, three-arm, randomized, controlled clinical trial combined with qualitative interviews. N = 102 participants with elevated perceived stress levels and physical stress-related symptoms (e.g., muscle tension) were randomly assigned to (1) integrative yoga classes which combined physical exercises, mindfulness training, and ethical/philosophical aspects of traditional yoga; to (2) Iyengar yoga classes which focused on physical exercises; or to (3) mindfulness training without any physical exercises. The allocation ratio was 1:1:1. Each group received the same amount of instruction and daily exercise over a period of 6 months (12-week intervention period, 12 weekly classes of 90 min each, followed by 12-week follow-up period; Figure 1). A home exercise practice was recommended for participants in all groups (30 min daily; also during the follow-up period). The primary outcome was the group difference on the Perceived Stress Scale by Cohen (PSS) after 12 weeks. Secondary outcomes included burnout, quality of life, physical complaints, depression, anxiety, mindfulness, interoceptive awareness, self-regulation, spirituality, mysticism, and posttraumatic stress. All outcomes were assessed at baseline, after 12 weeks, and after 24 weeks (follow-up) by validated questionnaires in the German language. In addition, adherence was monitored weekly via an online questionnaire for 12 weeks (practice time in minutes per week).

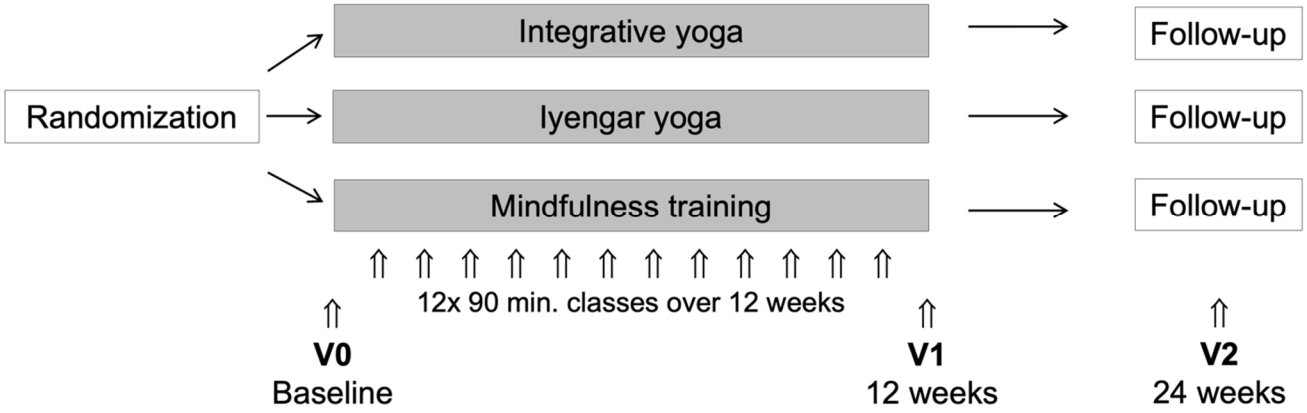

Figure 1. Study structure.

A randomly chosen subset of participants from each group participated in qualitative interviews. Semi-structured individual interviews were conducted during the follow-up period. A mixed-method approach was chosen to enable a deeper understanding of patients' experiences with each relaxation technique, and to generate future hypotheses about their mode of action. Initially, progressive muscle relaxation was supposed to be the non-physical control instead of mindfulness training. Popularity for this intervention was very low among potential study participants during early recruitment. Therefore, mindfulness training was introduced as a replacement before interventions started. The study registration and ethics approval were amended accordingly.

2.2. Recruitment

Patients were recruited from July 2019 until January 2021 in Berlin, Germany. The study was advertised for in Berlin public transport, on social media, on the premises of the Charité University hospital via flyers, and on the website of the Charité Outpatient Clinic for Integrative Medicine. Volunteers were screened on the telephone, and later checked for eligibility by a study physician. Baseline assessment directly followed if patients were eligible (Table 1).

Table 1. Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
• Age 18–65 years • Subjectively perceived stress $\geq$ 4 out of 10 on a numeric analog scale (Numeric Rating-Scale, NRS 0–10, 0 = no stress at all to 10 = maximum stress) for $\geq$1 month • At least 3 of the following 8 stress symptoms: sleep disorder, inappetence or increased appetite, shoulder neck tension/back pain, tension headache, concentration disorder, exhaustion, nervousness/irritability, stress-associated digestive problems	• Pregnancy or breastfeeding • Serious acute or chronic illness • Serious mental illness • Immobility/limitation for gymnastic exercises due to orthopedic, neurological, or other medical reason • Participation in another study

2.3. Randomization

Patients were enrolled and randomly assigned to one intervention after baseline assessment by a study physician. The randomization list had been generated by an independent researcher from another project, using blockrand library (v 1.4) with varying block lengths in R (v 3.5). The sequence was not known to the study physicians. Intervention groups were

filled until each group had at least four participants. Then, a 12-week program started for one cohort. Recruitment was ongoing. In total, there were four cohorts of three groups each.

2.4. Setting

Yoga/meditation classes were taught exclusively for the study participants by certified instructors in commercial studios for each integrative yoga, Iyengar yoga, and mindfulness training. The instructors for integrative yoga were required to have completed a 4-year program by the Professional Association of Yoga Teachers in Germany (BDY/EYU). The instructors for Iyengar yoga were required to have a certification of Iyengar Yoga Germany (IYD), a program which involves 1000 h of training. The instructors for mindfulness training had to be qualified psychologists with experience in mindfulness meditation. Applicable studios in central Berlin were asked to support the trial. Three studios were chosen based on their willingness to participate and accessibility. All instructors taught exclusive classes of 4–12 study participants once per week for 12 weeks. Every session lasted 90 min. The premises of all studios were of comparable dimensions, lit, unfurnished, painted in neutral colors, quiet, and warm. The content of each lesson was determined in advance in collaboration with the study physicians and logged. The teaching instructors remained the same during every 12-week program. No evaluation or examination was carried out by the instructors. Only the 1st cohort with 15 participants took place on site; all other 3 cohorts were offered online due to the COVID-19 pandemic.

All examinations were carried out by the study physicians and took place in the Charité Outpatient Clinic for Integrative Medicine. In the first cohort, study participants visited the study center for examinations at baseline, and at the end of the 12-week intervention. However, due to the COVID-19 pandemic, on-site study visits were not possible, so these were conducted online in the following cohorts.

2.5. Interventions

2.5.1. Integrative Yoga

Participants in group 1 received an established integrative yoga program in the sense of a "Whole Medical System". "Whole Medical System" refers to an independent, comprehensive, and self-contained philosophy about health, including an owned (medical) practice [62]. Classes contained meditation and relaxation techniques, as well as the exercise of yoga postures (asanas), breathing techniques (pranayama), and ethical/philosophical aspects of yoga (Supplementary Materials: Standard Operating Procedures-Integrative Yoga Practice). The methods and content could also be tailored specifically to the individuals' wishes and needs to further reflect the idea of integrative yoga [55]. Therefore, the operationalization was supposed to reflect the inherent adaptability of yoga practice [51,52,63]. The integration and combination of the individual contents of yoga was to allow for a concentration of positive effects.

2.5.2. Iyengar Yoga

The participants of group 2 received an established yoga program based on the internationally renowned yoga school of B.K.S. Iyengar [56]. Classes focused on the physical aspects of yoga and did not entail meditation or the ethical and philosophical aspects of yoga. They focused on executions of yoga postures (asanas) and a final relaxation (Shavasana; Supplementary Materials: Standard Operating Procedures—Iyengar Yoga Practice). In accordance with the teachings of B.K.S. Iyengar, assistive devices could be used when practicing yoga postures. A similar program had produced increases in quality of life and reductions in anxiety, stress, and depression in a prior study [57].

2.5.3. Mindfulness Training

The participants in group 3 received mindfulness training on healthy stress management by a trained psychologist. The program was based on the principles of Mindfulness-Based Stress Reduction (MBSR) by Kabat-Zinn [64], but was expanded to 12 weeks to match

the other two intervention groups. In addition, the "mindful stretching" portion included in the original program by Kabat-Zinn was omitted. The classes included mindfulness-based meditation and practical strategies for stress management (Supplementary Materials: Standard Operating Procedures—Mindfulness Training). The main goal was to improve the perception of inner processes and needs by practicing a conscious, moment-oriented, and open attitude. This was supposed to enable an early and adequate response to stress, and, thus, reduce perceived stress in general [65].

2.6. Primary Outcome

The main endpoint, the subjective stress experience, was examined using the Perceived Stress Scale that was originally developed by Cohen, Kamarck, and Mermelstein in 1983 [66]. It is based on Lazarus' psychological stress model [67]. The scales are intended to measure the extent to which life situations have been experienced as stressful in the past month, especially the extent to which a person feels that everyday coping is characterized by unpredictable, uncontrollable, and over-stressful experiences. In addition, it assesses whether the individual stress limit has been exceeded. The assessment of the subjective stress experience is made on a scale of never (1), almost never (2), sometimes (3), quite often (4), and very often (5). The original 14 items are applicable to the general population due to their universality [68]. The PSS has high internal consistency and test–retest reliability [66]. Due to the superiority of the reliability of the 10-item short version (Cronbach $\alpha = 0.78$ vs. Cronbach $\alpha = 0.75$), the applicability of this scale in clinical settings is indicated [68]. The German translation used has been validated [68,69].

2.7. Secondary Outcomes

2.7.1. Maslach Burnout Inventory (MBI)

Burnout syndrome can be a consequence of prolonged stress exposure [70]. The Maslach Burnout Inventory (MBI) is the most used tool in research on burnouts, and assesses three components with 22 items of burnout syndrome: cynicism, exhaustion, and reduced professional efficacy [71,72]. A validated German version (MBI-D) was being used [73,74].

2.7.2. Short Form 36 Health Survey (SF-36)

The Short Form 36 Health Survey (SF-36) is an internationally renowned tool to assess quality of life in medical, psychological, and economic research [75]. It provides a comprehensive assessment of a person's health status in 8 dimensions, ranging from physical functioning to emotional and social functioning. These can be summarized to a mental and to a physical component summary score [76].

2.7.3. Beschwerden-Liste/Zerssen Symptom List (B-LR and B-LR')

The Zerssen Symptom List was developed as a self-assessment tool for general and somatic symptoms [77]. Two parallel forms exist, which are closely correlated with each other ($r \approx 0.9$). They allow an assessment of the subjectively perceived physical well-being.

2.7.4. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a clinically meaningful 14-item psychological instrument used for screening states of depression and anxiety in the setting of a hospital medical outpatient clinic [78,79]. The HADS allows tracking the course of diseases and the response to psychotherapeutic and psychopharmacological intervention over time [80]. It is recognized as an economical, reliable, and sufficiently valid self-assessment method [81,82]. A validated German Version (HADS-D) has been used [81].

