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RESEARCH ARTICLE

Effects of a multidomain intervention against cognitive decline on dementia risk profiles — Results from the AgeWell.de trial

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Abstract

INTRODUCTION: Dementia risk scores constitute promising surrogate outcomes for lifestyle interventions targeting cognitive function. We investigated whether dementia risk, assessed using the LIfestyle for BRAin health (LIBRA) index, was reduced by the AgeWell.de intervention.

METHODS: Secondary analyses of the AgeWell trial, testing a multicomponent intervention (including optimization of nutrition, medication, and physical, social, and cognitive activity) in older adults with increased dementia risk. We analyzed data from $n = 461$ participants with complete information on risk/protective factors comprised by LIBRA at the 24-month follow-up. Intervention effects on LIBRA and LIBRA components were assessed using generalized linear models.

RESULTS: The intervention reduced LIBRA scores, indicating decreased dementia risk at follow-up ($b = -0.63$, 95% confidence interval [CI]: −1.14, −0.12). Intervention

effects were particularly due to improvements in diet (odds ratio [OR]: 1.60, 95% CI: 1.16, 2.22) and hypertension (OR: 1.61, 95% CI: 1.19, 2.18).

DISCUSSION: The AgeWell.de intervention reduced dementia risk. However, several risk factors did not improve, possibly requiring more intensive interventions.

KEYWORDS

dementia, lifestyle, prevention, randomized controlled trial, risk factor

Highlights

- The AgeWell.de intervention reduced dementia risk according to LIfestyle for BRAin health (LIBRA) scores.
- Beneficial effects on LIBRA are mainly due to changes in diet and blood pressure.
- A pragmatic lifestyle intervention is apt to reduce dementia risk in an at-risk population.

1 | BACKGROUND

Despite recent pharmacological advancements, for example, the development of amyloid beta (Aβ) antibodies able to slow cognitive decline in early Alzheimer's disease (AD),[1,2] dementia currently cannot be cured.[3] The eligible patient population for the respective therapies includes patients with mild cognitive impairment (MCI) due to AD or prodromal AD. While the prevalence of prodromal AD has been estimated to amount to 15.2 million persons in Europe,[4] low detection rates of MCI and barriers to diagnosis may limit potential benefits. The population in Europe potentially eligible for treatment with lecanemab is estimated at 5.4 million. Assuming pricing similarly as in the United States, treating all eligible patients would amount to 133 billion Euro per year, > 50% of the overall expenditures for pharmaceuticals in the European Union.[5] Therefore, prevention of cognitive decline and dementia is emphasized as a key priority by the World Health Organization in its global action plan on the public health response to dementia.[6]

Evidence suggests that up to 40% of dementia cases could be prevented by risk factor modification.[7] These findings encouraged the design of numerous lifestyle interventions, targeting modifiable risk factors to preserve cognitive function and reduce dementia risk. Owing to the multifactorial etiology of dementia, interventions addressing several risk factors simultaneously are considered particularly promising. First evidence that a multidomain intervention, targeting nutrition, physical and cognitive activity, as well as management of vascular risk factors, improved cognitive function against treatment as usual (TAU) and regular health advice was provided by the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER).[8]

To provide targeted means of dementia risk reduction, identifying individuals at increased risk is crucial. Several multifactorial scores have been developed to quantify dementia risk, including the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score,[9] the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI),[10] and the LIfestyle for BRAin health (LIBRA) score.[11] The use of dementia risk scores as outcome measures in multidomain preventive trials has been limited so far, although smaller short-term trials have used, for example, the ANU-ADRI as primary outcome, suggesting beneficial effects of a multidomain intervention on dementia risk.[12] Including dementia risk scores as outcomes in respective studies has been suggested a promising approach, especially as lifestyle interventions require rather long time spans to result in changes in cognitive function.[13,14] A reduction in dementia risk could in turn contribute to lower rates of incident dementia in the long term. Post hoc analyses of FINGER showed that the intervention reduced total LIBRA scores.[15] As LIBRA exclusively relies on modifiable risk factors, it is particularly suitable for detecting changes due to lifestyle interventions, possibly providing more realistic estimates for prevention potential than risk scores relying on non-modifiable factors.[16] In line with this, the LIBRA was found more responsive to change in joint post hoc analyses of the Multidomain Alzheimer Preventive Trial (MAPT), Prevention of Dementia by Intensive Vascular Care (preDIVA), and Healthy Ageing Through Internet Counselling in the Elderly (HATICE) trial than the established CAIDE score.[14] LIBRA emphasizes the role of vascular, metabolic, and lifestyle risk factors for dementia, domains targeted by the AgeWell.de intervention (see "Study Design and Participants"), while ANU-ADRI is also largely influenced by age and sex. This might make the LIBRA a more fitting surrogate outcome for a FINGER-like intervention. Post hoc analyses of FINGER revealed no intervention effects on changes in ANU-ADRI scores at 24-month follow-up.[17] Further, the ANU-ADRI algorithm does not take into account risk factors like obesity and elevated cholesterol for people aged ≥ 60 years, factors targeted by our intervention. Last, certain information required for calculation of ANU-ADRI was not available in our data (pesticide exposure). The present study therefore aims to assess intervention effects on dementia risk, assessed using the LIBRA score, in participants of the AgeWell.de trial.

