

Multimodal Intervention Intensity and Change in Dementia Risk and Cognition: A Harmonized Analysis Across Five Prevention Trials

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Background

- Adherence** measures protocol compliance (observed/planned dose, %) but ignores absolute dose and intervention duration, meaning two participants can be fully adherent to protocols of very different intensities — and adherence alone cannot distinguish them.
- Adherence offers **limited value for cross-study comparisons**.
- Intervention **intensity**, incorporating both **dose and duration**, offers a more sensitive and comparable measure of actual exposure across studies.^[1]

Aim

To examine whether intervention intensity is associated with longitudinal changes in dementia risk and cognitive performance across five multimodal prevention studies.

References

[1] Soldevila-Domenech N, et al. *Alzheimers Res Ther*. 2025. doi: 10.1186/s13195-025-01691-0.

Methods

1. Study design and participants

Table 1. Description of the included studies (intervention groups)

	FINGER	MIND-AD ^{multi}	PENSA	ALFA-LIFE	PREDIMED-Plus-Cognition
N	631	63	104	395	240
Country	Finland	Sweden, Finland, Germany, France	Spain	Spain	Spain
Population	60–77y at elevated CAIDE risk	60–85y with prodromal AD and vascular/lifestyle risk factors	60–80y, APOE-ε4 carriers with SCD	45–75y, cognitively normal with parental AD history	55–75y, cognitively normal with overweight/obesity and metabolic syndrome
Intervention	Diet Physical activity Cognitive training Vascular risk monitoring	Diet Physical activity Cognitive training Vascular risk monitoring	Diet Physical activity Cognitive training Psychoeducation Social stimulation Epigallocatechin gallate (EGCG) or placebo	Diet Physical activity Cognitive/social stimulation*	Diet Vascular risk monitoring Physical activity
Medical food	-	Fortasyn Connect (Souvéniaid™)	-	-	-
Duration (m)	24	6	12	12	36

2. Intervention exposure definitions

- Observed dose:** total number of sessions attended by each participant across domains
- Planned per-protocol dose:** total number of sessions offered

$$\text{Adherence (\%)} = \frac{\text{observed dose}}{\text{planned dose}} \times 100$$

