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Exploring the effect of multi-modal intervention against cognitive decline on atrophy and small vessel disease imaging markers in the AgeWell.de imaging study

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ABSTRACT

Background: Multimodal lifestyle interventions might help to maintain healthy cognition in older age and to delay onset of dementia. Here, we studied the effects of a multi-modal lifestyle-based intervention, based on the FINGER trial, on magnetic resonance imaging (MRI) markers of hippocampal-limbic atrophy and cerebral small vessel disease in older adults at increased risk for dementia in Germany.

Methods: Leipzig participants of the multicenter AgeWell.de randomized controlled trial underwent neuroimaging before and after a two year intervention at 3 Tesla MRI. We extracted hippocampal volume and entorhinal cortex thickness (ECT), free water fraction (FW), peak width of skeletonized mean diffusivity (PSMD), white matter hyperintensity volume and mean gray matter cerebral blood flow and assessed the effect of the intervention on these imaging markers using linear mixed models. We also tested the effect of the intervention on the hippocampus-dependent Mnemonic Similarity Test and fixel-based white matter microstructure.

Results: 56 individuals (mean (sd) age: 68.8 (4.2) years, 26 females, 24/32 intervention/control group) were included at baseline and 41 returned after an average of 28 months for the second assessment. ECT and FW exhibited stronger decline in the intervention compared to the control group in preregistered models but not when adjusted for baseline differences. All other markers progressed similarly across groups, however sample size was smaller than expected. In exploratory analyses, cerebral blood flow increased more in the intervention group and this change was associated with decreases in systolic blood pressure.

Conclusions: In this group of older adults at risk for dementia, we find no conclusive evidence whether a multimodal lifestyle intervention improves brain imaging markers of neurodegeneration and small vessel disease. Preliminary evidence suggested an association of the intervention, increased cerebral blood flow and systolic blood pressure reductions.

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Abbreviations: ECT, entorhinal cortex thickness; FW, free water fraction; WHO, world health organization; AD, Alzheimer's disease; VCI, vascular cognitive impairment; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; MTL, medial temporal lobe; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay diet; cSVD, cerebral small vessel disease; WMH, white matter hyperintensities of presumed vascular origin; PSMD, peak width of the mean diffusivity distribution; WW-FINGERS, world wide FINGER studies; CAIDE, Cardiovascular Risk Factors, Aging, and Incidence of Dementia; GPP, general practitioner praxis; MRI, magnetic resonance imaging; MST, Mnemonic Similarity Test; TE, echo time; TR, repetition time; FA, flip angle; FOV, field of view; GRAPPA, GeneRalized Autocalibrating Partial Parallel Acquisition; CMRR, Center for Magnetic Resonance Research; BOLD, blood oxygenation level dependent; pcASL: pseudo-continuous arterial spin labeling; EPI, echo-planar imaging; FLAIR, fluid attenuated inversion recovery; CBF, cerebral blood flow; QA, quality assessment; GM, gray matter; HCV, hippocampal volume; eICV, estimated intracranial volume; DWI, diffusion-weighted imaging; MD, mean diffusivity; FA, fractional anisotropy
TBSS: tract-based spatial statistics; CSF, cerebral spinal fluid; ISI, inter-stimulus interval; LDI, lure discrimination index; REC, recognition score; CG, control group; IG, intervention group; MoCA, Montreal Cognitive Assessment; CASMIN, Comparative Analysis of Social Mobility in Industrial Nations; BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure; OSF, open science framework; LMM, linear mixed model; ANOVA, analysis of covariance.

1. Introduction

1.1. Background

Late-life cognitive impairment and dementia pose significant challenges to global health. According to the WHO Global action plan on the public health response to dementia 2017–2025 (World Health Organization, 2017); they are leading causes of disability and dependency among older adults worldwide.

Dementia can be caused by multiple neurodegenerative and neurovascular pathologies, where Alzheimer's disease (AD) and vascular cognitive impairment (VCI) are the most common causes (Knopman et al., 2021; Gorelick et al., 2011; Karanth et al., 2020). Pathological processes leading to AD and VCI begin years before symptom onset, giving rise to a window of opportunity for prevention (Jack et al., 2018; Sargurupremraj et al., 2020). While biological aging is the primary risk factor for dementia, epidemiological studies have identified various vascular and lifestyle-related risk factors associated with cognitive impairment, offering potential avenues for prevention (Livingston et al., 2024). These risk factors encompass physical inactivity, obesity, poor diets, tobacco and alcohol use, diabetes, mid-life hypertension, depression, air pollution, low education, social isolation, cognitive inactivity, and hearing and vision loss. Multidomain interventions targeting several of these risk factors simultaneously may therefore be effective in decreasing the risk for dementia, delaying dementia onset and/ or modifying the course of dementia. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) demonstrated using a randomized clinical trial design that such an intervention in older individuals could enhance cognitive function (Ngandu et al., 2015). The German Agewell-study was successful in decreasing a summary score composed of modifiable factors that has predicted dementia in other epidemiological studies (Zülke et al., 2024).

Little is known however on the underlying mechanisms. There is strong evidence that modifiable risk factors for cognitive decline and dementia are associated with imaging markers of gray matter atrophy and neurovascular pathology (Jacka et al., 2015; Beauchet et al., 2013; Brundel et al., 2014; Lammer et al., 2023), suggesting multiple routes of how these risk factors could trigger or contribute to brain aging and cognitive decline. Yet, few studies have comprehensively investigated whether lifestyle interventions could mitigate these brain changes. The hippocampus and medial temporal lobe (MTL) are key regions affected in AD, showing atrophy related to accumulation of misfolded Tau protein early in the disease course (Berron et al., 2021). The MTL is also known to be particularly susceptible to environmental influences, and may be modulated by interventions (Walhovd et al., 2016). Physical activity interventions for example have shown small positive effects on hippocampal atrophy in older adults (Wilckens et al., 2021; David et al., 2025). Regarding dietary interventions, the effects are mixed: while the large MIND diet study did not show a beneficial effect of a three-year Mediterranean diet intervention on hippocampal atrophy in over 600 individuals (Barnes et al., 2023), several smaller trials reported positive effects of a Mediterranean-like diet, specific dietary components of this diet such as polyphenols or Omega-3 fatty acids or dietary restriction to have positive effects (Kaplan et al., 2022; Köbe et al., 2017; Witte et al., 2014; Prehn et al., 2017). In FINGER participants, no positive effect of the multidomain intervention on hippocampal atrophy or cortical thickness was observed (Stephen et al., 2019), however, Moon et al. reported increased cortical thickness after 24 weeks of multidomain intervention designed according to the FINGER concept, compared to control, in 36 older at risk participants (Moon et al., 2022).

factors in individuals living with hypertension or diabetes have shown evidence for reduced progression of WMH (Nasrallah et al., 2019; Espeland et al., 2018). This is in line with genetic evidence for a causal role of hypertension for development of cSVD (Sargurupremraj et al., 2020; Taylor-Bateman et al., 2022). In FINGER, a trend towards reduced fractional anisotropy, interpreted as reduced axonal swelling, (Stephen et al., 2020), but no effects on WMH progression were detected in the intervention compared to the control group (Stephen et al., 2019). Note that neuroimaging markers were acquired on two different MRI scanners with different field strengths, which may have affected the estimates of imaging markers (Medawar et al., 2021). Effects of lifestyle interventions on more recently developed markers with presumably higher sensitivity towards cSVD, such as white matter microstructural integrity assessed as peak width of the mean diffusivity distribution (PSMD), or free water fraction (FW), an estimate of extracellular free water, (Duering et al., 2018; Maillard et al., 2019) have not yet been explored.

With regard to other modifiable risk factors like social isolation and depressive symptoms, little is known about intervention effects on imaging markers of brain health.

Part of World Wide FINGERS network (WW-FINGERS) (Rosenberg et al., 2020), the AgeWell.de study investigated a multi-component intervention's potential to prevent cognitive decline in at-risk individuals aged 60–77 years in Germany (Zülke et al., 2024). Here, we aimed to evaluate the synergistic effects of the AgeWell.de multimodal intervention on brain structure using sensitive magnetic resonance imaging (MRI) markers at 3 T, knowing that unimodal interventions had positive effects in previous studies (Wilckens et al., 2021; Nasrallah et al., 2021; Mendez Colmenares et al., 2021). Specifically, we hypothesized that the intervention would attenuate brain atrophy in regions known to be affected by AD and limit the progression of imaging markers of cSVD. In light of recent findings suggesting lower cerebral blood flow (CBF) as a marker of cerebral hypoperfusion early in the course of disease (Weijs et al., 2023; Korte et al., 2020), we also explored the intervention effect

on CBF and the relationship of blood pressure changes and neuroimaging markers. We also explored intervention effects on memory pattern separation and advanced metrics of white matter microstructure fiber density (FD), fiber cross-section (FC) and their product fiber density cross-section (FDC) derived from fixel-based analysis.