2 | METHODS

2.1 | Study design and participants

This study uses data from the multicentric cluster-randomized AgeWell.de trial, testing the effectiveness of an adapted FINGER intervention on global cognitive performance (primary outcome) and several secondary outcomes in a sample of older primary care patients at increased risk for dementia in Germany. Global cognitive performance (primary outcome) was assessed using a composite *z* score, based on a cognitive test battery covering the domains attention (Trail Making Test A [TMT-A]),[18] executive function (TMT-B–TMT-A),[18] learning/memory (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] Word List Memory),[19] language (Verbal Fluency Test "Animals"),[19] perceptual-motor skills (CERAD Constructional Praxis),[19] and social cognition (Reading the Mind in the Eyes Test, revised version).[20] The composite score was calculated by averaging *z* scores of the respective domain-specific tests. Secondary outcomes included intervention effects on quality of life (QOL), health-related quality of life (HR-QOL), depressive symptoms, mortality, nursing home placement, (instrumental) activities of daily living, and cost effectiveness of the intervention. Study design and rationale,[21] baseline characteristics of participants,[22] and main results[23] are described in detail elsewhere. Results revealed no between-group differences in global cognitive performance (primary outcome) at follow-up after 2 years. In the overall sample, however, the intervention improved HR-QOL, while in women, the intervention reduced depressive symptoms.[23]

In short, participants were recruited via general practitioner (GP) practices at five study sites in Germany (Leipzig, Halle, Munich, Kiel, and Greifswald). GP patients aged between 60 and 77 years at increased risk for dementia, according to a CAIDE[9] score ≥ 9 points were eligible for participation. Exclusion criteria were a diagnosis of dementia; severe impairments of hearing, vision, or mobility; insufficient command of the German language; severe illness prohibiting safe participation in the multidomain intervention; and concurrent participation in another intervention trial.

Baseline assessments were conducted from July 2018 to October 2019, with $n = 1030$ participants randomized to either the multidomain intervention ($n = 487$) or control group (CG; 543). Intervention group (IG) participants conducted a multidomain intervention, comprising the following components:

1. Enhancement of physical activity: standardized exercises for strength and flexibility/balance, conducted at home twice/week; individual goals for aerobic exercises (3–5 times/week), based on participants' preferences; pedometer to track daily steps walked
2. Enhancement of social activity: individual goals for social activities with participants
3. Enhancement of cognitive activity: cognitive training using tablet computers and the cognitive training software NeuroNation, to be used three times/week for ≥ 15 minutes; individual goals for cognitively stimulating activities, based on participants' preferences
4. Optimization of nutrition: advice based on guidelines of the German Nutrition Society (DGE), targeting, for example, consumption of ≥ 5 portions of fruit and vegetables per day, limiting intake of salt and sugar, drinking unsweetened beverages
5. Optimization of medication: information obtained from attending GP and participant; electronic evaluation to identify anticholinergic drugs, potentially missing medication for cardiovascular diseases or diabetes mellitus, potentially serious drug–drug interactions, potential contraindications due to renal impairment; standardized recommendations (mail) to attending GP with suggestions for modification of participants' medication, if applicable
6. If applicable: management of cardiovascular risk factors for dementia (smoking, obesity): oral and written information on the respective risk factors and ways to reduce risk (e.g., smoking cessation)
7. If applicable: intervention targeting depressive symptoms and grief after bereavement: encouragement to contact attending GP; information on depression, grief reactions, addresses of local self-help groups and help lines

Following instructions by study nurses after the baseline interview at participants' homes, the intervention was conducted by the participants independently. During the same intervention period (24 months), the CG received an information brochure on lifestyle and dementia risk and GP treatment as usual (GPTAU).

Research in context

1. **Systematic review**: We searched PubMed for publications describing effects of multidomain interventions on dementia risk scores. Dementia risk scores appear modifiable by multidomain lifestyle interventions; respective publications are cited accordingly. Several ongoing trials include dementia risk scores as outcomes. Risk scores comprising non-modifiable risk factors (e.g., apolipoprotein E ε4 genotype) showed slightly less responsivity than risk scores solely including modifiable risk factors.
2. **Interpretation**: Aligning with previous findings, we found that a multidomain lifestyle intervention can reduce dementia risk captured using multifactorial dementia risk scores.
3. **Future directions**: Our findings suggest that even multidomain interventions that are less intensive than those tested in previous trials are apt to reduce dementia risk in a population at increased risk for dementia, strengthening the rationale for including dementia risk scores as outcomes in future trials. Further studies are warranted to assess the utility of dementia risk scores for monitoring adherence to multidomain lifestyle interventions throughout trials.