2.7.5. Freiburg Mindfulness Inventory (FMI)

The Freiburg Mindfulness Inventory was developed to reflect the concept of mindfulness, including its Buddhist tradition [83]. The items consist of statements such as "I

accept unpleasant experiences" and are rated on a 4-point frequency scale from "almost never" to "almost always". The 14-item version has been validated for both individuals who meditate regularly and for normal samples. The original German version has a high internal consistency and validity [84].

2.7.6. Multidimensional Assessment of Interoceptive Awareness (MAIA)

The Multidimensional Assessment of Interoceptive Awareness reflects 8 dimensions of mind–body interaction or body awareness [85]. It is used in research to evaluate the effects of diseases such as major depression or fibromyalgia on mind–body interaction [86,87].

2.7.7. Self-Regulation Inventory (SRI)

The Self-Regulation Inventory consists of 16 questions concerning the assessment of self-regulation according to Grossarth-Maticek [88]. The items have a scale from 1 (very weak) to 6 (very strong), and are calculated into a sum value. The questionnaire was applied and tested regarding validity and reliability [89]. It was found to have excellent internal consistency (Cronbach $\alpha = 0.948$) and sufficient test–retest reliability ($r = 0.796$) [90].

2.7.8. Aspects of Spirituality (ASP)

The Aspects of Spirituality questionnaire is an open 40-item multidimensional construct to measure the distinct expression of spirituality with both religious and secular forms [91,92]. The questionnaire is suited for skeptical, areligious, and religious individuals [93]. It was used to monitor possible changes in spirituality, especially in the integrative yoga group, whose participants were also exposed to spiritual content (these were communicated in an ideologically neutral way).

2.7.9. Hood's Mysticism Scale (HMS)

Hood's Mysticism Scale is a questionnaire that allows the quantification of spirituality and the perceived attainment of insight [94]. Its three-factor structure has been validated for followers of different faiths [95]. The 8-item short form was used in this study [96].

2.7.10. Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5)

The Posttraumatic Stress Disorder Checklist was used to monitor possible inherent posttraumatic stress. It comprises 17 items which resemble the PTSD symptom criteria [97]. It is the most widely used measure of posttraumatic stress disorder and has high internal consistency ($\alpha = 0.94$), test–retest reliability ($r = 0.82$), and discriminant ($rs = 0.31$ to 0.60) validity [98].

2.8. Sample Size

For the 12-week comparison of the groups, an effect size of $f = 0.15$ (corresponding to a Cohen's $d = 0.3$) was assumed in favor of integrative yoga. An optimal sample size per group of $n = 30$ was calculated for a repeated measures ANOVA, of which only the interaction between time × groups would be evaluated, further with 80% statistical power, and a correlation between measures of 0.6 (estimated from previous studies) and an alpha of 0.05. The total optimal sample size of $n = 90$ was increased by 20% to compensate for dropouts. The recruitment target was, therefore, $n = 108$.

2.9. Statistical Methods

The data collected were analyzed using SPSS 25. Outliers were supposed to be identified by visually checking raw boxplots. No data were excluded as a result. Missing values were imputed (MICE algorithm). Descriptive statistics were applied to present the sample characteristics. To test the hypotheses that integrative yoga is superior to Iyengar yoga and mindfulness training in terms of stress reduction and health-related quality of life, individual differences (gains) were first calculated, followed by a single-factor analysis of variance. As the number of 34 patients in each group was larger than 30, the distribution

of the data was assumed to be asymptotically normal. Results are given as F, p, and eta^2 effect sizes (with small, medium, and large effects assessed for eta$^2 \geq 0.01$, 0.06, and 0.14, respectively). Multiple *t*-tests were employed in an exploratory manner to present changes (gains) within each of the three groups separately. Results here are given as T, p, and effect-size Cohen's d (with small, medium, and large effects assessed for Cohen's d ≥ 0.20, 0.50, and 0.80, respectively (Cohen and Sawilowsk [99,100]). All statistical analyses were performed as intention-to-treat analyses.

2.10. Qualitative Approach

The study questions of how the interventions were experienced, and in what ways they potentially affected the subjects' experience of stress in their daily lives, required a qualitative design [101]. We chose semi-structured individual interviews in conjunction with a content analysis according to Mayring [102]. Interviewees should have been present in at least 6 out of 12 classes to ensure a minimum level of exposure. From all study participants who met this requirement and were interested, participants were randomly selected for the qualitative interviews. All study participants received an invitation to volunteer in the interviews. Participation was incentivized with a book voucher worth 10€. In the absence of theoretical saturation, more interviews could have followed.

The two researchers involved in the qualitative part of the study (JMF and TRH) each contemplated their own experience and beliefs regarding stress, mindfulness, and yoga. None of them had prior experiences with yoga or mindfulness, but they reported formative personal experiences with stressful experiences in college and academia. Both reported considering stress exposure to be a relevant problem and acknowledged the possibility of being personally influenced in this regard.

The interview guideline was created according to the study questions. It contained a brief explanation of the interview process for the participants to create an open and judgment-free discussion atmosphere. This was followed by three open questions on the subjective experience of the respective intervention, possible changes in everyday life, and an outlook for the future. Each question was accompanied by key points on possibly relevant topics that could be asked additionally (Supplementary Materials: Interview Guide).

Due to COVID-regulations, the interviews were held online. There were no time limits, and 30 min was estimated. The raw data were transcribed, and a semantic transcription of the content was carried out. The interviews were transcribed uniformly, word for word. Filler words such as "hmm" were removed, and dialects were translated into plain German.

Data evaluation and category building were performed according to Mayring's content analysis [102]. In this work, the focus was only on verbal communication. Body-language-specific elements were not considered. The categories were formed inductively [103]. MAXQDA® software (version 2018.2, Berlin, Germany) was used for the analysis.

In the initial systematic coding of the material, the texts were carefully read sentence by sentence, and sections of meaning were recorded, their meaning identified, and a code was formed from this. This was carried out independently by JMF and TRH to achieve a degree of intersubjectivity. Moreover, at this point, both researchers independently concluded that a theoretical saturation had been reached. No further interviews were conducted.

The initial rough coding identified and summarized relevant passages from the interviews. Simple sentences, sections of meaning, or short dialogues counted as codes. Single statements could be coded several times, and a section could be assigned to an already existing code. The codes were structured, combined, and assigned to different topics. In this way, potential topics and subtopics were compiled, and an overview of possible relationships between these topics was created. A review, restructuring, and revision of the codes took place until a meaningful structure emerged and an overview of the themes and their relationships to each other could be depicted. The resulting category system allowed to identify relevant themes and their relation to each other. In the last step of the analysis, an overview of all relevant data (category system and content) was examined considering the research questions. For this purpose, individual statements were paraphrased concisely

and limited to the content in the summary analysis. In this paraphrasing, text components that were unimportant for the content were omitted, and those that occur frequently were summarized [102].

3. Results

3.1. Quantitative Results

The trial ended after the planned number of participants reached the end of the follow-up period. We analyzed the data of n = 102 study participants in the intention-to-treat analysis. Three-hundred and five volunteers were initially screened for eligibility, and two-hundred and three were excluded prior to randomization (Figure 2). One-hundred and two were randomized and did receive an intervention. Out of 35 participants assigned to the integrative yoga group, 30 completed the study. Three dropped out because they felt regular attendance only added to tightening their daily schedules. Two dropped out because they felt the program was not effective. Thirty-three participants were assigned to the Iyengar yoga group, twenty-six of which completed the study. A total of seven were lost to follow-up, three because regular attendance added to their stress, three because they felt the Iyengar yoga program was not working for them, and one person reported she did not get along with her instructor. Thirty-four participants were assigned to the mindfulness training group, and twenty-eight of them completed the study. Six were lost to follow-up, four because they struggled with regular attendance, one because they felt mindfulness training was not effective, and one because they were dissatisfied with the group they were randomly assigned to. No participants changed intervention groups.

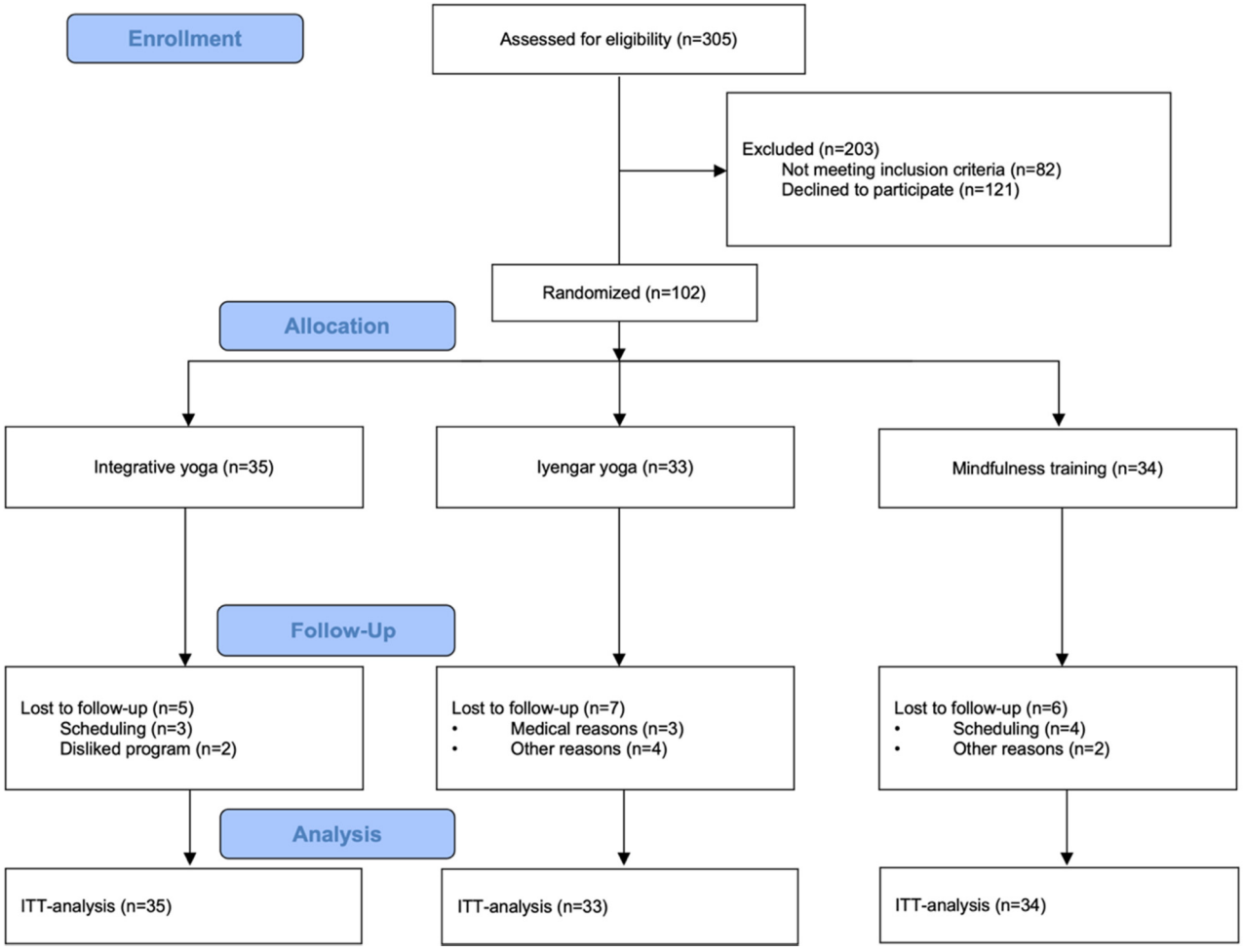

Figure 2. Participant flow.