2. Methods

2.1. Study design

AgeWell.de is a two-year, multi-centric, cluster-randomized intervention trial, which was conducted at five study sites across Germany (Leipzig, Kiel, Greifswald, Munich, and Halle) (Zülke et al., 2024). The aim of the trial was to test the effects of a multi-component intervention, including lifestyle interventions and optimization of medication, on cognitive function and measures of mental and physical health in primary care patients at increased dementia risk. Details on participant recruitment, baseline characteristics and randomization procedure of the trial can be found in (Röhr et al., 2021). In brief, participants were between 60 and 77 years old and at increased risk of dementia, quantified by the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score of ≥ 9 points. Participants were recruited via their attending GP practice (GPP), with GPPs (clusters) randomized to the multi-domain intervention or control group in a 1:1-ratio. Exclusion criteria were dementia diagnosed or suspected by the GP, medical conditions potentially affecting safe engagement in the intervention (malignant disease, fatal illness, severe clinical depression, symptomatic cardiovascular disease, revascularization within the previous year) as judged by the GP, severe loss of vision, hearing, or communicative ability to speak and read German, severe mobility impairment, and coincident participation in another intervention trial.

Participation in the magnetic resonance imaging (MRI) study was offered to every participant without major MRI exclusion criteria (metal clips, stents, prosthesis or other implants, claustrophobia, tattoos or permanent make-up) in the baseline Leipzig subsample of the AgeWell.de study (N = 274). 110 individuals confirmed interest in participating in the MRI study. Out of these, 56 could be included in the study and performed the Mnemonic Similarity Test (MST), and 54 completed MRI imaging at baseline (two could not be scheduled for MRI). At follow-up, 41 individuals completed the MRI and performed the MST (see Fig. 1). In the intervention group, five individuals dropped out of the MRI study and one discontinued the complete intervention. In the control group, three dropped out of the MRI study and four discontinued the overall study. Overall, the sample size was thus smaller than expected.

2.2. Intervention

The intervention included two conditions over a two-year period: a

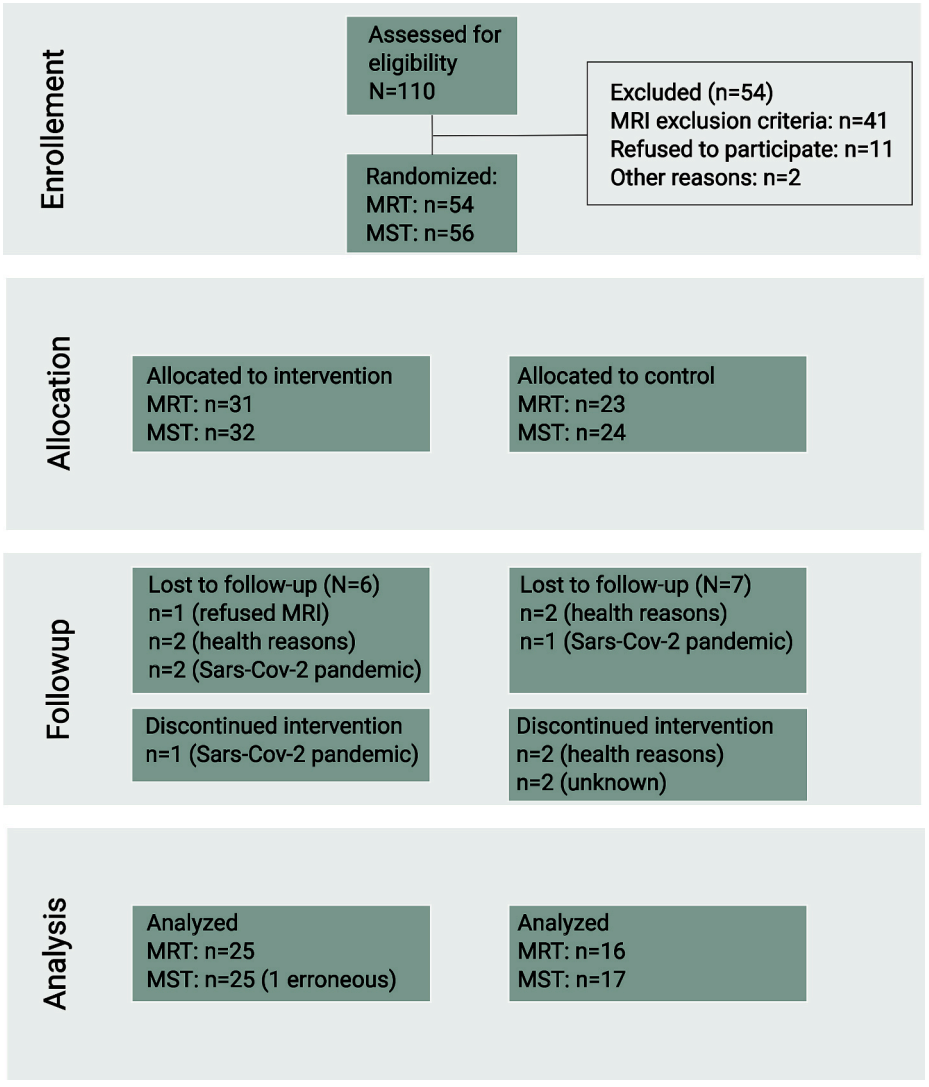

Fig. 1. Flowchart of the AgeWell.de-MRI study. Shown are samples with complete MRI and cognitive assessment (MST) separately.

multi-component intervention including nutritional counseling, physical activity enhancement, cognitive training, monitoring of vascular risk factors, optimization of medication, social activity enhancement, and, if necessary, interventions targeting depression and/or bereavement (intervention group) vs. GP treatment as usual and general health advice on the intervention components (control group).

Briefly, trained study nurses introduced participants to the intervention components during the face-to-face baseline visit. For the physical activity component, exercises for strength and flexibility/balance were demonstrated and individual goals set with participants for aerobic exercise. Cognitive training using the cognitive training program NeuroNation © was scheduled three times per week for at least 15 min. Social activity was targeted by setting individual goals with the participants, and if necessary, assistance in case of prevalent depressive symptoms or bereavement was provided. Medication was optimized by comparing laboratory values, medication information provided by the GP and the participants, and providing a standardized feedback letter to the attending GP on potential medication risks (e.g. anticholinergic drugs). In the nutritional intervention component, study nurses advised participants to follow the guidelines of the German Nutrition Society by e.g. consuming at least five portions of fruit and vegetables a day, eating fish regularly and reducing the consumption of salt and sugar. For more details on the intervention procedure see (Zülke et al., 2024).

2.3. Imaging

2.3.1. Acquisition

At baseline and follow-up, anatomical and functional MRI was acquired on a 3 Tesla Siemens MAGNETOM Skyra scanner with a 32-channel head coil to assess imaging markers of gray matter atrophy and cSVD (Fig. 2). The T1-weighted anatomical scan was acquired using MP2RAGE (Marques et al., 2010) (TI 1 = 700 ms, TI 2 = 2500 ms, TR = 5000 ms, TE = 2.92 ms, FA 1 = 4°, FA 2 = 5°, FOV = 256 × 240, 176 slices, 1x1x1 mm^3, GRAPPA-factor = 3, acquisition time: 8.22 min). Diffusion-weighted imaging and ap/pa-encoded B0-images for distortion correction were acquired with CMRR echo planar imaging (TR 6420 ms, TE 100 ms, flip angle 90°, FOV 220x220 mm^2, resolution: 128x128, 72 slices, 1.7x1.7x1.7 mm^3, GRAPPA-factor = 2, partial-Fourier = 6/8, 60 diffusion directions, b = 1000 s/mm2, multiband-factor 2, prescan-normalize = OFF, acquisition time: 8:14 min + 2*45 s). We acquired a resting-state functional MRI along with ap/pa encoded images for distortion correction using CMRR BOLD echo planar imaging (TR 1400 ms, TE 22 ms, flip angle 69°, 60 slices, 2.3x2.3x2.3 mm^3, multiband-factor 3, prescan-normalize = ON, acquisition time: 9:56 min + 1.05 min).

Pseudo-continuous arterial spin labeling (pCASL) was realized by labeling arterial blood in a plane 65 mm caudal from the nasal root for a duration of 3000 ms using an optimized pCASL radiofrequency pulse train with an in-house implementation (Zülke et al., 2024). Following a post-labeling delay of 1200 ms, 24 slices were acquired with a gradient-echo EPI readout (matrix 64x64, in-plane resolution 3x3 mm, slice thickness 4 mm, slice gap 0.4 mm, partial Fourier factor 6/8, GRAPPA factor 2, TR/TE = 5020/9.2 ms). A total of 30 label/control pairs preceded by the acquisition of two volumes without pCASL preparation were recorded (total acquisition time: 5.30 min).Fluid-attenuated inversion recovery was acquired with 3D turbo spin-echo sequence (TR 5000 ms, TE 395 ms, TI 1800 ms, FOV 230x230 mm^2, resolution: 192x256x256, sagittal orientation, 0.9x0.9x0.9 mm^3, GRAPPA-factor = 2, acquisition time: 5.40 min). All MRI scans were deemed usable based on the absence of brain tumors, acute ischemic, hemorrhagic and traumatic lesions as reviewed by study physicians.