The study was approved by the responsible ethics boards of the coordinating study center of AgeWell.de (Ethics Committee of the Medical Faculty of the University of Leipzig; 369/17-ek) and of all participating study sites. AgeWell.de is registered at the German Clinical Trials Register (DRKS; ID: DRKS00013555).

2.1.1 | Diversity, equity, and inclusion

During the planning of the AgeWell.de study, members of the community senior citizen board of the city of Leipzig were involved in discussing the study design and intervention. Criteria for inclusion and exclusion aimed to facilitate participation for as many GP patients as possible. Applying a multicentric study design, with recruitment centers at both urban and rural areas in Germany, AgeWell.de was set out to include GP patients from a variety of different regional and sociodemographic backgrounds.

2.1.2 | Outcomes and covariates

The main outcome of the current study is dementia risk, as captured by the LIBRA score, at follow-up 24 months after the baseline examination. LIBRA captures an individual's potential for dementia risk reduction, based on 12 modifiable risk (coronary heart disease, diabetes mellitus, hypercholesterolemia, arterial hypertension, depression, obesity, smoking, physical inactivity, and chronic kidney disease) and protective factors (low-to-moderate alcohol consumption, high cognitive activity, healthy diet) by calculating a weighted sum score (range: −5.9 to 12.7, higher scores indicating higher risk for dementia). Conceptualization of LIBRA is based on results of a systematic review and Delphi consensus study.[24] Information on all 12 risk and protective factors contributing to LIBRA was collected at baseline and follow-up in AgeWell.de. Study nurses assessed anthropometric measures (height, weight) during the baseline and follow-up assessments, which were used to assess obesity (body mass index [BMI] $\geq$ 30 kg/m^2) and systolic and diastolic blood pressure (SBP, DBP). Participating GPs provided information on participants' diagnoses including coronary heart disease, diabetes mellitus, hypercholesterolemia, renal dysfunction, and depression using structured questionnaires both at baseline and follow-up. During the baseline and follow-up assessment, participants provided information on nutrition and alcohol consumption, using a validated food frequency questionnaire. The original LIBRA score considers adherence to a Mediterranean diet as a protective factor. Since respective information were not available in AgeWell.de, a point for healthy nutrition was awarded for high consumption of fruit and vegetables, that is, eating $\geq$ 650 g of fruit and vegetables daily, which constitutes a key component of a Mediterranean diet. Participants further provided information on physical and cognitive activities, using structured questionnaires, as well as smoking (current smokers vs. non-smokers). Depressive symptoms were assessed using the Geriatric Depression Scale (GDS), with $\geq$ 6 points indicating depressive symptoms, or a respective diagnosis of depression. Table S1 in supporting information summarizes operationalization of individual LIBRA factors in AgeWell.de.

Diagnoses of chronic diseases such as coronary heart disease or renal dysfunction are treated as permanent diagnoses in the German health-care system, regardless of treatment or changes in, for example, blood sugar levels. Therefore, if the attending GP did not provide information on LIBRA components coronary heart disease, diabetes mellitus, hypercholesterolemia, and renal dysfunction at follow-up, baseline information of said diagnoses were assumed to further apply at follow-up to avoid loss of observations for analyses.

Due to the dichotomous assessment of individual risk factors (present/absent) and the respective cutoffs, the responsiveness of dementia risk scores to change may be limited. For instance, a BMI of $\geq$ 30 corresponds to a 1.6 point higher risk for dementia according to LIBRA. If a person's BMI at baseline was 30.1, a much smaller change in BMI (i.e., 0.2) would be sufficient to induce a reduction in the total LIBRA score than for a person with a BMI of 34 at baseline. Therefore, it has been suggested that *z* score versions of risk scores like the LIBRA may be suitable approaches for detecting changes due to a multidomain lifestyle intervention. Based on the approach of Coley et al.,[14] we used (1) the original LIBRA score and its components, (2) a *z* score version of LIBRA, based on *z* scores of all modifiable risk factors comprised by the index (see Table S1 for details) as outcomes in our analyses.

Information on the covariates age, sex, and education was collected during the baseline assessment, using structured face-to-face-interviews. To control for potential confounding effects of cognitive function, we further included baseline cognitive performance in our analyses (composite *z* score, based on performance in domain-specific tests of attention, memory, executive function, language, perceptual-motor abilities, and social cognition; for further details see Zülke et al.[23]).