$$\text{Intensity} = \frac{\text{observed dose}}{\text{duration}}$$

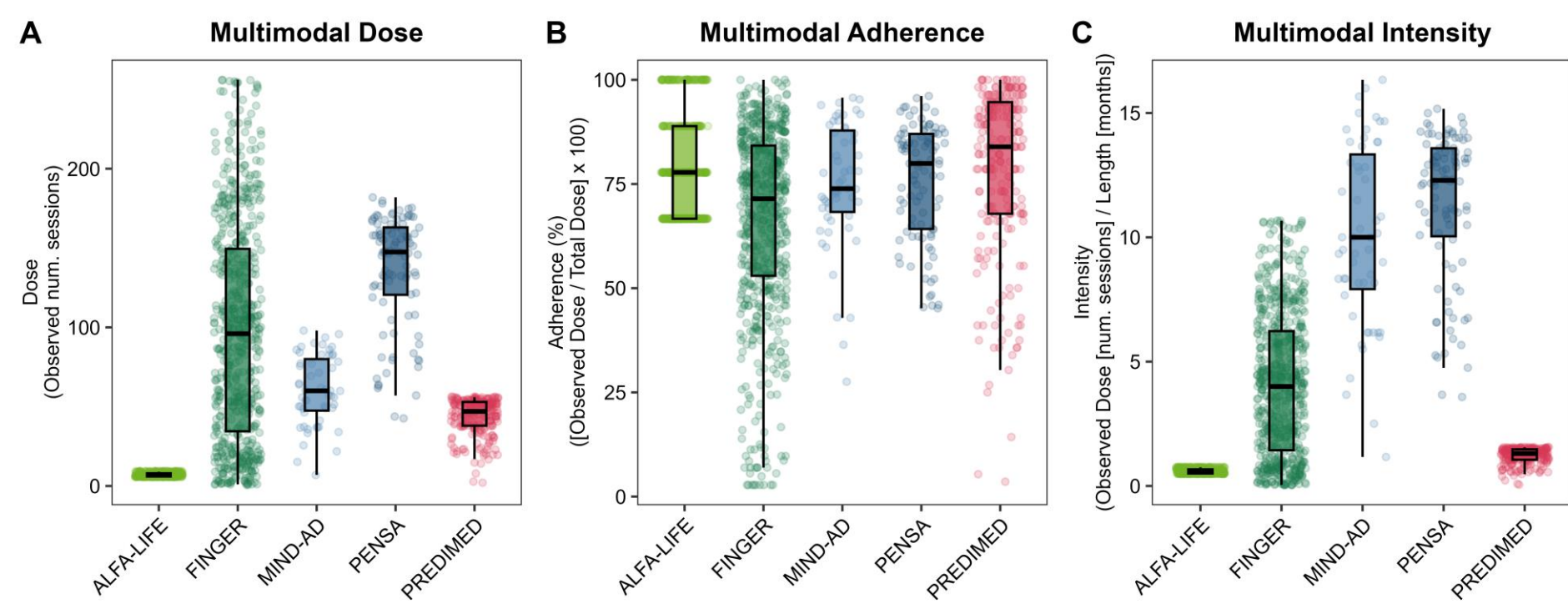


Figure 1. Distribution of (A) multimodal dose (attended sessions per participant), (B) adherence (%) of total sessions offered, and (C) intensity (ratio of multimodal dose to intervention length) across five studies.

3. Dementia risk harmonization

Table 2. Harmonization and operationalization of the Lifestyle for BRAIN Health (LIBRA) index across studies.

LIBRA factor	FINGER	MIND-AD	PENSA	PREDIMED-Plus	ALFA-LIFE
1. Obesity	BMI ≥ 30 kg/m ²				
2. Hypertension	Systolic BP > 140 mg/dL				
3. High blood sugar level	Glucose ≥ 126 mg/dL				
4. Hypercholesterolemia	Total Cholesterol >240 mg/dL				
5. Depression	Zung Self-Rating Depression Scale total score ≥ 50 points	Geriatric Depression Scale total score ≥ 5 points	HADS-depression score ≥ 7 points	BDI total score ≥ 14 points	HADS-depression score ≥ 7 points
6. Smoking	Self-reported current smoking status				
7. Physical inactivity	Sedentary or modestly active				
8. Low-to-moderate alcohol use	<2 unit/week of alcohol				
9. Healthy Diet	MEDAS-14 ≥10 points				