2.3.2. Preprocessing

Imaging analysis was performed in an environment including CBSTOOLS 3.0, MRTRIX 3.0.3, AFNI 23.2.03, ANTS version 2.3.5, FSL version 6.0.1, FreeSurfer version 7.4.1 (initially 6.0.0, see below) and SPM12. Preprocessing was implemented in a publicly available nipype v1.2.0 workflow (https://github.com/fBeyer89/preproc_AgeWell).

2.3.3. T1-weighted imaging

We initially used the functions JistIntensityMp2rageMasking and JistBrainMp2rageSkullStripping implemented in CBSTOOLS to remove the random noise in the T1w images generated by the MP2RAGE acquisition. We then processed the skull-stripped T1 images with the cross-sectional stream in FreeSurfer version 6.0.0p1. As preregistered, all cross-sectional FreeSurfer output underwent visual quality control according to the recommendations by Klapwijk et al. (Klapwijk et al., 2019). Each scan was rated as 1 ('Excellent'), 2 ('Good'), 3 ('Doubtful') or 4 ('Failed'), based on a set of specific criteria (e.g., affection by movement, missing brain areas in reconstruction, inclusion of dura or skull in reconstruction). We had preregistered to remove scans rated 4, but this did apply to none of the acquisitions. During the follow-up QA, we noticed the inclusion of the tentorium of the cerebellum into the GM boundary in both baseline and follow-up FreeSurfer reconstructions. This was resolved by using a different noise removal (MPRAGize instead of CBSTOOLS functions) and including the FLAIR image in FreeSurfer version 7.4.1 to help surface placement with the option (−FLAIRpial). This resolved the issue of bad parahippocampal and entorhinal cortex delineation and generally improved cortical segmentation. We then ran the Freesurfer longitudinal stream to ensure high within-subject reliability of GM structural measures, again using the −FLAIRpial option. We extracted hippocampal volume (HCV) and estimated total intracranial volume (eICV) and entorhinal cortex thickness (ECT) from the Desikan-Killiany parcellation. We averaged HCV and ECT over hemispheres and adjusted HCV for head size according to the following formula: hippocampal $volume_{adjusted}$, i = hippocampal $volume_{raw}$, i − β * (ICV_{raw}, i − ICV_{mean}).

2.3.4. FLAIR processing

We used the SHIVA-WMH detector, a deep-learning-based software

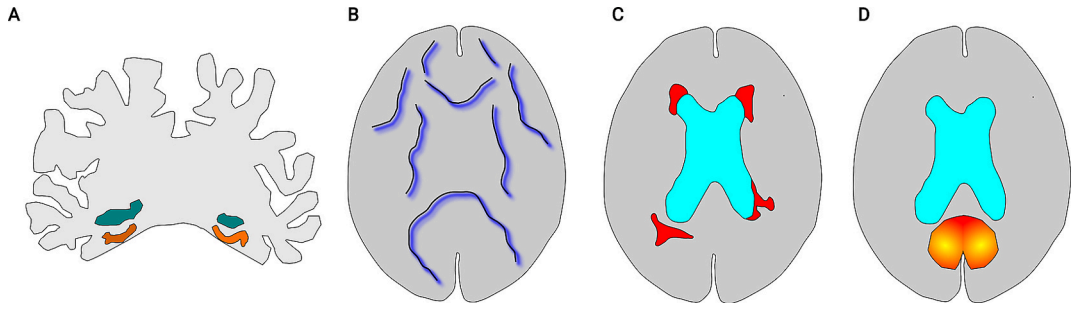

Fig. 2. Schematic depiction of neuroimaging markers of gray matter atrophy and cSVD. A: hippocampal volume (green) and entorhinal cortex thickness (orange). B: Peak width of skeletonized mean diffusivity (PSMD) and free water fraction (FW) in white matter. C: White matter hyperintensity volume (red). D: Cerebral blood flow (CBF) in gray matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tool developed for the automatic detection and segmentation of WMH (Tsuchida et al., 2024). The software was trained with manual segmentations in a wide range of WMH severity and has been shown to reliably quantify WMH volume and track WMH progression over time. T1w and FLAIR input images were reoriented to RAS standard, coregistered to T1w, resampled to 1 mm isotropic and cropped to 160x214x276 using publicly available code https://github.com/atsuch/SHIVApreproc. The intensity inside the brain mask provided by Freesurfer was normalized such that the maximum was set to the 99th percentile of the brain voxel values. WMH probability was then predicted from the preprocessed images using the publicly available deep learning model. WMH volumes were extracted as the sum of all voxels with WMH probability > 0.5 as recommended (Tsuchida et al., 2024) and asinh-transformed for statistical analysis. We visually checked WMH probability maps and did not notice any scans with poor scan quality, registration issues, brain pathologies or other gross abnormalities.

2.3.5. DWI processing

We performed the following steps to preprocess DWI images of baseline and follow up: denoising using MRTrix's dwidenoise, field distortion correction based on ap/pa acquisition using topup, motion correction and outlier replacement using EDDY and tensor fitting with FSL's dtifit. We visually checked FW and MD images and did not notice any scans with poor scan quality, registration issues, brain pathologies or other gross abnormalities.

2.3.6. Free Water (FW)

To extract the average FW fraction, we used the MarkVCID2 FW Biomarker Kit with its publicly available scripts (Maillard et al., 2022). First, in the eddy corrected DWI image, the tissue compartment was modeled by a diffusion tensor characterizing the "tissue" molecules as well as the fractional volume of the FW compartment, resulting in the FW fraction map. Then, each individual's FA map was non-linearly registered to the standard FSL FA template space (FMRIB 1-mm FA template) and the resulting transformation parameters were applied to the FW map. Finally, a white matter mask defined by thresholding the FSL FA template at a value of 0.3 to reduce cerebrospinal fluid partial volume contamination was used to calculate average FW fraction within these WM voxels.

2.3.7. Peak width of skeletonized mean diffusivity (PSMD)

To extract PSMD, we applied the MarkVCID2 PSMD Biomarker Kit and related scripts (Maillard et al., 2022). First, we performed the FSL-TBSS pipeline on the FA images derived from dtifit with the standard FMRIB skeleton as the target. Then, we projected the MD maps onto the skeleton. MD values from the masked skeleton (cerebral hemispheres and to exclude areas with frequent CSF contamination) were used to perform histogram analysis and calculate PSMD as the difference between the 95th and 5th percentile of voxel-based MD values within the MD skeleton.

2.4. Fixel based analysis

Fixel based analysis (FBA) was implemented using MRtrix3 following the recommended pipeline (Raffelt et al., 2017). After DWI preprocessing described above, we performed bias field correction (Tustison et al., 2010) and up-sampling to a voxel size of 1.25 mm with cubic b-spline interpolation (Raffelt et al., 2012). We estimated the fibre orientation distribution (FOD) within each voxel using single-shell three-tissue CSD (Dhollander et al., 2016) with group-averaged response functions for WM, GM and CSF followed by a global intensity normalization to correct for intensity inhomogeneities to enable quantitative group comparisons (Raffelt et al., 2017). We created a study-specific longitudinal WM FOD template on WM FODs from all 38 participants with two MRI sessions following Genc et al. (Genc et al., 2018). For each participant, FOD maps of baseline and follow-up were rigidly transformed to their midway space using FSL midspace and then averaged to generate an unbiased intra-subject template. All 41 intra-subject FOD templates were used to generate a longitudinal population template. Then, FOD maps from individual time points and individuals without a second MRI were registered to this longitudinal population template and segmented to produce a set of discrete fixels. In order to use connectivity-based fixel enhancement (CFE) for fixel statistics, a whole-brain probabilistic tractogram was generated from the population template (Raffelt et al., 2015). First, twenty million streamlines were generated and subsequently filtered to 2 million streamlines using the spherical deconvolution informed filtering of tractograms algorithm (SIFT1) to reduce reconstruction bias and improve biological plausibility. Then we smoothed the resulting fiber density (FD), fiber cross-section (FDC) and fiber density cross-section metrics (FDC) using the resulting fixel-fixel connectivity matrix..