When the COVID-19 pandemic hit Germany in early 2020, all classes were seamlessly converted to an online format (live-streaming of the classes). Single patients had technical difficulties at first, which could be resolved with the help of the instructors and the study-personnel. The online format was fully implemented for every participant after a transitional period of two weeks. The overall mean attendance for the 12 weekly training sessions in each group was: integrative yoga: 9.0 ± 2.3 sessions; Iyengar yoga: 7.2 ± 3.1 sessions; mindfulness: 8.0 ± 4.2 sessions.

A total of 18 participants was lost to follow-up across all groups. Missing data were checked for systematic bias. Little's test was non-significant with a Chi^2 of 253.3 (at df = 350 degrees of freedom); $p = 0.999$. Therefore, it was assumed that data were missing completely at random.

Baseline characteristics in all groups were similar, as a sign of successful randomization (Table 2). As expected, the primary outcome of perceived stress (PSS) was more than two standard deviations higher before the intervention in all groups (PSS scores: integrative yoga: 33.91 ± 4.80; Iyengar yoga: 33.39 ± 5.91; mindfulness: 34.44 ± 5.84) compared with the general population (PSS in the general population: age 20–39: 12.74 ± 6.67; age 40–59: 12.82 ± 6.42) [68].

Table 2. Baseline characteristics.

Characteristic	Total	Integrative Yoga	Iyengar Yoga	Mindfulness
Female (%)	91 (89.2%)	31 (88.6%)	28 (84.8%)	32 (94.1%)
Male (%)	11 (10.9%)	4 (11.4%)	5 (15.2%)	2 (5.9%)
Age (SD)	46.7 (11.5)	46.0 (11.5)	48.4 (10.6)	45.7 (12.5)
Highest level of education				
University (%)	73 (71.6%)	25 (71.4%)	24 (72.7%)	24 (70.6%)
Highschool (%)	13 (12.7%)	4 (11.4%)	4 (12.1%)	5 (14.7%)
Secondary school (%)	12 (11.8%)	4 (11.4%)	3 (9.1%)	5 (14.7%)
No graduation (%)	4 (3.9%)	2 (5.7%)	2 (6.1%)	0 (0.0%)
Employment status				
Full-time (%)	39 (38.2%)	16 (45.7%)	9 (27.3%)	14 (41.2%)
Part-time (%)	27 (26.4%)	7 (20.0%)	13 (39.4%)	7 (20.5%)
Student/training (%)	5 (4.9%)	1 (2.9%)	1 (3.0%)	3 (8.8%)
Unemployed (%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
Pension (%)	5 (4.9%)	2 (5.7%)	3 (9.1%)	0 (0.0%)
Self-reported monthly income				
<1000€ (%)	16 (15.7%)	8 (22.9%)	4 (12.1%)	4 (11.8%)
1001€–1500€ (%)	13 (12.7%)	5 (14.3%)	3 (9.1%)	5 (14.7%)
1501€–2000€ (%)	14 (13.7%)	5 (14.3%)	7 (21.2%)	2 (5.9%)
2001€–3000€ (%)	25 (24.5%)	10 (28.6%)	6 (18.2%)	9 (26.5%)
3001€–4000€ (%)	7 (6.9%)	2 (5.7%)	2 (6.1%)	3 (8.8%)
>4000€ (%)	4 (3.9%)	0 (0.0%)	4 (12.1%)	0 (0.0%)
Not stated	1 (1.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)
Most common pre-existing conditions [1]				
Sleep disorder	29 (28.4%)	8 (22.9%)	12 (36.4%)	9 (26.5%)
Neck pain	28 (27.5%)	10 (28.6%)	10 (30.3%)	8 (23.5%)
Back pain	23 (22.5%)	5 (14.3%)	10 (30.3%)	8 (23.5%)
Digestive complaints	22 (21.6%)	9 (25.7%)	6 (18.2%)	7 (20.6%)
Tension headache	13 (12.7%)	4 (11.4%)	4 (12.1%)	5 (14.7%)
Hypertension	8 (7.8%)	6 (17.1%)	1 (3.0%)	1 (2.9%)
Stress (PSS)				
Score (SD)		33.91 (4.80)	33.39 (5.91)	34.44 (5.84)
Burnout (MBI)				
Cynicism (SD)		12.94 (8.79)	10.33 (6.90)	12.94 (6.96)
Exhaustion (SD)		18.83 (6.36)	19.52 (6.89)	20.53 (6.19)
Professional Efficacy (SD)		25.46 (6.22)	25.48 (6.88)	24.21 (7.06)

Table 2. *Cont.*

Characteristic	Total	Integrative Yoga	Iyengar Yoga	Mindfulness
Quality of Life (SF-36)				
Mental Component Summary (SD)		36.79 (7.30)	38.86 (6.56)	37.94 (7.46)
Physical Component Summary (SD)		45.74 (6.06)	44.25 (6.35)	45.30 (7.22)
Physical Wellbeing (B-LR)				
Score (SD)		25.46 (7.72)	26.30 (8.38)	26.00 (8.81)
Depression (HADS)				
Anxiety (SD)		10.34 (2.91)	10.15 (3.46)	9.91 (3.53)
Depression (SD)		7.86 (3.79)	8.36 (3.80)	7.12 (4.00)
Mindfulness (FMI)				
Score (SD)		2.28 (0.48)	2.35 (0.50)	2.35 (0.37)
Interoceptive body awareness (MAIA)				
Noticing (SD)		3.23 (1.06)	3.21 (0.95)	3.33 (1.03)
Not-distracting (SD)		2.06 (0.91)	1.95 (1.00)	1.73 (0.65)
Not-worrying (SD)		2.06 (1.08)	2.24 (1.21)	2.15 (0.81)
Attention regulation (SD)		2.01 (1.00)	1.95 (1.05)	1.96 (0.93)
Emotional awareness (SD)		3.65 (0.92)	3.08 (1.12)	3.28 (1.02)
Self-regulation (SD)		1.99 (0.94)	1.75 (1.12)	1.87 (1.05)
Body listening (SD)		1.80 (0.97)	1.69 (1.38)	1.67 (1.13)
Trusting (SD)		2.51 (1.15)	2.33 (1.40)	2.42 (1.18)
Self-regulation (SRI)				
Score (SD)		3.35 (0.87)	3.36 (0.74)	3.58 (0.76)
Spirituality (ASP)				
Religious orientation (SD)		2.10 (0.95)	1.89 (0.91)	1.88 (0.93)
Search for wisdom (SD)		2.24 (0.72)	2.19 (0.65)	2.23 (0.70)
Conscious interactions (SD)		2.86 (0.55)	2.79 (0.81)	2.86 (0.67)
Transcendence conviction (SD)		1.83 (0.97)	1.68 (0.90)	1.72 (0.94)
Mysticism (HMS)				
Introvertive mysticism (SD)		1.74 (3.51)	3.18 (3.23)	2.74 (3.46)
Extrovertive mysticism (SD)		1.03 (2.29)	0.91 (2.47)	1.12 (2.88)
Interpretation (SD)		2.46 (3.23)	2.70 (3.57)	2.65 (3.67)
Posttraumatic stress (PCL-5)				
Score (SD)		26.77 (13.80)	26.03 (13.33)	27.00 (15.02)

[1] A complete presentation of all pre-existing conditions can be found in the Supplementary Materials: Pre-existing conditions.

The primary outcome, PSS, decreased similarly post-intervention in all groups. Effect sizes ranged from large (Cohen's d = 1.08 integrative; d = 0.81 Iyengar) to very large (d = 1.25 mindfulness). Effect sizes were very large in all groups after the end of the follow-up period, and ranged from d = 1.23 mindfulness to d = 1.41 integrative (Table 3; Figure 3). There were no significant differences between groups except for a superiority of mindfulness training over Iyengar yoga from V0 to V1 (p = 0.048; η^2 = 0.057). Differences from V0 to V2 were not statistically significant between all groups. In all groups, a slightly greater reduction in stress (PSS) was observed with longer self-reported exercise time in n = 76 participants (n = 28 integrative; n = 23 Iyengar; n = 23 mindfulness); however, the significance level was not reached (r = 0.167, p = 0.156; Supplementary Materials: Plot Practice Time).

Table 3. Perceived Stress Scale (Primary Outcome—Mean ± SD).

	n	V0	V1	V2	ΔV0–V1	d V0–V1	ΔV0–V2	d V0–V2
Integrative yoga	35	33.91 ± 4.80	27.23 ± 6.77	26.03 ± 4.91	−6.69 ± 6.19	1.08	−7.89 ± 5.60	1.41
Iyengar yoga	33	33.39 ± 5.91	27.39 ± 6.98	23.88 ± 5.58	−6.00 ± 7.37	0.81	−9.52 ± 6.94	1.37
Mindfulness	34	34.44 ± 5.84	24.71 ± 6.67	23.62 ± 6.43	−9.74 ± 7.80	1.25	−10.82 ± 8.77	1.23

	ΔV0–V1			ΔV0–V2		
	F	**p**	**η^2**	**F**	**p**	**η^2**
ANOVA	2.621	0.078	0.050	1.439	0.242	0.028
	ΔV0–V1			**ΔV0–V2**		
Post-hoc comparisons	**t**	**p**	**η^2**	**t**	**p**	**η^2**
Integrative–Iyengar	−0.414	0.680	0.003	1.062	0.292	0.017
Integrative–Mindfulness	1.795	0.077	0.045	1.653	0.104	0.039
Iyengar–Mindfulness	2.016	0.048	0.057	0.678	0.500	0.007

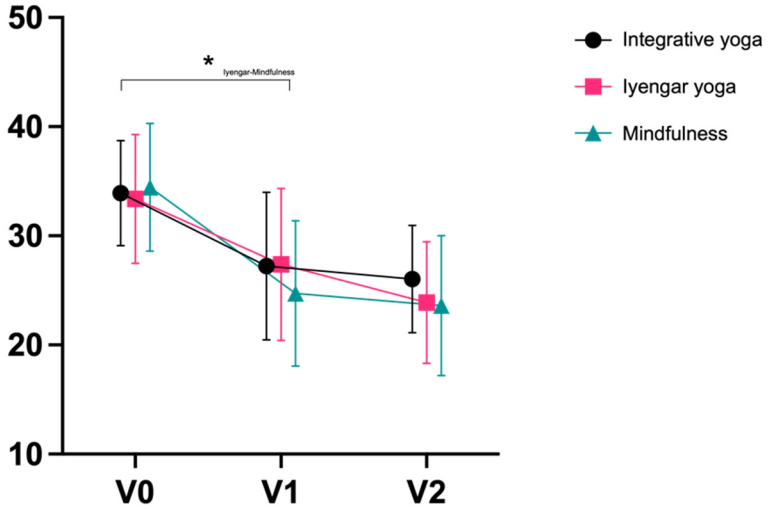

Figure 3. Perceived Stress Scale (Mean ± SD). * = $p < 0.05$.