2.1.3 | Statistical analyses

Observations with available data on all 12 factors of the LIBRA score were compared to observations with missing data on LIBRA factors using chi^2 and two-sided *t* tests, as appropriate. Descriptive analyses of the study sample were conducted using chi^2 and two-sided *t* tests to compare IG and CG participants with regard to sociodemographic information, cognitive performance, presence of individual LIBRA factors, and total LIBRA score.

Effects of the multidomain intervention on the LIBRA score were analyzed using generalized linear mixed models (GLM) with cluster-robust standard errors to account for clustering of participants in GP practices. Because values of LIBRA approximately followed a normal distribution, analyses were run with identity link and Gaussian distribution errors. LIBRA score at follow-up served as outcome and group (IG vs. CG) as predictor. We adjusted for sex, age, and education, and also included the baseline LIBRA score to account for possible differences in LIBRA scores between IG and CG, which might otherwise induce regression to the mean and lead to underestimation of intervention effects.[25] Further, as previous studies using data from the FINGER

study suggest associations between cognitive performance and LIBRA score, with higher LIBRA scores being linked to lower levels of cognitive function,[15] we further controlled for differences in global cognitive performance at baseline. Substituting the main analyses, we conducted stratified analyses by sex and age group to assess possible differences in intervention effects on LIBRA scores.

We further assessed intervention effects on individual LIBRA components (risk factor present = 0 versus risk factor absent = 1 / protective factor absent = 0 versus protective factor present = 1) using logistic regression analyses, controlling for sex, age, education, cognitive performance, and baseline value of respective component. All outcomes were recoded such that odds ratios (ORs) > 1 implied higher odds of absence of a risk factor/presence of a protective factor at follow-up.

3 | RESULTS

3.1 | Sample characteristics

Of $n = 1030$ participants at baseline, $n = 819$ completed the follow-up assessment 24 months after baseline (IG/CG: 378/441). After excluding participants with missing information on any component of the LIBRA score at baseline ($n = 184$) or follow-up ($n = 173$), $n = 461$ participants were available for analyses (IG/CG: 217/244). Participants with missing LIBRA information at baseline tended to have lower baseline cognitive function than those with available information ($P = 0.002$). No differences regarding sex ($P = 0.319$), age ($P = 0.345$), intervention group ($P = 0.601$), or education ($P = 0.266$) were detected between participants with available and missing LIBRA information (not tabulated).

Table 1 describes participants in the current analyses at baseline. Regarding individual LIBRA factors, hypertension was observed more often in IG than in CG participants ($P = 0.001$). No other differences regarding LIBRA factors, sociodemographic information, or cognitive performance were observed between IG and CG participants. Total LIBRA scores ranged from −5.9 to 8.8 points (IG: −5.9, 8.0; CG: −4.6, 8.8; no significant difference in mean LIBRA score between groups, $P = 0.103$). Men and women did not differ in baseline LIBRA scores ($P = 0.070$). Older age was linked to higher LIBRA scores at baseline ($P = 0.003$), while a high level, but not an intermediate level, of education was associated with a lower baseline LIBRA score (ref.: low level of education; $P < 0.001$; $P = 0.098$, respectively). Better cognitive performance at baseline (composite *z* score) was linked to lower LIBRA scores ($P < 0.001$).

3.2 | Intervention effects on dementia risk (LIBRA score)

Results of multivariable generalized linear regression analyses are described in Table 2. Adjusted for covariates, participants in the IG had lower LIBRA scores at follow-up ($b = -0.63$, 95% confidence interval [CI]: −1.14, −0.12) than participants in the CG. Stratifying analyses by sex, men in the IG had lower LIBRA scores at follow-up ($b = -0.94$, 95% CI: −1.61, −0.27), while this was not observed in women ($b = -0.40$, 95% CI: −1.02, 0.21). Stratifying analyses by age group, younger (60–69 years) IG participants had lower LIBRA scores at follow-up ($b = -0.86$, 95% CI: −1.48, −0.24), while this was not observed in older IG participants ($b = -0.36$, 95% CI: −1.01, 0.29).

3.3 | Intervention effects on individual LIBRA components

Effects of the multidomain intervention on individual LIBRA components, assessed using logistic regression analyses, are described in Table 3.