2.5. Arterial spin labeling

The pCASL time series were first realigned with FSL's McFlirt and normalized to MNI space based on the T1w images with a 2-mm isotropic resolution using Coregister and Reslice in SPM12. The normalized time series were finally 3D-Gaussian filtered at 2 mm full width at half maximum. CBF-values were estimated by applying a general linear model (GLM) that contained the control and label conditions with the outputs of the motion correction added as confounds. The ASL contrast (difference between baseline and label signals) obtained from the GLM was scaled by the baseline contrast (control signal). This quantity was then converted to values in units of ml/100 g/min, respectively, by using a two-compartment model (Wang et al., 2002; Mildner et al., 2014). The following model parameters were assumed (Lorenz et al., 2018): brain-blood partition coefficient 0.9 ml/g, gray-matter (GM) density 1.04 g/ml, pCASL inversion efficiency 90 %, arterial blood and tissue relaxation times and of 1664 ms and 1330 ms, and of 50 ms and 55 ms, respectively. The model also included assumed values of the arterial and the tissue transit time of 1000 ms and 1600 ms, respectively. Note that the different slice acquisition times were considered during CBF quantification by a map of post-labeling delays which was transformed to MNI space. In addition to the CBF map, a map of p-values for the difference between control and label signals was obtained from the GLM which served as a measure of the quality of the ASL contrast.

We combined different quality control steps to obtain a mask with reliable CBF values for each individual. First, we created a mask based on the p-maps derived from preprocessing. We only considered voxels with $p < 0.001$ to exclude voxels in which the difference between label and control image was too small to reliably derive CBF values. Further, we performed GM segmentation of the MNI-coregistered T1w image using SPM in MATLAB version 9.3. We thresholded the GM probability maps at 0.9 for each participant to ensure only CBF in GM voxels was included (Van Dalen et al., 2021). We then intersected this map with the thresholded p-map for each individual and time point. We excluded the cerebellum by masking with a publicly available cerebellum atlas (Diedrichsen, 2006) because in some individuals the labeling plane affected this area and resulted in unphysiological CBF levels. Finally, we intersected the masks for all participants with two timepoints in order to ensure that the same voxels were compared across time and extracted the average CBF within these masks.

We visually checked all masked CBF maps for remaining artifacts induced by malpositioning of the labeling plane, inefficient labeling and other artifacts. In two individuals, the labeling plane was positioned over the occipital and temporal lobe in one of the two timepoints which led to the exclusion of these individuals from the analyses.

2.6. Cognitive function

In the main trial, cognitive functions were assessed at baseline and at follow-up using a neuropsychological test battery, covering six cognitive domains: attention, executive function, learning/memory, language, perceptual-motor abilities, and social cognition (Zülke et al., 2024). Here, we only investigated the MST which was additionally performed by all participants of the MRI subgroup. This computerized test targets the pattern separation performance, a hippocampus-dependent function (Stark et al., 2019). We presented participants with 192 color photographs of objects (publicly available here: http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/). In the first phase of the task, participants were asked to indicate whether the presented objects belonged inside or outside via a button press (128 items total, 2 s object presentation, 0.5 s ISI). In the second phase, 64 of the objects were presented again, along with 64 new and 64 similar images (lures). Participants were instructed to rate the images as "old", "similar" or "new" via a button-press. The images appeared for 2 s and then the next item was shown with 0.5 s ISI. As in previous work by the original developers (Stark et al., 2013), we calculated the lure discrimination index (LDI) as the difference between the rate of lure items identified as "similar" minus new items identified as "similar". Similarly, an indicator of recognition memory (REC) was assessed as the difference between the rate of correctly recognized old images minus the rate of new items identified as old. We preregistered to exclude participants who missed more than 44 items in any of the categories (Stark et al., 2015), or if one of the options was never chosen (indicating that the instructions were not understood or could not be followed) [https://osf.io/ba9ex]. In the baseline assessment, the data of 9 individuals (CG: 6, IG: 3) was not correctly recorded, and in the follow-up, one participant did not respond with "similar" to any of the items. This led to a final sample of 47 in the baseline and 41 in the follow-up for the MST analysis.

2.7. Other assessments

Demographic information (age, sex, education) and the Montreal Cognitive Assessment Score (MoCA) were assessed at the baseline visit of the main trial. CAIDE scores were determined by the GP before inclusion. Education was assessed using the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN)-scale, and participants were grouped into two groups (primary/secondary and tertiary education) in order to ensure comparable group sizes (Brauns et al., 2025).

Over the course of the intervention, study nurses assessed the adherence to the intervention. At seven occasions, they rated to what extent participants had been able to reach their goals in the intervention domains nutrition, physical activity, cognitive and physical activity (response options: not at all (0) – absolutely (4)). Following (Zülke et al., 2024), we created a total adherence score by summing up all domains and excluding individuals with a total score < 12 in sensitivity analyses. During the baseline and follow-up assessments, systolic and diastolic blood pressure (SBP/DBP) were measured by study nurses twice in the seated position and averaged for analysis. Body mass index (BMI) was also measured at the baseline assessment.

2.8. Statistical analyses

We preregistered the interventional analyses on the OSF (https://osf.io/687du) and the analyses code is on github (https://github.com/fBeyer89/preproc_AgeWell/).

2.8.1. Preregistered analyses

We tested the preregistered hypotheses on imaging outcomes using linear mixed models (LMM) with lme4 in R version 4.2.2.

More specifically, we determined the significance of the intervention effect by comparing a full model (including the interaction of group and timepoint) to a null model (including only group and timepoint). The standard significance threshold of 5 % was used for rejection of the null hypothesis. In addition to the prespecified analyses, we calculated two additional models for main imaging outcomes: first, we used time between measurements as predictor instead of a categorical predictor of measurement time point because the range of time elapsed between MRI scans was larger than initially expected. Secondly, we followed the approach in (Zülke et al., 2024) and estimated mean group differences between IG and CG at 24-month follow-up in linear models accounting for baseline differences in age, sex, education and baseline value of the respective outcome. Baseline differences in age and education were present and adjusting for such predictive covariates has been shown to increase power in randomized trials (Kahan et al., 2014).

2.8.2. Exploratory analyses

In exploratory analyses, we tested whether the intervention had an effect on LDI and REC performance derived from the MST using a LMM as above. Further, we assessed the intervention effect on mean gray matter CBF derived from ASL. Here, we used the LMM model and the linear model adjusting for baseline characteristics of age, sex and education.

Further, we explored the relationship between blood pressure and imaging markers over the intervention period as hypertension has been shown to be particularly improved by the intervention (Zülke et al., 2024).

First, we tested whether the intervention affected SBP and DBP in the MRI sample. Then, we used LMM including baseline and change in SBP/DBP to assess their associations with imaging markers. Significance testing was performed by comparing full models including baseline/change terms to null models. We also used a linear model adjusting for baseline differences to assess the effect of blood pressure change.

Finally, we checked whether intervention adherence could possibly modify the intervention effect as demonstrated in Zülke et al. (Zülke et al., 2024) by checking the number of non-adherent individuals based on the cut-off defined in Zülke et al. (Zülke et al., 2024) and by associating adherence to nutrition and social activity components of the intervention with brain changes in the intervention group in linear models. We tested assumptions of linear models as preregistered using the check_model function in R.

2.8.3. Fixel-based analyses

We analyzed the fixel-wise metrics FD, FC and FDC with connectivity-based fixel enhancement method (CFE) in MRTRIX 3.0 (Raffelt et al., 2015). In order to use a longitudinal design matrix for statistical analysis, we subtracted the baseline from the follow-up smoothed metric images for FD, FC and FDC. We then tested a group difference between intervention and control group in the difference images, adjusting for age at baseline and sex like in the models described above, using 5000 random permutation of group assignment. We defined fixels as significant if their family-wise error (FWE)-corrected p value was below 0.05].

3. Results

3.1. Sample description

The intervention group ($N = 24$) was slightly older, more educated and had higher SBP than the control group ($N = 32$). There were no significant differences in the sex distribution, BMI, CAIDE and MoCA scores, imaging outcomes at baseline and time between MRI scans (see Table 1).

3.2. Effects of the intervention on GM imaging markers

There were no significant effects of the intervention on hippocampus volume change (ANOVA model comparison Chi-square = 0.248, p-value = 0.62). The same was found for the linear model or when using

Table 1
Baseline characteristics of the AgeWell.de-MRI study.

	Control			Intervention			Group Difference
	N	Mean	SD	N	Mean	SD	
Age (y)	32	67.6	3.95	24	70.4	4.14	F = 6.43*
Sex (females)	32	17 (53.1 %)		24	9 (37.5 %)		X2 = 0.79
Education (tertiary education)	32	12 (37.5 %)		24	16 (66.7 %)		X2 = 3.57
MoCA score	32	25.4	2.31	24	25.6	2.7	F = 0.078
CAIDE score	32	9.97	1.09	22	9.95	1.09	F = 0.002
BMI (kg/m^2)	32	31.9	4.62	24	30.9	3.43	F = 0.83
SBP (mmHg)	31	139	20.3	24	152	19.9	F = 5.45*
Time between MRI (months)	31	28.3	2.87	23	28.3	2.02	F = 0.003
mean EC thickness (mm)	31	2.99	0.19	23	2.97	0.199	F = 0.19
Hippocampus (mm^3)	31	3391	314	23	3287	297	F = 1.5
Free Water fraction	31	0.214	0.0299	23	0.214	0.0277	F = 0
PSMD (mm^2/s)	31	3.5*10–4	0.6*10–4	23	3.71*10–4	0.64*10–4	F = 1.62
WMH volume (cm^3)	31	4672	7397	23	4494	5987	F = 0.009

BMI: body mass index, MoCA: Montreal Cognitive Assessment, CAIDE: Cardiovascular Risk Factors, Aging and Dementia, EC: entorhinal cortex, PSMD: peak width of skeletonized mean diffusivity, SBP: systolic blood pressure, WMH: white matter hyperintensity, F: test statistic of F-test, X^2: test statistic of X^2 test. *: $p < 0.05$.

time between MRI as continuous predictor. Across groups, HC volume declined by β(SE) = -86.39(10.45) mm^3 between assessments (see Fig. 3), which corresponds to an annual atrophy rate of 1.1 (0.9)%.