For secondary outcomes, we observed large effects in terms of decreases on the exhaustion subscale of the Maslach Burnout Inventory ($d_{V0–V2}$ 0.80 integrative; 0.94 Iyengar; 1.13 mindfulness), with a statistically significant superiority of mindfulness meditation over integrative yoga post-intervention ($p_{V0–V1} = 0.044$) and after follow-up ($p_{V0–V2} = 0.017$; Figure 4). Large effect sizes were also observed for an improvement on the mental component summary score of the quality-of-life questionnaire, SF-36 ($d_{V0–V2}$ 1.13 integrative; 0.74 Iyengar; 0.81 mindfulness; Figure 5). Physical well-being (B-LR) improved with a large-to-very-large effect size in all groups ($d_{V0–V2}$ 1.34 integrative; 1.28 Iyengar; 1.13 mindfulness; Figure 6). Mindfulness (FMI) increased with borderline-large-to-large effect sizes in all groups ($d_{V0–V2}$ 0.73 integrative; 0.81 Iyengar; 0.73 mindfulness; Figure 7). Both subscales of the Hospital Anxiety and Depression Scale (HADS) improved in all groups with moderate-to-large effect sizes (subscale anxiety: $d_{V0–V2}$ 0.89 integrative, 0.79 Iyengar, 0.92 mindfulness, Figure 8; subscale depression: $d_{V0–V2}$ 0.71 integrative, 1.05 Iyengar, 0.68 mindfulness, Figure 9).

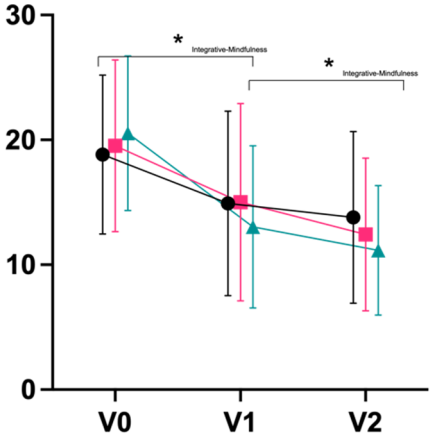

Figure 4. Exhaustion MBI (Mean ± SD). * = $p < 0.05$.

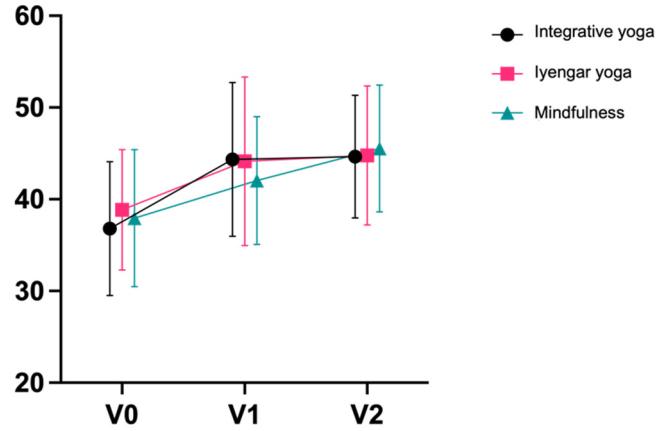

Figure 5. Mental Component—Quality of Life SF-36 (Mean ± SD).

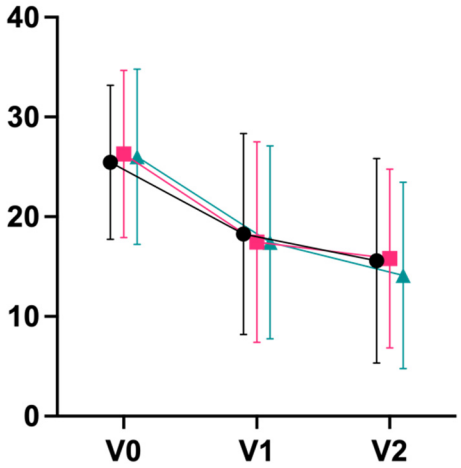

Figure 6. Physical Wellbeing B-LR (Mean ± SD).

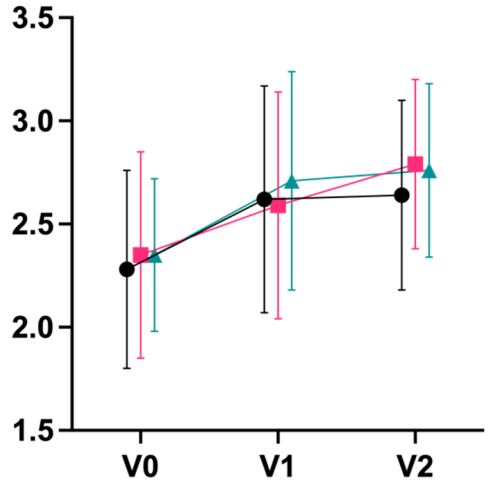

Figure 7. Mindfulness FMI (Mean ± SD).

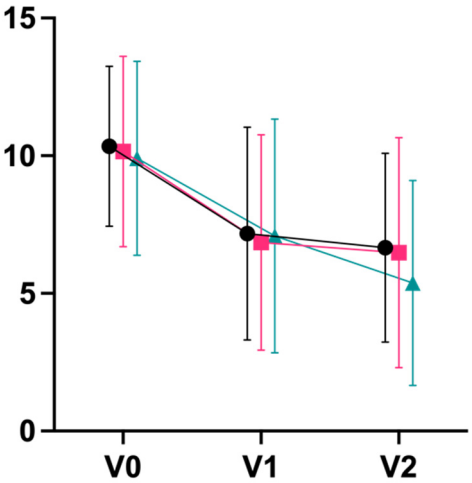

Figure 8. Anxiety HADS (Mean ± SD).

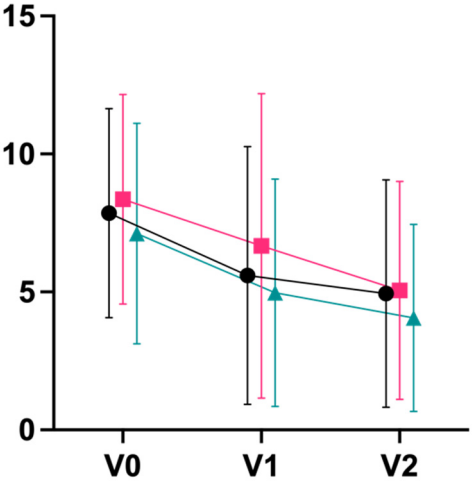

Figure 9. Depression HADS (Mean ± SD).

Moderate-to-large effect sizes were also observed on the self-regulation subscale of the interoceptive body awareness questionnaire (MAIA) ($d_{v0–v1}$ 0.89 integrative; 0.52 Iyengar; 0.88 mindfulness) and on the trusting subscale ($d_{v0–v2}$ 0.61 integrative; 0.62 Iyengar; 1.06 mindfulness). Small-to-moderate effect sizes were found for the other subscales

(noticing, not distracting, not worrying, attention regulation, emotional awareness, and body listening). Small-to-very-small effect sizes were observed for both the spirituality questionnaire (ASP) and the mysticism questionnaire (HMS). Posttraumatic stress (PCL-5) improved in all groups, with medium-to-borderline-medium effect sizes by the end of the follow-up period in all groups ($d_{v0–v1}$ 0.49 integrative; 0.56 Iyengar; 0.73 mindfulness). Among these, there were no relevant statistically significant differences between groups, except for a weak superiority (small vs. very small effect size) of both integrative yoga and mindfulness meditation over Iyengar yoga on the cynicism subscale of the Maslach Burnout Inventory (MBI) post-intervention ($p_{integrative–Iyengar} = 0.017$; $p_{mindfulness–Iyengar} = 0.036$). Moreover, there was a superiority of mindfulness over Iyengar yoga on the search for wisdom subscale (medium vs. very small effect size) and on the religious orientation subscale (small vs. very small effect size) of the Aspects of Spirituality questionnaire (ASP) post-intervention. These three group differences were no longer significant at the end of the follow-up period (Supplementary Materials: Results—Randomized Controlled Trial).

3.2. Qualitative Results

Out of the study participants who had attended at least six out of twelve classes and volunteered to participate in the qualitative interviews, six were chosen at random (Table 4). The interviews were conducted in November and December 2020.

Table 4. Participant information qualitative interviews.

Interview	Intervention	Participations	Gender	Course Period	Age
1	Iyengar yoga	11/12	female	January–April	48
2	Mindfulness training	11/12	male	January–April	50
3	Integrative yoga	8/12	female	January–April	58
4	Integrative yoga	10/12	female	January–April	47
5	Iyengar yoga	7/12	female	August–November	64
6	Mindfulness training	11/12	female	August–November	63

Using Mayring's content analysis, three main categories with thirteen subcategories were formed (Table 5).

Table 5. Qualitative codes.

Changes
Everyday life
Self-care
Psychological changes
Somatic changes
Change as a process that takes time
Course evaluation
General evaluation
Educational share
Course instructor
Other
Hopes/Fears
Lockdown situation
Previous experience
Future

In the following, the results of the content analysis are summarized and presented, including some selected examples (Supplementary Materials: Results—Qualitative Interviews for a comprehensive presentation of qualitative results). All interventions were reported to allow time in daily life to be set aside for one's own well-being.

"My daily life is, it went on as it was before, or still is now. But I include an hour for myself."

(Participant 5—Iyengar yoga)

Participants from all groups reported that it also encouraged them to be proactive about their own well-being.

"But a little bit, I have achieved that I allow myself more. [. . .] I have a Jacuzzi in the bathroom, I've never used it, for 15 years, [. . .] because I didn't allow myself that. [. . .] because that was a pampering for me and I'm not allowed to do that. I've overcome those little things now and that's what I do now."