The intervention reduced the odds of hypertension (OR: 1.61, 95% CI: 1.19, 2.18) in the total sample. In stratified analyses, reduced odds of hypertension were also detected for men (OR: 2.07; 95% CI: 1.31, 3.27), in younger (OR: 1.53; 95% CI: 1.02, 2.31) and older participants (OR: 1.69; 95% CI: 1.08, 2.65), but not for women (OR: 1.38; 95% CI: 0.96, 2.00). When using SBP as outcome, intervention effects were highly similar (b_{total}: −2.59, 95% CI: −5.08, −0.10; $b_{men} = -4.10$, 95% CI: −7.85, −0.35; $b_{women} = -1.51$, 95% CI: −4.68, 1.65; $b_{60\text{-}69} = -1.12$, 95% CI: −4.18, 1.95; $b_{70\text{-}77} = -4.40$, 95% CI: −8.36, −0.43). Mean change in SBP amounted to −5.9 mmHg in the IG and −1.3 mmHg in the CG ($P = 0.014$, not tabulated). Further, beneficial effects of the intervention were detected for a healthy diet in the total sample (OR: 1.60, 95% CI: 1.16, 2.22). Stratifying analyses by sex and age, respectively, this beneficial effect was found among women (OR: 1.93; 95% CI: 1.26, 2.96) and older participants (OR: 1.95; 95% CI: 1.32, 2.88), but not among men (OR: 1.30; 95% CI: 0.81, 2.08) or younger participants (OR: 1.36; 95% CI: 0.86, 2.15). While no intervention effect on high cognitive activity was detected in the overall sample (OR: 1.42; 95% CI: 0.95, 2.13), the intervention increased the odds of high cognitive activity for younger participants (OR: 2.00; 95% CI: 1.20, 3.34). For the remaining LIBRA factors, no effect of the intervention was found either in the total sample or in age- and sex-specific analyses.

When applying a *z* score version of the LIBRA index as outcomes, results were highly similar (Table S2 in supporting information). Participants in the IG had lower LIBRA scores at follow-up ($b = -0.60$; 95% CI: −1.18, −0.01). Further, *z* scores for LIBRA factors hypertension ($b = -0.13$; 95% CI: −0.26, −0.01) and nutrition ($b = 0.21$; 95% CI: 0.36, 0.07; inversely coded) indicated improvement in said risk factors in IG participants at follow-up. In female IG participants, depressive symptoms were reduced ($b = -1.25$; 95% CI: −2.25, −0.25).

To control for possible influences of changes in participants' medication on the observed intervention effect on hypertension, we assessed rates of participants with hypertension taking any kind of hypertensive medication at baseline and follow-up. At baseline, 93.2% of participants with hypertension were regularly taking antihypertensive medication (IG/CG: 92.3%/94.2%, $P = 0.435$). These figures were changed only marginally at follow-up (% total: 93.6, IG/CG: 92.4%/94.7%, $P = 0.354$). The number of participants with untreated hypertension at baseline

TABLE 1 Sample characteristics at baseline, by intervention group.

Variable	Total ($n = 461$)	Intervention group ($n = 217$)	Control group ($n = 244$)	*P*
Sociodemographic information				
Age, M (SD)	68.7 (4.8)	68.7 (4.8)	68.6 (4.8)	0.850
Female, *n* (%)	230 (49.9)	104 (47.9)	126 (51.6)	0.426
Education, *n* (%)				
Low	102 (22.1)	54 (24.9)	48 (20.0)	0.298
Intermediate	239 (51.8)	112 (51.6)	127 (52.1)	
High	120 (26.0)	51 (23.5)	69 (28.3)	
Cognitive performance total score; M (SD)	0.1 (0.9)	0.1 (1.0)	0.2 (0.9)	0.372
LIBRA factors				
Coronary heart disease, *n* (%)	75 (16.3)	38 (17.5)	37 (15.2)	0.495
Hypertension, *n* (%)	228 (49.5)	125 (57.6)	103 (42.2)	**0.001**
Hypercholesterolemia, *n* (%)	270 (58.6)	126 (58.1)	144 (59.0)	0.836
Diabetes mellitus, *n* (%)	337 (73.1)	153 (70.5)	184 (75.4)	0.236
Depression, *n* (%)	17 (3.7)	9 (4.2)	8 (3.3)	0.621
Obesity, *n* (%)	118 (25.6)	57 (26.3)	61 (25.0)	0.756
Smoking, *n* (%)	49 (10.6)	25 (11.5)	24 (9.8)	0.558
Low/moderate alcohol consumption, *n* (%)	215 (46.6)	96 (44.2)	119 (48.8)	0.330
Physical inactivity, *n* (%)	203 (44.03)	87 (40.1)	116 (47.5)	0.108
High cognitive activity, *n* (%)	186 (40.4)	79 (36.4)	107 (43.9)	0.104
Healthy diet, *n* (%)	222 (48.2)	105 (48.4)	117 (48.0)	0.925
Renal dysfunction, *n* (%)	98 (21.3)	42 (19.4)	56 (23.0)	0.346
LIBRA total score, M (SD)	1.5 (2.7)	1.7 (2.6)	1.3 (2.8)	0.103

Note: Education assessed according to CASMIN; *n* denotes participants with available information at baseline; significant group differences highlighted in bold type.
Abbreviations: CASMIN, comparative analyses of social mobility in industrial nations; LIBRA, LIfestyle for BRAin health; SD, standard deviation.