In the preregistered analysis, EC thinning was more pronounced in the intervention group (ANOVA model comparison Chi-square = 6.47, p-value = 0.01). Specifically, while the ECT in the control group declined by β(SE) = -0.13 (0.02) mm on average between baseline and follow-up, the decline in the intervention group declined by β(SE) = -0.21(0.03). This result was no longer significant when adjusting for baseline covariates using the linear model approach (mean group difference(SE) IG vs CG: −0.06(0.036), p = 0.14) or when using time between MRI as continuous predictor (ANOVA model comparison; ECT: Chi-square = 1.01, p-value = 0.31).

3.3. *Effects of the intervention on cSVD imaging markers*

Regarding cSVD markers, we found a more pronounced increase of FW in the intervention compared to the control group (ANOVA model

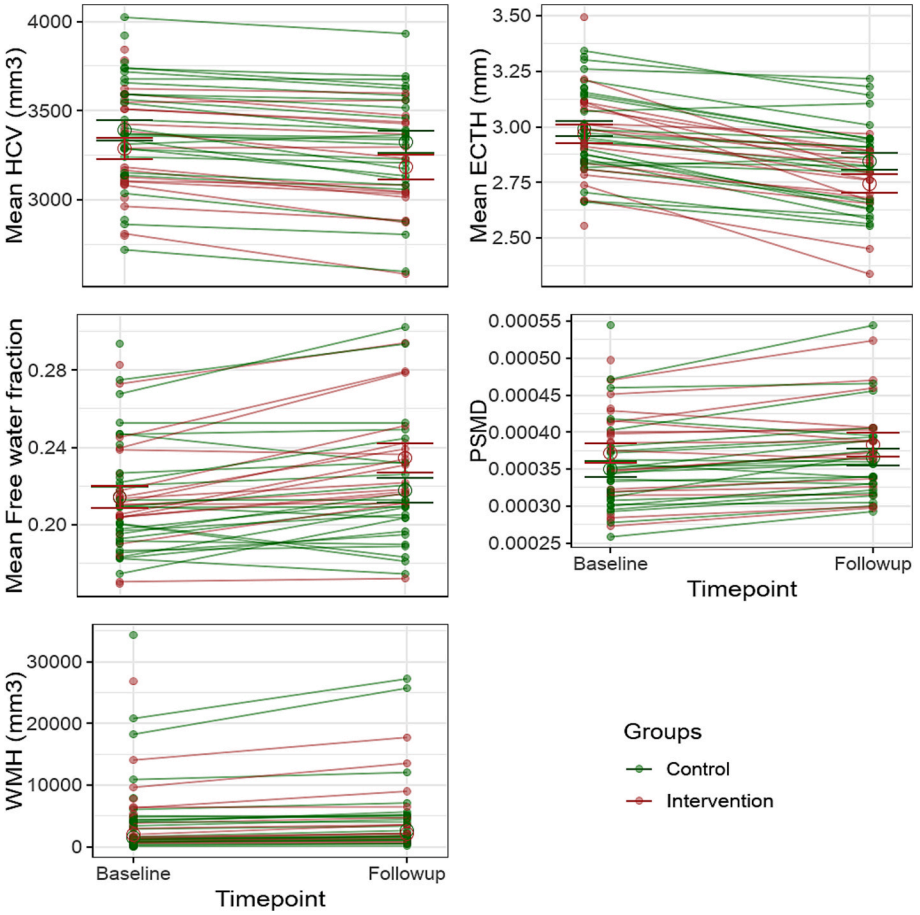

Fig. 3. Effect of the intervention on neuroimaging markers. Shown are individual data of control (green) and intervention (red) participants as well as the average per group and time point with 95% CI. HCV: hippocampus volume, ECTH: entorhinal cortex thickness, PSMD: peak width of skeletonized mean diffusivity, WMH: white matter hyperintensity volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

comparison Chi-square = 7.65, p-value = 0.01). While FW in the control group increased by β(SE) = 0.0066(0.0028) on average, the increase in the intervention group was more pronounced (β(SE) = 0.019(0.0044)). When adjusting for baseline covariates, this result was no longer significant (mean group difference(SE) IG vs CG: 0.01(0.005), p = 0.07). Similarly, when using time between MRI as continuous predictor, there was no significant interaction of time and intervention group (Chi-square = 2.1, p-value = 0.15)).

PSMD increased similarly across both groups (β(SE) = 1.88 10^{-5} (4.4 10^{-6}) mm^2/s) with no intervention effect (ANOVA model comparison Chi-square = 1.19, p-value = 0.28). The same was found in models adjusting for time between MRI and baseline covariates.

We observed similar WMH progression in both groups (β(SE) = 0.24 (0.04) asinh(mm^3)) with no intervention effect (ANOVA model comparison Chi-square = 0.39, p-value = 0.53). Similarly, no differences in WMH progression was present in models adjusting for time between MRI and baseline covariates.

3.4. Exploratory analyses

3.4.1. Fixel-based metrics

There was no fixel-wise significant difference in the change from baseline to follow-up FD, FC and FDC between the intervention and control group (pFWE > 0.05).

3.5. MST

We did not find an intervention effect on pattern separation performance LDI (ANOVA model comparison Chi-square = 0.62, p-value = 0.43) in the LMM and when adjusting for baseline covariates in a linear model (mean group difference(SE) IG vs CG: −0.08(0.06), p = 0.2). Similarly, even though there was a significant effect of the intervention for recognition performance REC (ANOVA model comparison Chi-square = 5.2, p-value = 0.02) in the LMM, this effect disappeared when adjusting for baseline covariates (mean group difference(SE) IG vs CG: 0.04(0.04), p = 0.28).

3.6. Intervention effect on CBF and the relationship with blood pressure

In an exploratory analysis of mean CBF in cortical and subcortical GM, we found a significant intervention effect (ANOVA model comparison Chi-square = 5.31, p-value = 0.02) where mean CBF increased in the intervention group (β(SE) = 6.19(2.69)) while it slightly declined in the control group (β(SE) = -2.78(1.68), Fig. 4). When adjusting for baseline covariates, this result was no longer statistically significant (mean group difference(SE) IG vs CG: 4.96(2.55), p = 0.06).

The intervention group had higher SBP at baseline compared to the control group (β(SE): 13.4(5.33), p = 0.05). There was no difference in DBP (β(SE): 0.5(3.32), p = 0.96). After the intervention, SBP declined more in the intervention group (β(SE): −10.22(5.92). but this was not statistically significant (ANOVA model comparison Chi-square = 3.02, p-value = 0.08).

In the intervention group, greater decline in SBP was associated with greater increase in mean CBF (β(SE) = -0.23(0.06), p = 0.0014, Fig. 4). This was also found in the baseline covariate adjusted linear model approach where one mmHG of SBP decrease in the intervention group was associated with 0.29 ml/100 mg/min increase in CBF (N = 14 with pre-post scan, p = 0.03). There was no significant effect of change in DBP (β(SE) = -0.18(0.17), p = 0.27).

When exploring the association of SBP with other imaging markers in the intervention group, we found that decreases in SBP over the intervention period were associated with decreases in HC volume according to LMM (N = 23, β(SE) = 3.15(0.94), p = 0.0026. This effect was not found using the baseline-adjusted linear model approach (N = 14 with pre-post scan, β(SE): 0.14(1.16), p = 0.91). No significant associations were present for the other imaging marker.

3.7. Intervention adherence & brain changes

Out of 17 individuals from the intervention group who completed the second MRI, only 1 participant was non-adherent to the intervention based on the cut-off of 12. Excluding this participant did not change the above mentioned results.

Better adherence to intervention components nutrition and social activity did not relate to brain changes within the intervention group (N = 17).