(Participant 6—Mindfulness training)

Participants from the mindfulness group and integrative yoga group reported that they had started to consciously practice mindfulness in their everyday life because they found it helpful for their well-being.

"Yes, so this mindfulness of what's happening to me and where I am right now and I'm trying to control that better. [. . .] And now I always try to be aware of how each step is happening, what I'm doing and try not to get distracted. That's not always successful, but that's what I try to do."

(Participant 6—Mindfulness training)

The reported psychological changes were mainly related to stress management. The participants felt that they were generally better able to distance themselves from demands and were more relaxed; the degree varied.

"Yes, so a little bit. Not as much as I would have liked, and as I've heard with the other women."

(Participant 6—Mindfulness training)

Both participants from the mindfulness group also reported very deep emotional confrontations with themselves. In one case, meditating and practicing relaxation exercises supposedly helped with both the grief processing of the death of a family member, as well as to question and alter learned structures of upbringing. In the other, it enabled a change in the participant's relationship with himself, which was perceived as emotionally significant.

"There were also moments when I really noticed a fundamental change. And where I really became aware that I had done too much to myself before. And one of the greatest moments was when, after a meditation, I stood there on my mat and started to cry and asked my body out loud for forgiveness for what I had done to it for 20 years in the job in which I now work. Nobody had told me to do that, that came from within, and I was very aware of that at that moment, that that came from me. And there were a few things like that then, during the course and even later."

(Participant 2—Mindfulness training)

Reported somatic health changes varied widely. Participants from the mindfulness group and from the Iyengar yoga group expressed disappointment that stress-associated conditions (tremor, back pain) did not change during the study. At the same time, participants from the integrative yoga group and from the mindfulness group reported a marked improvement of preexisting psoriasis, migraine, and back aches. One participant from the mindfulness group had lost 5 kg of excessive body weight. Eating had been a stress-coping mechanism for him. No perceived changes in flexibility or general physical fitness were reported spontaneously, with the exception of one participant from the integrative yoga group. She reported less neck pain due to increased neck mobility. Interestingly, participants from both yoga interventions expressed that yoga practice is a process that generally takes time to facilitate positive change.

All classed were described as positive overall, even by participants who expressed they would not take part again. The criticism focused on failed expectations and the monotony

of the respective programs. One Iyengar participant wished for more exercises and poses to choose from. One participant from the integrative yoga group found the same sequence of poses throughout the class boring. One participant from mindfulness training and one from the Iyengar group found the exercises not challenging enough for them personally. One participant from the mindfulness group expressed frustration because she found her thoughts constantly wandering off during mindfulness meditation. Both participants of the integrative yoga class felt that they particularly benefited from a group exchange about stress in daily life.

> *"You're not so completely alone in the world, it's not an exceptional problem, it's something that a lot of people have."*
>
> (Participant 3—Integrative yoga)

Both participants of the Iyengar yoga class would have wanted advice and training on stress management, something their class did not entail. In contrast, both participants from the integrative yoga class, who received such content as part of their class, perceived it as particularly helpful. All instructors were perceived exclusively positively. They were described as good, professional, competent, helpful, and motivating.

Both participants from the Iyengar group claimed they did not learn coping mechanisms for stress in daily life, but found momentary relaxation when practicing yoga poses. One participant from the mindfulness group felt he had improved his stress management. The other participant from that group stated he now handled fear better in daily life. One participant from the integrative yoga group expressed that she had learned to handle stress better by better distancing herself from it.

An improved ability to handle stress was an expectation that was formulated by participants from all groups. The fears were that yoga or mindfulness would be uncomfortably alien and regular participation would be too stressful. This was despite the fact that all interviewees had prior experiences with yoga or mindfulness. All interviewees had resolved to practice yoga or mindfulness regularly in the future.

3.3. Harms

No physical or psychological harms or adverse effects related to the study interventions were reported. Yet, out of the participants who dropped out, some gave as a reason increased perceived stress due to the additional scheduling commitments of study participation. None of them reported a deterioration compared to their pre-study state. No SARS-CoV-2-transmissions were reported among study participants, instructors, or study personnel.

4. Discussion

The aim of this three-arm, randomized, controlled clinical trial was to compare the effects of integrative yoga, Iyengar yoga, and mindfulness training on participants with elevated stress levels and stress-related symptoms. All three interventions showed equally very large and stable effects in stress reduction and large effects in improvement of quality of life in the quantitative part of the study. There were no statistically significant group differences or indications of relevant synergistic effects of an "integrative" intervention combining mindfulness, physical exercises, and ethical/philosophical aspects of yoga over mindfulness or physical yoga exercise alone. The superiority of the integrative yoga approach in the sense of a Whole Medical System could not be demonstrated on the basis of the parameters examined during the study period. The observed effect sizes are consistent with those from a preliminary study of our research team [57], and with a systematic review by Della Valle et al. from 2020 which evaluated yoga interventions against inactive controls [104]. The relaxation procedures were studied in a form that largely corresponds to the usual application in clinical/psychological practice. We, therefore, assume that the results are generally transferable to clinical practice and prevention.

Major limitations of this study include: no blinding, a sample that was not representative of the overall population, a randomly selected sub-sample instead of a theoretical sample for the qualitative interviews, the onset of the COVID-19 pandemic during the study period, the resulting switch to an online format for the interventions, and a high dropout rate. An objective measurement of individual stress levels would have enriched the study. Measurements of cortisol levels or heart rate variability (HRV) were considered at a planning stage. Both methods allow objective conclusions about the activity of the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenocortical axis (HPA). Twenty-four-hour HRV was measured before and after the intervention in the first cohort of study participants. However, due to the COVID-19 pandemic, on-site visits were not possible, so too few data sets were available to perform an analysis.

Blinding was initially considered, but then deemed not fully feasible. It became apparent that too large a proportion of those interested in the study would have been able to independently infer their own group allocation. Despite advertising in public spaces, it appears that predominantly well-educated middle-aged women with an existing interest in mindfulness or yoga were recruited (this may also explain the low interest in the originally planned progressive muscle relaxation intervention.) The reasons for this could be higher stress levels in women and a higher likelihood of women seeking help for stress. A 2021 study on stress in the German population found that more women feel stressed occasionally or frequently (65% vs. 63%), and significantly more women reported seeking help in cases of severe stress (75% vs. 54%) [20]. This selection bias limits the transferability of the results to the general population. However, transferability to a population that is interested, and, thus, particularly amenable to the methods, can be discussed. Further studies evaluating stress reduction interventions including, e.g., low-income, racially diverse adults are warranted [105].

The occurrence of the COVID-19 pandemic during the study is a strong confounder with respect to subjective stress levels. The population average had a greatly increased stress level [106,107]. At the same time, this varied greatly at the individual level [107]. Given successful randomization, it can be assumed that all groups were equally affected. Therefore, the interpretation of group differences is not affected, but effect sizes from baseline are to an unknown extent. The change to an online format represents an important confounder of its own. The operationalization of the studied relaxation procedures was changed considerably as a result. There were large changes in setting (exercise environment, including background noise, space available, and distractions), whereas temporal exposure, instructional content, and movement patterns were little affected to unaffected.

For the qualitative part of the study, a theoretical sample would have been the methodologically better choice. Nevertheless, theoretical saturation was achieved. The interviews showed that only participants in the mindfulness and integrative intervention felt they had acquired better skills for dealing with stress in everyday life. Yet, perceived stress reduced equally in all intervention groups in the quantitative data.

Several studies indicate improved efficacy with respect to various outcomes when different aspects of yoga and meditation are combined in the sense of a Whole Medical System [108]. One possible interpretation of the very similar effects of all interventions examined in this study is that "time spent relaxing" is a relevant factor in stress reduction. The duration of exposure to each intervention was identical in all groups. Differences in physical engagement or learning mindfulness in the sense of the study hypotheses made no relevant impact. It is, therefore, conceivable that a dose–response relationship exists, which is not primarily dependent on the choice of a relaxation method. This would also fit with the observations of Cramer et al., who postulated that the effectiveness of different yoga styles was due to the personal preferences of the practitioners [55]. This thesis can possibly be extended to other relaxation methods. In this context, it is noted that the physical aspect of yoga did not play a major role in the participants' perceptions. In relation to stress reduction, this factor may be less relevant. Time spent relaxing could, therefore, be a relevant factor in the effectiveness of relaxation techniques by itself.

Individual participants from all groups reported that the additional scheduling demands of study participation contributed to an increase in their stress experience. This led to the discontinuation of study participation for some. It is possible that continued study participation would still have had an impact on these participants. Nevertheless, it is questionable whether an additional appointment for relaxation is a viable option for all people with high subjective stress levels [57]. This observation does not necessarily allow conclusions to be drawn about the effectiveness of the methods studied. Rather, it should point to the societal problem of a high external stress load, which cannot be completely solved with improved methods of individual stress management.

5. Conclusions

All of the interventions studied were found to be comparably effective methods of stress reduction. There was no evidence of synergistic effects in stress reduction by combining yoga exercises with mindfulness or by using yoga as a Whole Medical System.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11195680/s1.

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2.5 Yoga im Schulsport – eine nicht-randomisierte kontrollierte Pilotstudie

Stress stellt ein zunehmendes Problem dar, auch bereits für Kinder, Jugendliche und junge Erwachsene. Mit dieser Studie sollten die potenziellen Effekte einer 10-wöchigen, einmal wöchentlich stattfindenden, 90-minütigen Yogaintervention im Vergleich zu einer Schulsport-Kontrollgruppe im regulären Sportunterricht bei Jugendlichen untersucht werden.

Besonderes Merkmal dieser *Mixed-Methods*-Studie ist die Miteinbeziehung quantitativer (*Patient-reported Outcomes* und Biomarker [Herzratenvariabilität, HRV]) und qualitativer Elemente [116-118]. In der statistischen Analyse konnten keine statistisch signifikanten Gruppenunterschiede detektiert werden, jedoch eine Reihe signifikanter und zum Teil klinisch relevanter Veränderungen innerhalb der Gruppen, mit deutlicheren Veränderungen in der Schulyoga-Gruppe – was auch die Resultate der qualitativen Analyse nahelegen [116, 117]. Weiterhin konnte ein Anstieg der HRV (mehr parasympathische Dominanz und insgesamt höhere HRV) nach zehn Wochen Yoga in der Schule im Vergleich zum regulären Schulsport nachgewiesen werden, was auf eine verbesserte Regulation des autonomen Nervensystems hinweist [118].