4. LIBRA risk stratification and meaningful change definition

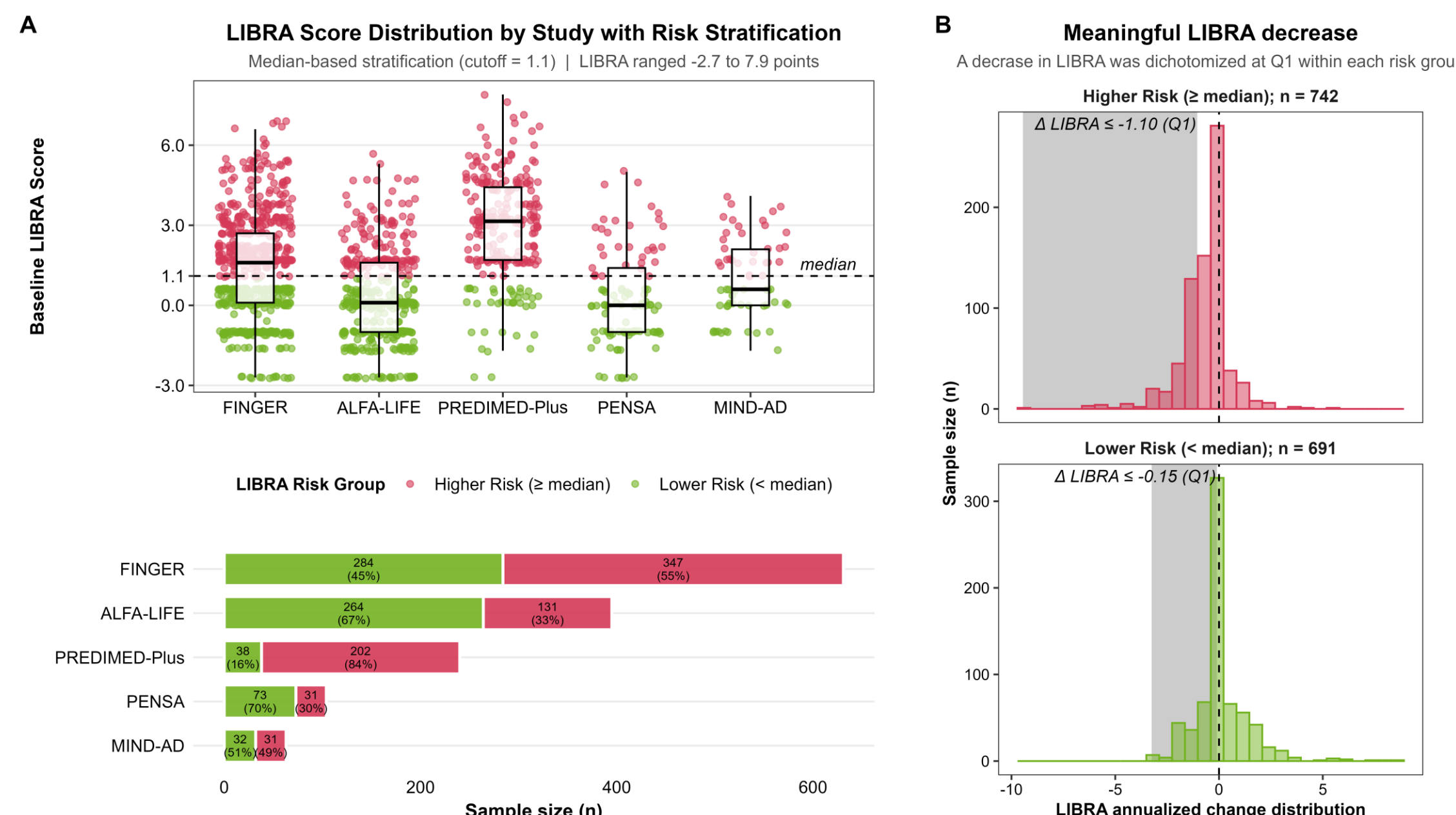


Figure 2. Baseline LIBRA index score distribution and risk stratification (A), and dichotomization of LIBRA change by baseline risk group (decrease defined as first quartile (Q1) or greater reduction) to define a meaningful decrease (B).

Conclusions

- Greater intervention intensity was linked to larger reductions in the LIBRA index, especially in those with higher baseline risk, and to better cognitive trajectories over time.
- These findings highlight intervention intensity as a key driver of both dementia risk reduction and cognitive response, suggesting that tailoring intensity to individual baseline risk profiles may optimize intervention effectiveness.

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Results

1. Participants' characteristics

Table 3. Description of the study population.