4. Discussion

We investigated the effects of the AgeWell.de multidomain intervention on the progression of MRI markers associated with hippocampal-limbic atrophy and cSVD in a subgroup of participants at a single site. Previous findings from the AgeWell.de intervention (Zülke et al., 2024) demonstrated no significant effect on global cognitive performance. Our substudy could not provide conclusive evidence on the effects of the intervention on neurodegeneration and cSVD markers. Both the control and intervention groups exhibited comparable progression in hippocampal volume decline, EC thinning, and increases in FW and PSMD, when taking into account baseline differences in age and education. Moreover, no significant impact on pattern separation or recognition performance in the MST or fixel-based white matter microstructure was detected. However, note that sample size was lower than expected, yielding the study potentially underpowered to detect significant effects. In addition, preliminary evidence suggested a potential beneficial effect on CBF, possibly mediated by reductions in SBP during the intervention.

4.1. MRI outcomes

The observed progression in imaging biomarkers is in line with

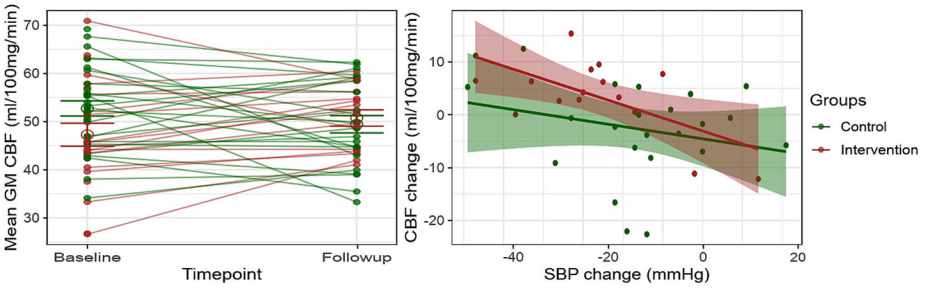

Fig. 4. Left: Mean GM CBF at baseline and follow-up. Shown are individual data of control (green) and intervention (red) participants as well as the average per group and time point with 95% CI. Right: Change in mean GM CBF in relation to change in SBP over the study period in the control (green) and intervention (red) group. CBF: cerebral blood flow, GM: gray matter. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

findings in populations at risk for cognitive decline (Maillard et al., 2019; Gullett et al., 2020; Jack et al., 2000; Devanand et al., 2007; Prins and Scheltens, 2015; Deary et al., 2019). The hippocampal atrophy rate in our study was 1.1 (0.9)%, which is comparable to previously reported 1.12 % in old age (Fraser et al., 2015). However, no effect of the intervention on atrophy or cSVD markers was found, similar to secondary analyses of other multidomain intervention trials (Stephen et al., 2019; Andrieu et al., 2017) or interventions targeting specific risk factors such as hypertension (Nasrallah et al., 2021) and diet (Barnes et al., 2023). WMH have been shown to be modulated by intensive antihypertensive treatment in (Nasrallah et al., 2019) but this study was performed entirely in hypertensive patients with an intervention duration of 4 years. This might imply that in the current study, the intervention was not efficient to induce improvements, or that the intervention duration was not long enough to manifest in significant differences, in the selected neuroimaging markers.

Preliminary evidence suggested a potential beneficial effect of the intervention on CBF. Even though the effect was not statistically significant when adjusting for baseline characteristics, it was robustly associated with reductions in SBP, making the association with the intervention plausible. The intervention has been shown to specifically improve SBP and hypertension, making it 1.61 times more likely to not be hypertensive at follow-up (Zülke et al., 2024).

Reduced CBF is associated with the development and progression of cSVD, as impaired small vessels diminish blood supply to critical brain regions (Yu et al., 2020). Transient reductions in CBF can signal early dysfunction in cerebral circulation, potentially preceding permanent vascular damage. In cSVD, reduced CBF serves as a sensitive marker of transient flow alterations, making it a reliable indicator of early-stage vessel dysfunction and impending ischemic injury (Jennings et al., 2013).

We also found that the increases in CBF might have been mediated by reductions in SBP induced by the intervention. This is supported by previous studies, such as the SPRINT MIND sub-trial, which linked SBP reduction to improved CBF (Dolui et al., 2022). Thus it is possible that the intervention led to subtle functional changes, without translating into structural changes such as microstructural integrity and WMH volume which might be observed only after longer intervention and follow-up periods. Yet, biases in the ASL data, such as increased variance at baseline and reduced labeling efficiency in the elderly sample, could have affected the reliability of the CBF measurements.

4.2. Cognitive outcomes

Our findings did not show an effect on pattern separation performance, a function highly dependent on hippocampal integrity and susceptible to the beneficial effects of interventions (Brickman et al., 2014). This outcome is consistent with the main trial results, where no positive effect on global cognitive performance as well as domain-specific cognitive function was observed, except for a beneficial intervention effect on social cognition (Zülke et al., 2024). Participants in the AgeWell.de study had, on average, higher dementia risk scores compared to those in the FINGER study, as we exclusively enrolled individuals with a CAIDE score of $\geq$ 9 points (compared to $\geq$ 6 points in FINGER). In combination with a limited duration of the trial, this may have led to insufficient impact of the intervention in individuals with higher risk of cognitive decline (Kivipelto et al., 2006; Exalto et al., 2014).

4.3. Intervention adherence

While post-hoc analyses in the main Agewell.de study suggested that higher adherence to nutritional and social activity components was linked to cognitive improvements, we did not observe similar trends in the MRI sub-study. This may be attributed to the low statistical power due to sample size limitations. Nevertheless, evidence from FINGER and HATICE trials indicates that more intensive interventions and higher adherence rates could potentially enhance the effects on MRI markers of neurodegeneration and cSVD (Ngandu et al., 2015; Richard et al., 2019). Besides, the difference in intervention intensity between FINGER and AgeWell.de, where the latter relied on self-administered activities with remote support, may have contributed to the non-significant findings.

5. Strengths and limitations

This study's strength is the use of state-of-the-art and advanced imaging techniques to assess neuroimaging markers of atrophy and cSVD. We employed an ASL protocol which has been shown to be more efficient than the standard implementation to enhance the precision of CBF measurements. The research was conducted on a well-characterized sample, ensuring the robustness and reliability of the findings. Additionally, the study was guided by a preregistration and contained detailed statistical analyses, which further strengthens the validity of the results.

The trial faced several limitations that should be acknowledged. Firstly, the small sample size was a significant constraint, largely due to strict MRI exclusion criteria. As detailed in the study's flowchart, approximately 50 % of the initial participants were excluded due to the presence of stents and other MRI exclusion factors prevalent in an older population with enhanced proportion of vascular risk factors. The study was not powered to detect specific effects as it was a sub-study of the main AgeWell.de trial and negative results may therefore be due to lack of power. Besides, there were challenges in the implementation of the ASL imaging sequence, such as the label plane positioning, which may have affected the consistency and quality of the neuroimaging data collected. The COVID-19 pandemic posed significant challenges not only to the implementation of the intervention but also to the inclusion for the follow-up MRI session as often participants did not want to take the risk of an additional appointment.

6. Conclusions

Our study did not demonstrate conclusive evidence on the effects of a multimodal intervention on neuroimaging markers of neurodegeneration and small vessel disease in a population at risk for cognitive decline. Despite rigorous methodology and advanced imaging techniques, we could not observe conclusive evidence that the intervention significantly impacted hippocampal volume, entorhinal cortex thickness, or markers of white matter integrity, which may be due to a lack of statistical power. While exploratory analyses suggested a potential improvement in cerebral blood flow associated with reductions in systolic blood pressure, these findings were not statistically significant after adjusting for baseline covariates. The inconclusive results may be attributed to several factors, such as small sample size, the potential dilution of intervention effects due to the control group's high standard of care and due to the time gap between the end of the intervention and the second assessment. These results underscore the complexity of intervening in populations already at high risk for cognitive decline and highlight the need for future studies with larger sample sizes, longer intervention periods, and possibly more intensive intervention protocols to fully evaluate the potential of multimodal approaches in preventing dementia.

Authors' contributions

TF, JG, DC, BW, HHK, HK, WH, JT and SRH conceptualized and designed the AgeWell.de trial and AZ prepared the demographic, anthropometric and adherence data. FB and AVW conceptualized the design of the MRI study and collected the MRI data. FB and LK performed analysis of the imaging, MST and blood pressure data and conducted the statistical analysis. FB and LK drafted the manuscript. TM analyzed the ASL data and helped with the interpretation. AVW helped with the interpretation of the data and edited the manuscript. All

authors read, edited and approved the final manuscript.

CRediT authorship contribution statement

Frauke Beyer: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lukas Kleine:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Andrea Zülke:** Writing – review & editing, Resources, Project administration, Investigation, Conceptualization. **Melanie Luppa:** Investigation. **Toralf Mildner:** Writing – review & editing, Software, Methodology. **Jochen Gensichen:** Resources, Funding acquisition. **Thomas Frese:** Resources, Funding acquisition. **David Czock:** Writing – review & editing, Resources, Funding acquisition. **Birgitt Wiese:** Resources, Funding acquisition. **Hans-Helmut König:** Resources, Funding acquisition. **Hanna Kaduszkiewicz:** Resources, Funding acquisition. **Wolfgang Hoffmann:** Resources, Funding acquisition. **Jochen René Thyrian:** Writing – review & editing, Resources, Funding acquisition. **Arno Villringer:** Supervision, Resources, Funding acquisition. **Steffi Riedel-Heller:** Supervision, Resources, Funding acquisition, Conceptualization. **A.Veronica Witte:** Writing – review & editing, Supervision, Resources, Methodology.