TABLE 2 Effects of the multidomain intervention on LIBRA score at follow-up.

	Overall sample ($n = 461$)					
Variable	***b***	**95% CI**				***P***
Intervention group (ref.: control group)	−0.63	−1.14; −0.12				**0.016**
	Men ($n = 231$)			**Women ($n = 230$)**		
Variable	***b***	**95% CI**	***P***	***b***	**95% CI**	***P***
Intervention group (ref.: control group)	−0.94	−1.61; −0.27	**0.006**	−0.40	−1.02; 0.21	0.200
	Age 60–69 years ($n = 261$)			**Age = 70–77 years ($n = 200$)**		
	b	**95% CI**	***P***	***b***	**95% CI**	***P***
Intervention group (ref.: control group)	−0.86	−1.48; −0.24	**0.007**	−0.36	−1.01; 0.29	0.281

Note: Outcome: LIBRA score at follow-up; higher LIBRA scores indicate higher dementia risk, that is, negative values of *b* coefficients indicate lower dementia risk at follow-up; all models adjusted for age (except age-stratified analyses), sex (except sex-stratified analyses), education, baseline cognitive performance, and baseline LIBRA score. Significant effects highlighted in bold type.
Abbreviations: CI, confidence interval; LIBRA, LIfestyle for BRAin health; ref: reference

TABLE 3 Intervention effects on individual LIBRA factors.

	Total sample		Men		Women		60–69 years		70–77 years	
LIBRA factor	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Coronary heart disease	0.73 (0.36; 1.47)	0.380	0.65 (0.29; 1.48)	0.304	0.83 (0.34; 2.07)	0.693	0.39 (0.13; 1.20)	0.102	0.98 (0.43; 2.22)	0.964
Hypertension	1.61 (1.19; 2.18)	**0.002**	2.07 (1.31; 3.27)	**0.002**	1.38 (0.96; 2.00)	0.084	1.53 (1.02; 2.31)	**0.042**	1.69 (1.08; 2.65)	**0.022**
Hypercholesterolemia	No changes									
Diabetes mellitus	1.20 (0.73; 1.97)	0.466	0.78 (0.37; 1.68)	0.533	1.73 (0.87; 3.42)	0.118	1.50 (0.80; 2.81)	0.210	1.00 (0.50; 2.01)	0.993
Depression	1.02 (0.51; 2.03)	0.951	0.84 (0.32; 2.21)	0.721	1.31 (0.46; 3.75)	0.618	0.84 (0.26; 2.66)	0.767	1.24 (0.54; 2.84)	0.615
Obesity	0.92 (0.58; 1.46)	0.713	0.91 (0.49; 1.68)	0.753	0.91 (0.48; 1.72)	0.777	0.95 (0.57; 1.59)	0.843	0.89 (0.38; 2.08)	0.781
Smoking	0.60 (0.21; 1.74)	0.345	1.33 (0.32; 5.59)	0.694	0.26 (0.05; 1.54)	0.139	0.36 (0.10; 1.23)	0.103	No changes	
Low/moderate alcohol consumption	1.22 (0.81; 1.85)	0.340	1.26 (0.75; 2.10)	0.382	1.16 (0.60; 2.25)	0.664	1.48 (0.87; 2.54)	0.148	0.93 (0.43; 1.98)	0.843
Physical inactivity	1.26 (0.90; 1.78)	0.180	1.10 (0.64; 1.89)	0.736	1.40 (0.86; 2.27)	0.179	1.22 (0.81; 1.84)	0.349	1.36 (0.83; 2.24)	0.220
High cognitive activity	1.42 (0.95; 2.13)	0.087	1.67 (0.95; 2.94)	0.074	1.32 (0.79; 2.20)	0.295	2.00 (1.20; 3.34)	**0.008**	0.85 (0.45; 1.57)	0.595
Healthy diet	1.60 (1.16; 2.22)	**0.004**	1.30 (0.81; 2.08)	0.277	1.93 (1.26; 2.96)	**0.003**	1.36 (0.86; 2.15)	0.192	1.95 (1.32; 2.88)	< **0.001**
Renal dysfunction	1.10 (0.61; 1.99)	0.748	1.16 (0.53; 2.56)	0.714	1.07 (0.55; 2.11)	0.837	0.98 (0.46; 2.10)	0.968	1.21 (0.58; 2.53)	0.606

Note: Outcome: LIBRA components at follow-up; values > 1 indicate higher odds of positive outcome at follow-up (i.e., absence of risk factor or presence of protective factor); all models adjusted for age (except age-stratified analyses), sex (except sex-stratified analyses), education, baseline cognitive performance, and baseline value of respective LIBRA factor. Significant effects highlighted in bold type.