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Yoga in school sport – A non-randomized controlled pilot study in Germany

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ABSTRACT

Objectives: Distress is an increasing public health problem for adolescents and young adults. We aimed to evaluate potential effects of a 10-week 90-minute once-a-week yoga course.
Methods: A non-randomized controlled study with a school sport control group was implemented in two German secondary schools. Primary outcome was stress on the Perceived Stress Scale from baseline to week 10. Secondary outcomes included depression/anxiety, attention, quality of life, mood, visual analogue scales (for pain, headache, neck tension, exhaustion, sleep), and yoga-efficacy. Parameters were assessed at pre-baseline (before holidays), baseline (after 3-week holidays, before interventions started), week 10, and at a 6-months follow-up. An intention-to-treat analysis using ANCOVA was performed.
Results: 92 participants (67 % female; 19.6 ± 2.2 years) were included into the study. No significant differences were observed between the groups with regard to PSS, at either 10 weeks (Δ = -1.4; 95 % CI: -3.6;0.8; p = 0.22) or 6 months (Δ = 2; 95 % CI: -0.2;4.2, p = 0.08). Only VAS headache in favour of yoga and HADS-D in favour of school sport showed significant group differences at the 6-months follow-up. Significant intra-group mean changes for the primary outcome and several secondary outcomes were found in the yoga group.
Conclusions: Young adults in German secondary school settings might benefit from yoga, as the found effects were more prominent in the yoga group. However, the effects might be attributed to non-specific effects due to the chosen study design. Further studies are needed, which include high-quality study designs including randomization, longer-term follow-ups and larger sample sizes.

Abbreviations: PSS, Perceived Stress Scale; HADS, Hospital Anxiety and Depression Scale; VAS, Visual Analog Scale; d2-R, Test of Attention Revision; d2-R KL, concentration; d2-R BZO, number of processed target objects; d2-R F%, error percentage; POMS, Profile of Mood States; SOP, Standard Operating Procedure; YSES, Yoga Self-Efficacy Scale

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3. Diskussion

Chronische Krankheiten gehören zu den häufigsten und wirtschaftlich bedeutendsten Gesundheitsproblemen in Industrieländern [1]. In den dargestellten Studien wurden CIM-Interventionen sowohl bei chronischen Erkrankungen als auch im präventiven Bereich eingesetzt. Diese Arbeit zeigt, dass Ernährungsmodifikation, Fastentherapie und multimodale CIM-Interventionen günstige Effekte auf Parameter des metabolischen Syndroms haben können. Darüber hinaus können MBM-Interventionen – in dieser Arbeit exemplarisch für Meditation und Yoga dargestellt – günstige Auswirkungen auf Stress und Stress-assoziierte Beschwerden haben.

3.1 Diskussion der eigenen Arbeiten

Die dargestellte Studie in Kapitel 2.1 unterstreicht die positiven kardiometabolischen kurzfristigen Effekte der Fastentherapie, wie bereits in früheren Studien im Tiermodell, unkontrollierten Studien und Studien zu intermittierendem Fasten gezeigt [53, 58, 119].

In einer Kohortenstudie mit vergleichbaren Fastenregime (Buchinger-Fasten, max. 500 kcal täglich) nahm der Gewichtsverlust mit Länge der Fastentherapie zu (3,2±0,0 kg am 5. Fastentag und 8,6±0,3 kg am 20. Fastentag) und der Bauchumfang ab (4,6±0,1 cm am 5. Fastentag und 8,8±0,8 cm am 20. Fastentag) [119]; außerdem wurden mit der Studienpopulation vergleichbare günstige Auswirkungen der Fastentherapie auf den Blutdruck, die Blutfette und den Blutzuckerspiegel festgestellt [119].

Eine Einschränkung dieser Studie ist das Ausbleiben von signifikanten Gruppendifferenzen in den ko-primären Endpunkten ambulanter systolischer Blutdruck und HOMA-Index am Ende der 12-wöchigen Programme zur Lebensstiländerung. Es scheint wahrscheinlich, dass die bei der Berechnung des Stichprobenumfangs erwartete mittlere Differenz zwischen den Gruppen zu optimistisch gewählt wurde. Eine weitere Limitation dieser Studie ist die Verwendung von Surrogatmarkern. Jedoch darf die 6%ige Risikoreduktion des 10-Jahres-Herzinfarktrisiko (PROCAM) in Woche 12 zu Gunsten der Fastentherapie nicht unerwähnt bleiben. Zu möglichen Mechanismen für die Risikoreduktion gehören die Reduktion der Apoptose, die Beeinflussung der Insulin- und

IGF-1-Signalübertragung, der Induktion der Autophagie u.a., die noch eingehender in Studien untersucht werden müssen [51, 120].

Weiterhin hatte die Fastentherapie günstige Effekte auf psychische Parameter, insbesondere sind hier die Reduktion von Depressions- und Müdigkeitsscores zu nennen. Dies steht im Einklang mit früheren Studien, da (insbesondere prolongiertes) Fasten stimmungsmodulierende Effekte hervorrufen und auch die Konzentrationsfähigkeit steigern kann [121-124]. Fasten wird hier mit einer erhöhten Verfügbarkeit von neurotrophen Faktoren im Gehirn in Verbindung gebracht, darunter Serotonin, endogene Opioide, Endocannabinoide u.a., die günstige Effekte auf psychische Parameter haben können [125, 126].

Das Hauptziel der in Kapitel 2.2 dargestellten Studie bestand darin, Nährstoffprofile einer PBD mit denen einer omnivoren Ernährung zu vergleichen. Das Hauptaugenmerk lag auf Mikro-/Makronährstoffe, die bei einer Umstellung auf PBD von Bedeutung sein könnten; diesbezüglich wurde die empfohlene Zufuhr der meisten Vitamine und Mineralstoffe erfüllt [26,32]. Die Daten deuten darauf hin, dass die PBD verschiedene vorteilhafte Komponenten aufwies, darunter eine geringere Energiedichte, eine geringere Aufnahme von Cholesterin und gesättigten Fettsäuren, einen erhöhten Verzehr von Ballaststoffen und eine geringere Aufnahme von Salz; weiterhin führte die PBD-Intervention im Vergleich zur Kontrollgruppe zu einer signifikanten Reduktion von Körpergewicht, BMI, Taillenumfang, HbA1c und Nüchternblutzucker – dies ist im Einklang mit einer Vielzahl an Studien zur PBD [62-67].

Der größte Teil der Studie wurde unter pandemischen Bedingungen durchgeführt, so dass die Analyse der Nährstoffprofile auf einen Datensatz von nur 37 Patienten beschränkt war. Obwohl dreitägige Wiegeprotokollen den Goldstandard in der Aufzeichnung von Nährstoffprofilen darstellen, können sie auch anfällig für verschiedenste Verzerrungen/Bias sein. Zuverlässigere Ergebnisse über die Nährstoffaufnahme können durch Blutanalysen gewonnen werden. In Bezug auf unsere Daten wäre es besonders interessant, z.B. mittels Blutuntersuchungen festzustellen, ob kritische Nährstoffe in der Aufnahme zu niedrig waren, aber möglicherweise noch ausreichend im Organismus

vorhanden sind. Darüber hinaus könnten diese Parameter durch Mikrobiom- und Multi-Omics-Daten ergänzt werden [127].

Studien zu TIM-Therapiemodalitäten für Reizdarm-Patienten haben bisher nur Phytotherapeutika analysiert und bisher diätetische Aspekte des ayurvedischen Behandlungsansatzes bei IBS nicht untersucht [128, 129]. So liegt nun eine erste, in Kapitel 2.3 dargestellte Studie zur Wirksamkeit einer individualisierten Ernährungsberatung im Sinne der TIM im Vergleich zu konventionellen Ernährungsempfehlungen der DGE bei Patienten mit Reizdarmsyndrom vor.

In den letzten zehn Jahren wurden zahlreiche Studien zur Wirksamkeit der Low-FODMAP-Diät bei Reizdarm-Patienten veröffentlicht. In einer systematischen Übersichtsarbeit und Meta-Analyse wurden 9 Studien mit insgesamt 596 Teilnehmern untersucht, in denen eine Low-FODMAP-Diät mit verschiedenen Kontrolldiäten verglichen wurde. Die Low-FODMAP-Diät verbesserte die Symptome des Reizdarmsyndroms im Vergleich zu anderen Diäten in Bezug auf gastrointestinale Symptome, Bauchschmerzen und gesundheitsbezogene Lebensqualität [130]. Im Vergleich zu anderen Low-FODMAP-Studien hatte die TIM-Ernährungsberatung eine ähnliche, klinische relevante IBS-Reduktion zu verzeichnen [130].

Weiterführende Studien sind erforderlich, um insbesondere die Effekte von komplexen, multimodalen TIM/Ayurveda-Ansätzen im Sinne eines WMS bei Patienten mit Reizdarmsyndrom zu untersuchen. Komplexe TIM/Ayurveda-Interventionen enthalten Elemente, die alle fünf Säulen der Naturheilkunde einschließen (d.h. neben der in der Studie untersuchte Ernährungstherapie auch die Ordnungstherapie [regelmäßiger Lebensstil, gesunder Schlaf, Stressreduktion u.a.], Phytotherapie [unter Einschluss von Mono- und Komplexpräparaten der TIM], Hydrotherapie [z.B. Bäder] und Bewegungstherapie [z.B. Yoga]). Aus naturheilkundlicher Perspektive ist die Inklusion aller fünf Säulen in ein integrativmedizinisches Gesamtkonzept im Sinne einer ganzheitlichen und gleichzeitig individualisierten Therapie der Idealzustand naturheilkundlich-therapeutischen Behandelns – wie bereits in einer aus unserer Arbeitsgruppe publizierten Studie einer komplexen TIM/Ayurveda-Intervention bei

Patienten mit Gonarthrose gezeigt wurde [37, 131]. Weiterhin sind systematische Studien durchzuführen, die unspezifische Effekte, v.a. Erwartungseffekte im Rahmen von komplementärmedizinischen Interventionen – insbesondere TIM/Ayurveda – weiterführend untersuchen wie z.B. im Kontext Akupunktur bei Reizdarm-Patienten von Kaptchuk et al. bereits durchgeführt [132].

Mehrere Studien weisen auf eine verbesserte Wirksamkeit in Bezug auf verschiedene Endpunkte hin, wenn verschiedene Aspekte von Yoga und Meditation im Sinne eines WMS kombiniert werden [133]. Bei Probanden mit Distress jedoch scheint dies nach Daten der in Kapitel 2.4 dargestellten Studie und nach Daten anderer Arbeitsgruppen eher nicht zuzutreffen [133]. So ist eine mögliche Interpretation der sehr ähnlichen Wirkungen der untersuchten MBM-Interventionen bei Probanden mit Distress, dass die „mit Entspannung verbrachte Zeit“ ein relevanter Faktor bezüglich Stressreduktion ist.