Ethics approval

The main trial AgeWell.de was approved by the responsible ethics boards of all participating study sites. The MRI sub-study was approved as an amendment to the main study by the Ethical Committee at the Medical Faculty of Leipzig University (369/17-ek). Written informed consent for the main study was obtained at the GP practice. If they expressed interest to take part in the MRI study, a MRI briefing was scheduled and if they could be included, participants signed the informed consent for the MRI study.

Consent for publication

Not applicable

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

All code for preprocessing and statistical analysis is in https://github.com/fBeyer89/preproc_AgeWell/. The dataset analyzed during the current study is not publicly available, and is available upon request.

References

World Health Organization, 2017. Global action plan on the public health response to dementia 2017–2025. World Health Organization, Geneva.

Knopman, D.S., Amieva, H., Petersen, R.C., Chételat, G., Holtzman, D.M., Hyman, B.T., et al., 2021. Alzheimer Disease. Nat Rev Dis Primers. 7, 1–21.

Gorelick, P.B., Scuteri, A., Black, S.E., DeCarli, C., Greenberg, S.M., Iadecola, C., et al., 2011. Vascular contributions to cognitive impairment and dementia. Stroke. 42, 2672–2713.

Karanth, S., Nelson, P.T., Katsumata, Y., Kryscio, R.J., Schmitt, F.A., Fardo, D.W., et al., 2020. Prevalence and clinical phenotype of quadruple misfolded proteins in older adults. JAMA Neurology. 77, 1299–1307.

Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., et al., 2018. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia. 14, 535–562.

Sargurupremraj, M., Suzuki, H., Jian, X., Sarnowski, C., Evans, T.E., Bis, J.C., et al., 2020. Cerebral small vessel disease genomics and its implications across the lifespan. Nat Commun. 11, 6285.

Livingston, G., Huntley, J., Liu, K.Y., Costafreda, S.G., Selbæk, G., Alladi, S., et al., 2024. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. The Lancet 404, 572–628.

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., et al., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet. 385, 2255–2263.

Zülke, A.E., Pabst, A., Luppa, M., Oey, A., Weise, S., Fankhänel, T., et al., 2024. Effects of a multidomain intervention against cognitive decline on dementia risk profiles — Results from the AgeWell.de trial. Alzheimer's & Dementia. 20, 5684–5694.

Jacka, F.N., Cherbuin, N., Anstey, K.J., Sachdev, P., Butterworth, P., 2015. Western diet is associated with a smaller hippocampus: a longitudinal investigation. BMC Medicine. 13, 215.

Beauchet, O., Celle, S., Roche, F., Bartha, R., Montero-Odasso, M., Allali, G., et al., 2013. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. Journal of Hypertension. 31.

Brundel, M., Kappelle, L.J., Biessels, G.J., 2014. Brain imaging in type 2 diabetes. European Neuropsychopharmacology. 24, 1967–1981.

Lammer, L., Beyer, F., Luppa, M., Sanders, C., Baber, R., Engel, C., et al., 2023. Impact of social isolation on grey matter structure and cognitive functions: A population-based longitudinal neuroimaging study. eLife. 12, e83660.

Berron, D., Vogel, J.W., Insel, P.S., Pereira, J.B., Xie, L., Wisse, L.E.M., et al., 2021. Early stages of tau pathology and its associations with functional connectivity, atrophy and memory. Brain. 144, 2771–2783.

Walhovd, K.B., Westerhausen, R., de Lange, A.-M.-G., Bråthen, A.C.S., Grydeland, H., Engvig, A., et al., 2016. Premises of plasticity — And the loneliness of the medial temporal lobe. NeuroImage. 131, 48–54.

Wilckens, K.A., Stillman, C.M., Waiwood, A.M., Kang, C., Leckie, R.L., Peven, J.C., et al., 2021. Exercise interventions preserve hippocampal volume: A meta-analysis. Hippocampus. 31, 335–347.

David, S., Costa, A.S., Hohenfeld, C., Romanzetti, S., Mirzazade, S., Pahl, J., et al., 2025. Modulating effects of fitness and physical activity on Alzheimer's disease: Implications from a six-month randomized controlled sports intervention. J Alzheimers Dis. 103, 552–569.

Barnes, L.L., Dhana, K., Liu, X., Carey, V.J., Ventrelle, J., Johnson, K., et al., 2023. Trial of the MIND diet for prevention of cognitive decline in older persons. N Engl J Med. 389, 602–611.

Kaplan, A., Zelicha, H., Yaskolka Meir, A., Rinott, E., Tsaban, G., Levakov, G., et al., 2022. The effect of a high-polyphenol Mediterranean diet (Green-MED) combined with physical activity on age-related brain atrophy: the dietary intervention randomized controlled trial polyphenols unprocessed study (DIRECT PLUS). Am J Clin Nutr. 115, 1270–1281.

Köbe, T., Witte, A.V., Schnelle, A., Tesky, V.A., Pantel, J., Schuchardt, J.-P., et al., 2017. Impact of resveratrol on glucose control, hippocampal structure and connectivity, and memory performance in patients with mild cognitive impairment. Front Neurosci. 11.

Witte, A.V., Kerti, L., Hermannstädter, H.M., Fiebach, J.B., Schreiber, S.J., Schuchardt, J. P., et al., 2014. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cerebral Cortex. 24, 3059–3068.

Prehn, K., Jumpertz von Schwartzenberg, R., Mai, K., Zeitz, U., Witte, A.V., Hampel, D., et al., 2017. caloric restriction in older adults-differential effects of weight loss and reduced weight on brain structure and function. Cereb Cortex. 27, 1765–1778.

Stephen, R., Liu, Y., Ngandu, T., Antikainen, R., Hulkkonen, J., Koikkalainen, J., et al., 2019. Brain volumes and cortical thickness on MRI in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). Alz Res Therapy. 11, 53.

Moon, S.Y., Kim, S., Choi, S.H., Hong, C.H., Park, Y.K., Na, H.R., et al., 2022. Impact of multidomain lifestyle intervention on cerebral cortical thickness and serum brain-derived neurotrophic factor: the SUPERBRAIN exploratory sub-study. Neurotherapeutics. 19, 1514–1525.

Nasrallah, I.M., Pajewski, N.M., Auchus, A.P., Chelune, G., Cheung, A.K., Cleveland, M. L., et al., 2019. Association of intensive vs standard blood pressure control with cerebral white matter lesions. JAMA. 322, 524–534.

Espeland, M.A., Luchsinger, J.A., Neiberg, R.H., Carmichael, O., Laurienti, P.J., Pi-Sunyer, X., et al., 2018. Long term effect of intensive lifestyle intervention on cerebral blood flow. Journal of the American Geriatrics Society. 66, 120–126.