Abbreviations: CI, confidence interval; LIBRA, LIfestyle for BRAin health; OR, odds ratio.

who were taking newly prescribed antihypertensive medication at follow-up did not differ between groups ($n = 7$, IG/CG: 4/3, $P = 0.762$).

4 | DISCUSSION

We analyzed effects of a multidomain lifestyle intervention on dementia risk, assessed using the LIBRA score. Using data from the cluster-randomized AgeWell.de trial, conducted in a population at increased risk for dementia, we showed that the intervention successfully reduced overall LIBRA scores, indicating reduced risk for dementia. This effect was found in the overall sample, as well as in younger and male participants. Looking more closely at individual dementia risk and protective factors included in the LIBRA, this was particularly due to beneficial changes in hypertension and diet. Further, a beneficial effect of the intervention was found for cognitive activity in younger participants.

While not initially developed as outcome measures for these trials, dementia risk scores such as the LIBRA or CAIDE score have been investigated as surrogate outcomes of interventions aimed at preserving cognitive function in older adults.[14,15,26,27] Intervention effects on respective risk scores might, on a population level, lead to lower rates of incident cases of dementia in the long term.

The beneficial intervention effects on LIBRA scores as detected in our study are particularly due to favorable changes in hypertension (both dichotomously, i.e., SBP < 140 vs. ≥ 140, and continuously, i.e., SBP) and diet. This finding is in line with a previous study assessing effects of the MAPT, preDIVA, and HATICE trials, showing that said LIBRA factors were particularly responsive to change.[14] This indicates favorable changes in diet and blood pressure levels due to the AgeWell.de intervention that were large enough to induce a significant reduction of the overall LIBRA in the intervention group. Further corroborating the results of Coley et al.,[14] LIBRA factors like diabetes or coronary heart disease showed no responsiveness to the intervention.

We detected beneficial intervention effects on the LIBRA factor "high cognitive activity"; however, only in younger participants (aged 60–69 years). The respective intervention component relied particularly on regular use of a digital cognitive training program (NeuroNation, conducted using tablet PCs). Familiarity with apps and tablet use may have been greater in younger participants, possibly facilitating conduct of this intervention component. In line with this interpretation, older age was a significant predictor of lower adherence to the cognitive training component in the FINGER study.[28] Because we did not assess previous experience using computers or apps, however, this explanation needs to be interpreted with caution. As digital literacy and internet usage is increasing among older adults,[29] respective intervention components may be more feasible in future studies.

While particularly the MAPT and HATICE trials were able to increase levels of physical activity and decrease levels of alcohol intake, no respective effects were observed in the current analyses. Possibly, the AgeWell.de intervention, although aimed at increasing, among other factors, physical activity, was not intensive enough to result in meaningful changes in physical activity. Further, the intervention period was hampered by the COVID-19 pandemic, limiting participants' opportunities for physical activity throughout a long period of time.[30] On another note, participants conducted the respective intervention component independently, other than, for example, participants of FINGER, who attended supervised courses for aerobic and strength training,[31] which may have further reduced intensity of the respective intervention component.[23] Results from the AgeWell.de baseline assessment revealed that, among participants who were not regularly physically active, 41% reported no intention to increase their physical activity in the upcoming 6 months, implying relatively low levels of motivation for behavior change.[32]

Despite the promising finding of beneficial intervention effects on the total LIBRA score, several risk/protective factors revealed no change due to the intervention. One possible explanation lies in the study design, including an active control group: CG participants received GPTAU, which may have involved preventive elements similar to those of the multidomain intervention, as conditions like, for example, obesity, hypertension, and so forth were highly common among study participants due to the inclusion criteria (CAIDE ≥ 9). Our results therefore constitute rather conservative estimates. On another note, more intensive interventions might be needed to evoke changes in the other LIBRA factors, for example, by providing more support for participants regarding enhancement of physical activity, weight loss, or smoking cessation. In FINGER, adherence to the multidomain intervention was lowest for the intervention component that participants conducted independently, that is, cognitive training, while adherence was higher for intervention components that entailed more guidance and support.[28] Nevertheless, lifestyle changes are challenging, especially for older adults, and might also require longer intervention periods to consolidate new behaviors. Several studies point toward the crucial role of self-efficacy in behavior change in older age (for a review, see French et al.[33]). Analyses of the AgeWell.de study revealed that self-efficacy was the single strongest determinant of motivation for physical activity enhancement[32] and regular physical activity uptake (see Cardona et al.[34]). Enhancing older adults' self-efficacy and providing tailored interventions based on current stage of motivation for behavior change may improve intervention adherence and, in the long term, lead to even more pronounced improvements in dementia risk profiles.[35]

In addition to the original LIBRA score and its individual components, we further applied a *z* score version of the LIBRA to also detect small changes, which might not pass the cutoff of individual LIBRA factors. Respective results were highly comparable to those observed using the original LIBRA, except for a decrease in depressive symptoms observed in female IG participants, which was not detected when applying the original LIBRA. This implies that both the original LIBRA score and a continuous *z* score version are equally apt to detect changes in lifestyle factors after a 2-year intervention period.