Bestimmte Kombinationen von Yogapraktiken und MBM-Interventionen scheinen jedoch für bestimmte Studienpopulationen nützlicher zu sein als andere - welche Kombinationen genau, muss in künftigen Studien ermittelt werden, da die verfügbaren Erkenntnisse zu diesem Thema noch spärlich sind [133].

So sollten künftige Studien sollten auch Persönlichkeitsfaktoren und Patientenpräferenzen berücksichtigen, da mehrere Arbeiten zeigten, dass diese die Wirkung von Yoga und anderen MBM-Interventionen beeinflussen können [134]. In dieser Hinsicht sind Einzelfallforschungsdesigns vielversprechende Ansätze zu sein, siehe Kapitel 3.3.

Limitationen dieser Arbeit umfassen eine nicht-repräsentative Stichprobe für die Gesamtbevölkerung, da insbesondere Frauen mittleren Alters mit höherer Bildung rekrutiert wurden. Weiterhin mussten wegen der SARS-CoV-2-Pandemie die Interventionen auf ein Online-Format umgestellt werden. Insgesamt hatte die Studie eine hohe Abbrecherquote zu verzeichnen.

Selbstverständlich bringt der Pilotstudiencharakter der in Kapitel 2.5 dargestellten Publikationen des Schulyogaprojekts zahlreiche interpretatorische Unsicherheiten mit sich, dennoch ist auf der Basis dieser Daten und Daten aus anderen Untersuchungen zu vermuten, dass stressreduzierende Yogaeffekte eher bei Erwachsenen sichtbar werden und anscheinend weniger bei jüngeren Individuen, wie es auch in dieser Studie der Fall ist [135, 136]. Natürlich ist nicht auszuschließen, dass regelmäßige Yogainterventionen bei Jugendlichen dennoch präventive Effekte zeigen. Zur wissenschaftlichen Beantwortung solcher Hypothesen bedarf es jedoch weiterführender Forschung, vor allem auch im präventionsmedizinischen Bereich, um an dieser Stelle tiefere Erkenntnisse zu Wirkmechanismen und Wirksamkeit von Yoga-Interventionen bei Kindern und Jugendlichen zu generieren. Nicht zuletzt auch, um zu klären, wie und in welchem Umfang sich die Effekte von Yogainterventionen zwischen klinisch Gesunden und Erkrankten unterscheiden und falls Unterschiede bestätigt werden sollten, woran diese liegen könnten.

Insgesamt liefert diese Studie wertvolle Hinweise zur weiterführenden Forschung in diesem Bereich; die Ergebnisse implizieren beispielsweise, dass auch niederschwellige Interventionen im Schulsport, in diesem Fall Yoga, zur Stressreduktion beitragen können.

Für die weitere Etablierung von CIM-Interventionen sind eine Reihe von Maßnahmen erforderlich, die im Folgenden beschrieben werden sollen.

3.2 Gesunde Ernährung sollte (wieder) ein zentrales Thema der Medizin werden

Ernährungsbedingte Risikofaktoren gehören weltweit zu den Hauptursachen für den Verlust an Lebensjahren und Lebensqualität [137]. In Europa ist fast ein Drittel aller vorzeitigen Todesfälle auf eine ungünstige Ernährung zurückzuführen [138]. Deutschland hat eine der höchsten Raten an ernährungsbedingten kardiovaskulären Todesfällen in Europa [139]. Mehr als die Hälfte der erwachsenen deutschen Bevölkerung ist übergewichtig und etwa ein Viertel fettleibig [140]. Eine solche Fehlernährung ist v.a. durch einen unzureichenden Anteil unverarbeiteter, pflanzlicher Lebensmittel wie Obst,

Gemüse, Vollkornprodukte, Hülsenfrüchte und Nüsse sowie einen übermäßigen Verzehr von rotem und/oder verarbeitetem Fleisch, hochprozessierten Nahrungsmitteln und zuckerhaltigen Getränken gekennzeichnet [138].

"Du bist, was du isst" – dieses einfache Prinzip wird in der Medizin aktuell zumeist vernachlässigt, wenngleich die Evidenzlage zur Rolle der Ernährung bezüglich Prävention und Therapie verschiedener (chronischer) Krankheiten robust ist [26, 33, 59-61, 63, 70, 74, 101, 137]. Dies ist umso problematischer, da der heutige vorherrschende Ernährungsstil („*Western pattern* diet“) nicht nur die individuelle Gesundheit gefährdet, sondern auch maßgeblich an der Klimakrise und anderen drängenden Umweltproblemen beteiligt ist (z.B. Treibhausgasemissionen, Rodung für Landwirtschaftsnutzung, Dünger-/Pestizideinsatz, Artensterben u.a.) [141-144].

Die negativen Umweltfolgen unserer Ernährung und die damit verbundenen zunehmenden Gefahren für die menschliche Gesundheit sollten in Medizin und Gesundheitswissenschaften – insbesondere auch im Studium – viel stärker thematisiert werden. Die Ärzteschaft hat hier eine besondere Verpflichtung, sich für die notwendige gesellschaftliche Transformation bezüglich unseres Ernährungssystems einzusetzen, z.B. in der individuellen Ernährungsberatung, über Mitwirkung der Umstrukturierung des Speisenangebots in Kliniken, Kantinen, Schulen und Kindertagesstätten, im politischen Engagement u.a.

Das Bundesministerium für Ernährung und Landwirtschaft (BMEL) erarbeitet federführend die Ernährungsstrategie der Bundesregierung. Diese soll in mehreren Phasen kurz-, mittel- und langfristige ernährungspolitische Ziele und Leitlinien vorgeben, Handlungsfelder definieren und konkrete Maßnahmen benennen. Kernziele sind u.a. die Förderung einer gesünderen, ressourcenschonenden und pflanzenbasierten Ernährung sowie einer bewegungsorientierten Lebensweise. Nach dem Koalitionsvertrag 2021 sollen Kinder und Jugendliche besondere Berücksichtigung erfahren.

Neben den wichtigen verhaltenspräventiven Interventionen sollten ergänzend bevölkerungsweite verhältnispräventive Maßnahmen (transparente

Nährwertkennzeichnung, Umstrukturierung der Besteuerung von Lebensmitteln u.a.) konsequent umgesetzt werden [26, 145].

3.3 Vergütung der Lebensstilmedizin und Prävention

Ein Großteil der Bevölkerung leidet heutzutage schon im mittleren Alter unter chronischen Krankheiten [29]. Diese gelten überwiegend lebensstilbedingt bzw. lassen sich zumeist günstig mit einem gesunden Lebensstil beeinflussen [146]. Lediglich ein Sechstel der deutschen Bevölkerung wird mit präventiven und therapeutischen Maßnahmen zur Ernährung, Bewegung und Entspannung erreicht [146]. Leicht zugängliche und von Patienten gut umsetzbare Lebensstilmodifikationskonzepte der CIM können die zentralen Elemente Bewegung, Ernährung, und Achtsamkeit u.a. zu einem multimodalen Gesamtkonzept verbinden; die Vorzüge der CIM-Lebensstilinterventionen liegen in der praxisnahen Vermittlung, z.B. im Gruppensetting [34, 105, 106]. Der aktuelle Stand der Forschung sieht für multimodale Ansätze klare Vorteile gegenüber monomodalen Interventionen [146].

Das systematische Erlernen gesundheitsförderlicher Lebensstilaspekte kann Selbstwirksamkeit und Eigenkompetenz von Individuen im Hinblick auf ein präventives (inkl. Tertiärprävention) Verhalten stärken [34]. In Präventions- und Verhaltensforschung ist mittlerweile unumstritten, dass Eigenaktivität und Selbstwirksamkeit sowohl den Gesamtverlauf als auch die Prognose von chronischen Erkrankungen günstig beeinflussen können [34].

Gesetzliche Krankenversicherungen übernehmen in der Regel keine Kosten für multimodale (CIM-)Programme zur Änderung des Lebensstils zur Prävention und Behandlung chronischer Erkrankungen – mit Ausnahme an spezialisierten NHK-Einrichtungen wie die CIM-Versorgung am Immanuel Krankenhaus Berlin oder an den Charité Hochschulambulanzen für Naturheilkunde. Angesichts des erheblichen gesundheitlichen Nutzens multimodaler CIM-Lebensstilinterventionen u.a. zur Verbesserung der kardiovaskulären Parameter sollten solche Programme entsprechend des „Globalen Aktionsplans gegen nichtübertragbare Krankheiten“ der WHO insbesondere für Patienten mit chronischen Erkrankungen systematisch angeboten werden [26]. Die Kosten solcher Programme sollten gegen den Nutzen der Prävention

von Herzkrankheiten, Bluthochdruck, Diabetes und anderen Erkrankungen abgewogen werden, da bei erfolgreicher Prävention die Notwendigkeit (potenziell kostspieliger) medizinischer Folgeinterventionen entfallen könnte. Einschränkend zu erwähnen ist, dass *Cost-Effectiveness* und Nachhaltigkeit multimodaler CIM-Programme derzeit weitestgehend unklar sind – hier besteht Forschungsbedarf v.a. im Rahmen pragmatischer Studien in Settings der Routineversorgung. Gerade dieser Aspekt wird von den Entscheidungsträgern im Gesundheitswesen eine entscheidende Rolle für die Integration von CIM-Interventionen in die Gesundheitssysteme spielen – diese sollten perspektivisch nicht nur im Präventionsparagrafen vergütet werden, sondern auch als therapeutische Leistungen.

3.4 Weiterführende Forschung

3.4.1 Versorgungsforschung

RCTs schließen durch definierte Ein-/Ausschlusskriterien oftmals nur spezielle Studienpopulationen in die Studie ein und andere Patientengruppen (z.B. Multimorbidität) aus [147]. Ergo wird in RCTs nicht selten eine Patientenpopulation untersucht, die oft nur einen kleinen Teil der Allgemeinbevölkerung repräsentiert. So können Daten aus RCTs häufig nicht auf die alltägliche Versorgung außerhalb der jeweiligen Studienpopulationen übertragen werden. *Real World Data* (z.B. aus der Versorgungsforschung) können zumeist eine bessere Aussage zu Wirksamkeiten unter Alltagsbedingungen für verschiedene Therapieoptionen darstellen [148]. Gerade weil die mit dem demografischen Wandel einhergehende Versorgung chronisch (oft multimorbider) Erkrankter eine große Herausforderung der Medizin darstellt, wird die systematische Evaluation sog. komplexer Interventionen eine zentrale Herausforderung sein. Ein klassisches Instrument solcher Versorgungsforschung sind prospektive Beobachtungsstudien, deren vorrangiges Ziel ist, die alltägliche Praxis abzubilden [147]. Es werden daher heterogene Patientengruppen zugelassen (z.B. multimorbide Patienten, zusätzlich konventionell behandelte Patienten) und ggf. auch unterschiedliche Patientenpräferenzen berücksichtigt. Im CIM-Bereich wurden bisher wenige relevante Arbeiten im Bereich der Versorgungsforschung veröffentlicht. Bisher ist es nur im Bereich Akupunktur im Rahmen eines bis dato einzigartigen Modellvorhabens unter Federführung

der Charité gelungen, sowohl die *effectiveness* (d.h. die Wirksamkeit und in der Routineversorgung) als auch die *efficacy* (d.h. die Wirksamkeit an spezifischen Akupunkturpunkten) sowie die Therapiesicherheit und Wirtschaftlichkeit bei ausgewählten Indikationen zu untersuchen [149]. Dieses Projekt mündete schließlich 2006 in der Erstattungsfähigkeit von Akupunkturleistungen für die zwei Indikationen Gonarthrose und chronisch unspezifischer Rückenschmerz.