Taylor-Bateman, V., Gill, D., Georgakis, M.K., Malik, R., Munroe, P., Traylor, M., et al., 2022. Cardiovascular risk factors and MRI markers of cerebral small vessel disease. Neurology. 98, e343–e351.
Stephen, R., Solomon, A., Ngandu, T., Levälahti, E., Rinne, J.O., Kemppainen, N., et al., 2020. White matter changes on diffusion tensor imaging in the FINGER randomized controlled trial. Journal of Alzheimer's Disease. 78, 75–86.
Medawar, E., Thieleking, R., Manuilova, I., Paerisch, M., Villringer, A., Witte, A.V., et al., 2021. Estimating the effect of a scanner upgrade on measures of grey matter structure for longitudinal designs. PLOS ONE. 16, e0239021.
Duering, M., Finsterwalder, S., Baykara, E., Tuladhar, A.M., Gesierich, B., Konieczny, M. J., et al., 2018. Free water determines diffusion alterations and clinical status in cerebral small vessel disease. Alzheimers Dement. 14, 764–774.
Maillard, P., Fletcher, E., Singh, B., Martinez, O., Johnson, D.K., Olichney, J.M., et al., 2019. Cerebral white matter free water. Neurology. 92, e2221–e2231.
Rosenberg, A., Mangialasche, F., Ngandu, T., Solomon, A., Kivipelto, M., 2020. Multidomain interventions to prevent cognitive impairment, Alzheimer's disease, and dementia: from FINGER to world-wide FINGERS. The Journal of Prevention of Alzheimer's Disease. 7, 29–36.
Zülke, A.E., Pabst, A., Luppa, M., Roehr, S., Seidling, H., Oey, A., et al., 2024. A multidomain intervention against cognitive decline in an at-risk-population in Germany: Results from the cluster-randomized AgeWell.de trial. Alzheimer's & Dementia. 20, 615–628.
Nasrallah, I.M., Gaussoin, S.A., Pomponio, R., Dolui, S., Erus, G., Wright, C.B., et al., 2021. Association of intensive vs standard blood pressure control with magnetic resonance imaging biomarkers of Alzheimer disease: secondary analysis of the SPRINT MIND randomized trial. JAMA Neurology. 78, 568–577.
Mendez Colmenares, A., Voss, M.W., Fanning, J., Salerno, E.A., Gothe, N.P., Thomas, M. L., et al., 2021. White matter plasticity in healthy older adults: The effects of aerobic exercise. Neuroimage. 239, 118305.
Weijs, R.W.J., Shkredova, D.A., Brekelmans, A.C.M., Thijssen, D.H.J., Claassen, J.A.H.R., 2023. Longitudinal changes in cerebral blood flow and their relation with cognitive decline in patients with dementia: Current knowledge and future directions. Alzheimer's & Dementia. 19, 532–548.
Korte, N., Nortley, R., Attwell, D., 2020. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. Acta Neuropathol. 140, 793–810.
Röhr, S., Zülke, A., Luppa, M., Brettschneider, C., Weißenborn, M., Kühne, F., et al., 2021. Recruitment and baseline characteristics of participants in the agewell.de study—a pragmatic cluster-randomized controlled lifestyle trial against cognitive decline. International Journal of Environmental Research and Public Health. 18, 408.
Marques, J.P., Kober, T., Krueger, G., Van Der Zwaag, W., Van De Moortele, P.-F., Gruetter, R., 2010. MP2RAGE, a self bias-field corrected sequence for improved segmentation and T1-mapping at high field. NeuroImage. 49, 1271–1281.
Klapwijk, E.T., Van De Kamp, F., Van Der Meulen, M., Peters, S., Wierenga, L.M., 2019. Qoala-T: A supervised-learning tool for quality control of FreeSurfer segmented MRI data. NeuroImage. 189, 116–129.
Tsuchida, A., Boutinaud, P., Verrecchia, V., Tzourio, C., Debette, S., Joliot, M., 2024. Early detection of white matter hyperintensities using SHIVA-WMH detector. Human Brain Mapping. 45, e26548.
Maillard, P., Lu, H., Arfanakis, K., Gold, B.T., Bauer, C.E., Zachariou, V., et al., 2022. Instrumental validation of free water, peak-width of skeletonized mean diffusivity, and white matter hyperintensities: MarkVCID neuroimaging kits. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 14, e12261.
Raffelt, D.A., Tournier, J.-D., Smith, R.E., Vaughan, D.N., Jackson, G., Ridgway, G.R., et al., 2017. Investigating white matter fibre density and morphology using fixel-based analysis. Neuroimage. 144 (Pt A), 58–73.
Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., et al., 2010. N4ITK: Improved N3 Bias Correction. IEEE Trans Med Imaging. 29, 1310–1320.
Raffelt, D., Tournier, J.-D., Rose, S., Ridgway, G.R., Henderson, R., Crozier, S., et al., 2012. Apparent Fibre Density: a novel measure for the analysis of diffusion-weighted magnetic resonance images. Neuroimage. 59, 3976–3994.
Dhollander T, Raffelt D, Connelly A. Unsupervised 3-tissue response function estimation from single-shell or multi-shell diffusion MR data without a co-registered T1 image. 2016.
Genc, S., Smith, R.E., Malpas, C.B., Anderson, V., Nicholson, J.M., Efron, D., et al., 2018. Development of white matter fibre density and morphology over childhood: A longitudinal fixel-based analysis. NeuroImage. 183, 666–676.
Raffelt, D.A., Smith, R.E., Ridgway, G.R., Tournier, J.-D., Vaughan, D.N., Rose, S., et al., 2015. Connectivity-based fixel enhancement: Whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres. NeuroImage. 117, 40–55.
Wang, J., Alsop, D.C., Li, L., Listerud, J., Gonzalez-At, J.B., Schnall, M.D., et al., 2002. Comparison of quantitative perfusion imaging using arterial spin labeling at 1.5 and 4.0 Tesla. Magnetic Resonance in Medicine. 48, 242–254.
Mildner, T., Müller, K., Hetzer, S., Trampel, R., Driesel, W., Möller, H.E., 2014. Mapping of arterial transit time by intravascular signal selection. NMR in Biomedicine. 27, 594–609.
Lorenz, K., Mildner, T., Schlumm, T., Möller, H.E., 2018. Characterization of pseudo-continuous arterial spin labeling: Simulations and experimental validation. Magnetic Resonance in Med. 79, 1638–1649.
Van Dalen, J.W., Mutsaerts, H.J., Petr, J., Caan, M.W., Van Charante, E.P.M., MacIntosh, B.J., et al., 2021. Longitudinal relation between blood pressure, antihypertensive use and cerebral blood flow, using arterial spin labelling MRI. J Cereb Blood Flow Metab. 41, 1756–1766.
Diedrichsen, J., 2006. A spatially unbiased atlas template of the human cerebellum. NeuroImage. 33, 127–138.
Stark, S.M., Kirwan, C.B., Stark, C.E.L., 2019. Mnemonic similarity task: a tool for assessing hippocampal integrity. Trends in Cognitive Sciences. 23, 938–951.
Stark, S.M., Yassa, M.A., Lacy, J.W., Stark, C.E.L., 2013. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. Neuropsychologia. 51, 2442–2449.
Stark, S.M., Stevenson, R., Wu, C., Rutledge, S., Stark, C.E.L., 2015. Stability of age-related deficits in the mnemonic similarity task across task variations. Behavioral Neuroscience. 129, 257–268.
Brauns H, Scherer S, Steinmann S. The CASMIN Educational Classification in International Comparative Research J. 2025.
Kahan, B.C., Jairath, V., Doré, C.J., Morris, T.P., 2014. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. Trials. 15, 139.
Jack, C.R., Petersen, R.C., Xu, Y., O'Brien, P.C., Smith, G.E., Ivnik, R.J., et al., 2000. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology. 55, 484–490.
Devanand, D.P., Pradhaban, G., Liu, X., Khandji, A., De Santi, S., Segal, S., et al., 2007. Hippocampal and entorhinal atrophy in mild cognitive impairment: Prediction of Alzheimer disease. Neurology. 68, 828–836.
Prins, N.D., Scheltens, P., 2015. White matter hyperintensities, cognitive impairment and dementia: an update. Nat Rev Neurol. 11, 157–165.
Deary, I.J., Ritchie, S.J., Muñoz Maniega, S., Cox, S.R., Valdés Hernández, M.C., Luciano, M., et al., 2019. Brain peak width of skeletonized mean diffusivity (PSMD) and cognitive function in later life. Front Psychiatry. 10, 524.
Gullett, J.M., O'Shea, A., Lamb, D.G., Porges, E.C., O'Shea, D.M., Pasternak, O., et al., 2020. The association of white matter free water with cognition in older adults. NeuroImage. 219, 117040.
Fraser, M.A., Shaw, M.E., Cherbuin, N., 2015. A systematic review and meta-analysis of longitudinal hippocampal atrophy in healthy human ageing. NeuroImage. 112, 364–374.
Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., et al., 2017. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. The Lancet Neurology. 16, 377–389.
Yu, C., Lu, W., Qiu, J., Wang, F., Li, J., Wang, L., 2020. Alterations of the whole cerebral blood flow in patients with different total cerebral small vessel disease burden. Front Aging Neurosci. 12, 175.
Jennings, J.R., Heim, A.F., Kuan, D.-C.-H., Gianaros, P.J., Muldoon, M.F., Manuck, S.B., 2013. Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. Stroke 44, 2480–2485.
Dolui, S., Detre, J.A., Gaussoin, S.A., Herrick, J.S., Wang, D.J.J., Tamura, M.K., et al., 2022. Association of Intensive vs Standard Blood Pressure Control With Cerebral Blood Flow: Secondary Analysis of the SPRINT MIND Randomized Clinical Trial. JAMA Neurology. 79, 380–389.
Brickman, A.M., Khan, U.A., Provenzano, F.A., Yeung, L.-K., Suzuki, W., Schroeter, H., et al., 2014. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nat Neurosci. 17, 1798–1803.
Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H., Tuomilehto, J., 2006. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. The Lancet Neurology. 5, 735–741.
Exalto, L.G., Quesenberry, C.P., Barnes, D., Kivipelto, M., Biessels, G.J., Whitmer, R.A., 2014. Midlife risk score for the prediction of dementia four decades later. Alzheimer's & Dementia 10, 562–570.
Richard, E., Moll Van Charante, E.P., Hoevenaar-Blom, M.P., Coley, N., Barbera, M., Van Der Groep, A., et al., 2019. Healthy ageing through internet counselling in the elderly (HATICE): a multinational, randomised controlled trial. The Lancet Digital Health. 1, e424–e434.