5 | STRENGTHS AND LIMITATIONS

Our study is strengthened by being able to include all $n = 12$ LIBRA factors in our analyses, facilitating comparisons to other studies and using the full potential of the original LIBRA score. As AgeWell.de is part of

the WW-FINGERS consortium[36] and the intervention closely followed the FINGER approach, our results provide valuable insights for other randomized controlled trials (RCTs) adapting the FINGER intervention and testing multidomain interventions for the protection of cognitive function in older adults at increased dementia risk. By showing that modifiable dementia risk is amendable to change after a 2-year intervention period, this study further underscores the value of dementia risk scores as outcomes for RCTs aiming at dementia risk reduction.

Certain limitations need to be mentioned when interpreting our findings. Unfortunately, a large number of observations were excluded due to missing values on individual LIBRA factors. In cases in which this concerned diagnoses of, for example, diabetes or coronary heart disease, baseline values of respective diagnoses were assumed to remain present at follow-up. This rationale is deemed justified because these diagnoses are not discarded from patients' health records even despite ongoing treatment. Further, analyses from the MAPT, preDIVA, and HATICE trials suggested none to very small changes in these conditions due to a multidomain intervention.[14] Therefore, we are confident that this procedure did not significantly alter our findings. However, the rather high amount of missing data might limit generalizability of our findings. Further, we relied on different sources of information for calculating the LIBRA. While information on (chronic) conditions were provided by GPs, data on diet and physical and cognitive activity were gathered using self-report data, which might make this information more susceptible to social desirability. While 48.2% of participants were characterized as eating healthily, based on self-reported regular and sufficient consumption of fruit and vegetables, the share of older (≥ 65 years) men and women in Germany reporting daily consumption of fruit and vegetables was 28.9% and 48.7% in a recent population-based study,[37] indicating a small potential bias due to social desirability. However, we are confident that this did not substantially affect the observed beneficial change in nutrition due to the intervention. Last, hypertension at baseline was more common in IG than in CG participants. This might indicate that the observed intervention benefits on hypertension are, at least partially, due to more room for improvement in the IG. Analyses of the AgeWell.de intervention component regarding optimization of medication, including prescription/intensification of antihypertensive treatments, is currently pending and will further clarify this issue. However, analyses were controlled for baseline values for hypertension, and we assessed numbers of participants initiating antihypertensive treatment during the study; therefore, we do not expect that these differences should have significantly affected our findings.

6 | CONCLUSION

While the AgeWell.de intervention did not improve global cognitive function in a sample of older adults at increased risk for dementia in Germany, our results suggest that AgeWell.de reduced modifiable dementia risk as captured by the LIBRA score. Our findings imply that even an intervention less intensive in character than the successful FINGER intervention (due to both the pragmatic trial design and restrictions in intervention implementation due to the COVID-19 pandemic) can provide positive changes in lifestyle, particularly regarding nutrition and hypertension. If beneficial lifestyle changes are maintained beyond the intervention period, this might contribute to decreased rates of incident dementia in the long run. Future studies with extensive follow-up investigations and endpoints like incident dementia/cognitive decline are warranted to confirm these lines of thought. The findings underscore the utility of dementia risk scores as outcomes for lifestyle interventions in older adults and might further be used to monitor intervention conduct.

AUTHOR CONTRIBUTIONS

Conceptualization: David Czock, Jochen Gensichen, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. *Data curation*, *formal analysis*: Andrea E. Zülke. *Funding acquisition*: David Czock, Jochen Gensichen, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. *Investigation*: Andrea E. Zülke. *Methodology*: Andrea E. Zülke, Alexander Pabst. *Project administration*: David Czock, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. *Resources*: Jochen Gensichen, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, and Steffi G. Riedel-Heller. *Supervision*: David Czock, Thomas Fankhänel, Jochen Gensichen, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. *Validation*: David Czock, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. *Visualization*: Andrea E. Zülke. *Writing—original draft*: Andrea E. Zülke. *Writing—review and editing*: Alexander Pabst, Melanie Luppa, Anke Oey, Robert P. Kosilek, Hannah Schillok, Thomas Fankhänel, Solveig Weise, Christian Brettschneider, David Czock, Thomas Frese, Jochen Gensichen, Wolfgang Hoffmann, Hanna Kaduszkiewicz, Hans-Helmut König, Jochen René Thyrian, Birgitt Wiese, and Steffi G. Riedel-Heller. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Prior to participation, written informed consent to participate was obtained from all participants at their respective GP practice.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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