3.4.2 Grundlagenwissenschaften

In der letzten Dekade ist insbesondere das Fasten vor allem vor dem Hintergrund der grundlagenwissenschaftlichen Evidenz populärer geworden; mittels Grundlagenforschung sollten weitere CIM-Interventionen weiter ebenso systematisch beforscht werden [51]. Grundlagenwissenschaften und insbesondere Translationale Forschung könnten u.a. auf eine Auswahl zielgerichteter molekularer Mechanismen fokussieren, die Grundlage für „gesundes Altern“ darstellen und von Präventions- und Therapiestrategien der CIM beeinflusst werden können. Ein Fokus könnte z.B. auf die molekularen Auswirkungen von Stress und chronischer Inflammation, zirkadiane Disruption, Autophagie und Mikrobiom-Homöostase und deren Prävention und Therapie durch CIM-Interventionen gelegt werden [51, 127, 150-154]. Weiterführende klinische und experimentell-grundlagenwissenschaftliche Forschung kann u.a. auch Rationalen und Axiome naturheilkundlicher Systeme (sog. *Whole Systems Research,* siehe folgendes Kapitel) mitberücksichtigen.

Die Erforschung dieser Zusammenhänge erfordert den Einsatz und die Komplementierung innovativer und translationaler Forschungsansätze, um letztlich den potenziellen Zusatznutzen von CIM-Interventionen umfassender abzubilden. CIM-Interventionen könnten so einer möglichen Identifizierung salutogenetisch wirksamer molekularer Mechanismen dienen, welche wahrscheinlich nicht nur für das weiterführende Verständnis und der darauf basierenden optimierten klinischen Anwendung der CIM-Interventionen von Bedeutung sein könnte, sondern evtl. auch für die Medizin insgesamt, z.B. für das Verständnis bisher unentschlüsselter physiologischer oder pathologischer Wirkmechanismen.

3.4.3 Whole Systems Research

Whole Systems Research (WSR) ist ein Ansatz zur Untersuchung komplexer Systeme, welcher darauf abzielt, die Beziehungen und Wechselwirkungen verschiedener Komponenten eines Systems zu verstehen und zu extrapolieren, wie sie zum allgemeinen Funktionieren und Verhalten des Systems beitragen [155]. Insbesondere multimodale CIM-Interventionen, z.B. der TIM, könnten unter Berücksichtigung von WSR-Ansätzen geplant und durchgeführt werden, um so die individualisierten, multimodalen Therapiekonzepte der CIM umfassender zu untersuchen [156]. Ein weiterer vielversprechender Ansatz sind Einzelfallstudien in bereits etablierte Forschungsdesigns (z.B. RCTs) zu implementieren, wie bereits von unserer Arbeitsgruppe publiziert [157, 158].

3.4.4 Mixed-Methods Forschung

Die Komplementierung quantitativer und qualitativer Forschungsansätze wie den unter Kapitel 2.4 und 2.6 dargestellten Studien, beruht auf der sog. *Mixed-Methods* Forschung, die nun zunehmend auch in den Gesundheitswissenschaften angewandt wird [98, 159-162]. In den letzten Jahren wurden auch zunehmend qualitative Publikationen in der Medizin veröffentlicht, so auch im Bereich der CIM, in der subjektive Patientenerfahrungen aus qualitativer Perspektive wichtig sind für die Kontextualisierung von subjektiven Erfahrungsdimensionen und Generierung von Hypothesen, die wiederum mit quantitativen Forschungsansätzen weiterführend untersucht werden können [117, 161, 162]. Die *Mixed-Methods* Forschung ermöglicht die Vorteile beider Ansätze zu vereinen, um so eine umfassendere Antwort auf die Forschungsfrage zu erhalten [161, 162]. Insbesondere in der CIM-Forschung wird dieser Ansatz zunehmend wichtig sein, v.a. bei den größtenteils noch nicht mit hoher Evidenz hinterlegten erweiterten NHV.

3.4.5 Unspezifische Effekte

Unspezifische Effekte machen in der Medizin zumeist einen relevanten Teil des Gesamteffektes aus - dies trifft nicht nur auf CIM-Interventionen zu, sondern vermutlich auf den Großteil der medizinischen Fachgebiete [163]. Faktoren wie Erwartungseffekte, Settingeffekte, Zuwendung, Gruppendynamiken, Arzt-Patienten-Interaktionen wurden

bisher zufriedenstellend nur im Bereich Akupunktur, schwerpunktmäßig von der Arbeitsgruppe um Prof. Kaptchuk, gut untersucht; hier besteht Forschungsbedarf bezüglich anderer CIM-Interventionen und CIM-Settings [164].

In den letzten Jahren wandelt sich die Medizin (wieder) von einer entpersonalisierten/apparativen hin zu einer patientenzentrierteren/individualisierten Medizin. Dies beruht einerseits auf den Errungenschaften im Bereich der Molekularwissenschaften und Genetik, die eine individualisierte Arzneimitteltherapie und eine maßgeschneiderte Therapie ermöglichen [165]. Andererseits hat die Forschung zu Arzt-Patienten-Interaktionen, zu den psychosozialen und verhaltensbezogenen Bedingungen chronischer Krankheiten gezeigt, dass v.a. nicht-pharmakologische Faktoren wie Empathie wesentliche Parameter für den Therapieerfolg des Patienten sein können [166].

3.5 Integrative Medizin

Um den aktuellen medizinischen Problemen unserer Gesellschaft gerecht zu werden, benötigen wir eine patientenzentrierte, gesundheitsökonomisch effiziente und evidenzbasierte Medizin. V.a. im Bereich der chronischen Erkrankungen könnten die Potenziale der klassischen medizinischen Fachrichtungen mit naturheilkundlicher und komplementärmedizinischer Expertise zu einer Integrativen Medizin verbunden werden.

Die Inanspruchnahme von NHK in Deutschland ist im internationalen Vergleich überdurchschnittlich hoch, dennoch ist die CIM im akademischen Kontext derzeit noch nicht so etabliert wie in den Vereinigten Staaten. Hier wird CIM bereits an vielen renommierten Universitäten und Krankenhäusern praktiziert, z.B. existieren etablierte CIM-Kompetenzzentren in der *University of California*, San Francisco (sog. *Osher Center for Integrative Health*), in der *Cleveland Clinic for Functional Medicine* und in der *Mayo Clinic*, Minnesota, welche im Sinne der *best-practice* evidenzbasierte CIM-Interventionen in Verbindung mit konventioneller Medizin anbieten.

Während in einigen wenigen Bereichen der CIM, vor allem in der MBM - hier insbesondere in der (Achtsamkeits-)Meditation und in dem Yoga - sowie in der Ernährungstherapie die Datenlage und wissenschaftliche Qualität der Veröffentlichungen als gut zu bezeichnen

sind und dies auch zu einer veränderten gesellschaftlichen Wahrnehmung dieser Interventionen beiträgt, besteht in anderen Bereichen wie der Phytotherapie, den erweiterten Verfahren der NHK und der TIM u.a. erheblicher wissenschaftlicher Nachholbedarf. Unter Beteiligung des Autors wurden bisher Studien in den Bereichen Ernährungs- und Fastentherapie, Phytotherapie und MBM durchgeführt und publiziert; laufende Projekte beziehen insbesondere naturtherapeutische Ansätze, Hydrotherapie und MBM-Interventionen mit ein [36, 56, 159, 167-183].

Trotz dieser bisherigen ermutigenden Entwicklungen ist die Bewertung des integrativen Medizinansatzes als Gesamtsystem und seiner Wechselwirkungen mit anderen Leistungen der Patientenversorgung bisher nur begrenzt möglich. Wirksamkeit, Sicherheit und Kosten-Effektivität von CIM-Interventionen sollten deshalb weiterhin systematisch in methodologisch hochwertigen Studien untersucht werden. Perspektivisch sollten multizentrische (inter-)nationale Projekte durchgeführt und die CIM-Forschung in Deutschland koordinierter stattfinden. Für die künftige Entwicklung der CIM ist es daher von entscheidender Bedeutung, den *evidence gap* durch systematische Forschung zu schließen und diese Daten der Öffentlichkeit und den politischen Entscheidungsträgern im Gesundheitswesen zu kommunizieren.

4. Zusammenfassung

Der demografische Wandel und die Zunahme chronischer nicht-übertragbarer Krankheiten stellen Herausforderungen für die nächsten Dekaden dar. CIM ergänzt die konventionelle Medizin mit evidenzbasierten naturheilkundlichen Interventionen zu einem therapeutischen Gesamtkonzept, um Präventions- oder Therapiestrategien zu verbessern, insbesondere bei lebensstil- und verhaltensabhängigen chronischen Erkrankungen. Aus dieser Perspektive ist Gesundheit ein proaktiver, dynamischer Prozess, der die Selbstwirksamkeit und Eigenkompetenz des Einzelnen im Hinblick auf präventives Verhalten fördern soll, vor allem durch das systematische Erlernen gesundheitsförderlicher Lebensstilaspekte. Die Inanspruchnahme naturheilkundlicher Verfahren ist in Deutschland im internationalen Vergleich hoch, obwohl robuste Evidenz noch aussteht bzw. nur in Teilbereichen vorhanden ist. Mit Ausnahme weniger Bereiche der Naturheilkunde ist die Evidenzlage für die Wirksamkeit der CIM bei chronischen Erkrankungen unzureichend. Die Studien dieser Arbeit zeigten bei den Indikationen Metabolisches Syndrom, Distress und stress-assoziierte Beschwerden Hinweise auf günstige Effekte naturheilkundlicher Verfahren, insbesondere im Bereich der Ernährungstherapie, der Fastentherapie und der Mind-Body-Medizin. Für eine mögliche Integration der Komplementärmedizin in die konventionelle Medizin im Sinne einer Integrativen Medizin ist weitere Grundlagen- und klinische Forschung auf methodologisch hohem Niveau notwendig.

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Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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Datum Unterschrift