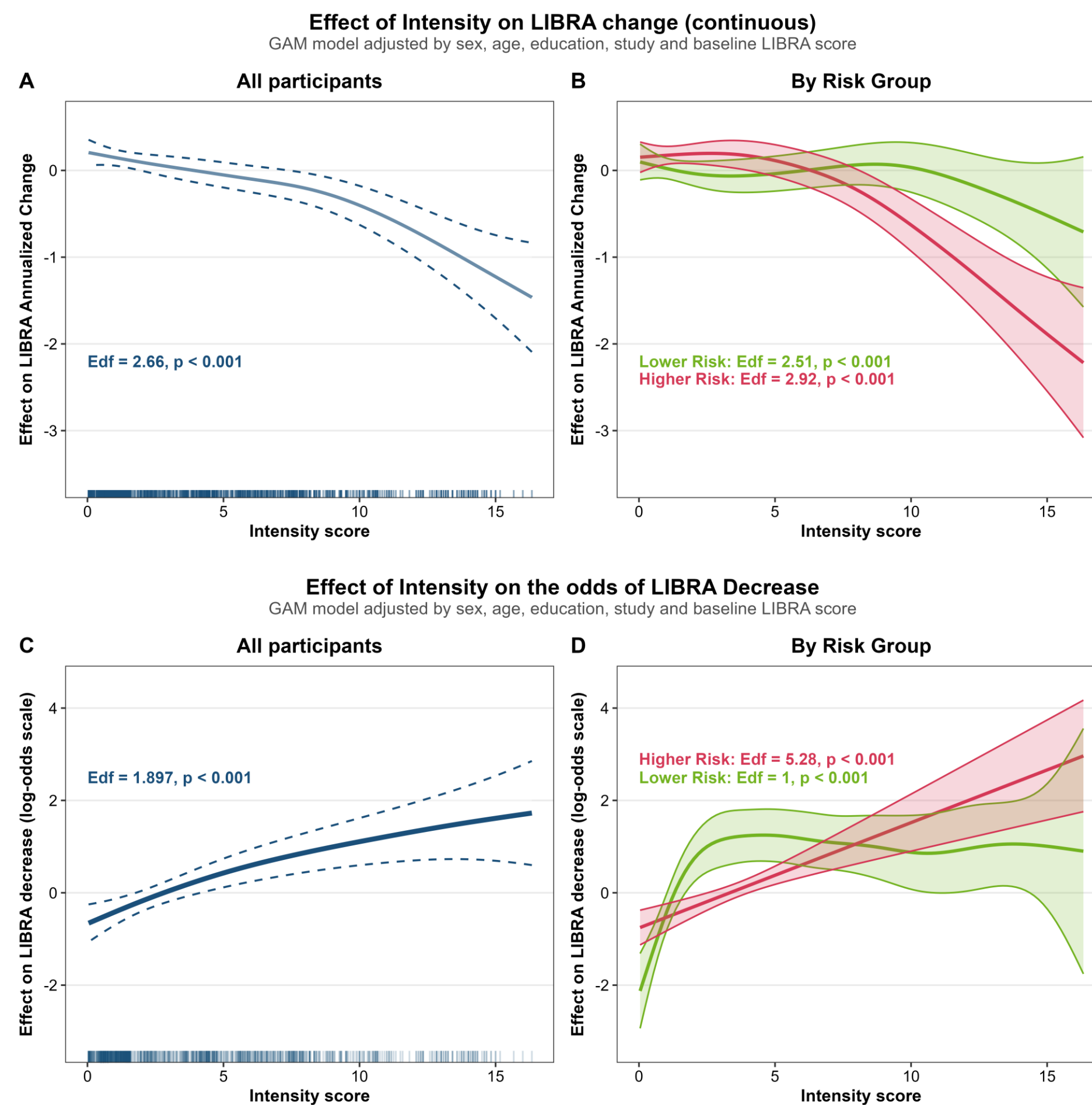
	Overall	ALFA-LIFE	FINGER	MIND-AD	PENSA	PREDIMED-Plus
Sample size	1433	395	631	63	104	240
Intervention factors						
Length (months)	21.0 (8.9)	12	24	6	12	36
Observed dose (total num. sessions)	64.4 (63.5)	7.0 (1.1)	97.3 (68.4)	60.2 (22.1)	135.9 (35.8)	44.1 (11.2)
Adherence (%)	72.6 (20.0)	78.1 (12.6)	66.2 (22.8)	74.9 (15.1)	75.7 (13.9)	78.8 (20.0)
Intensity (dose/length)	3.3 (3.7)	0.6 (0.1)	4.1 (2.8)	10.0 (3.7)	11.3 (3.0)	1.2 (0.3)
Dose - Diet	6.6 (2.5)	6.5 (2.6)	4.6 (2.4)	7.9 (1.1)	7.9 (1.1)	7.9 (1.1)
Adherence - Diet (%)	78.6 (25.7)	77.3 (25.3)	76.2 (39.3)	88.0 (12.5)	88.0 (12.5)	88.0 (12.5)
Dose - Physical activity	41.2 (32.1)	44.5 (34.4)	32.9 (9.5)	23.7 (11.8)	23.7 (11.8)	23.7 (11.8)
Adherence - Physical activity (%)	57.8 (35.4)	55.7 (37.0)	75.6 (18.7)	61.3 (28.8)	61.3 (28.8)	61.3 (28.8)
Dose - Cognitive training/stimulation	44.4 (46.4)	38.1 (43.5)	17.7 (17.2)	100.5 (33.1)	100.5 (33.1)	100.5 (33.1)
Adherence - Cognitive training/stimulation (%)	45.2 (31.2)	41.8 (29.6)	34.8 (33.7)	72.8 (24.0)	72.8 (24.0)	72.8 (24.0)
Dose - CV counselling	7.5 (2.6)	8.1 (1.9)	1.8 (0.6)	1.8 (0.6)	1.8 (0.6)	1.8 (0.6)
Adherence - CV counselling (%)	89.9 (21.7)	90.1 (21.1)	88.9 (27.6)	88.9 (27.6)	88.9 (27.6)	88.9 (27.6)
Sociodemographic characteristics						
Female gender	757 (52.9)	248 (63.1)	286 (45.3)	36 (57.1)	69 (66.3)	118 (49.2)
APOE-ε4 carriers	440 (38.8)	133 (34.2)	189 (32.0)	104 (100.0)	14 (27.5)	73 (30.4)
Age, years	65.2 (7.8)	57.4 (7.5)	69.0 (4.7)	72.5 (6.5)	67.3 (4.6)	65.4 (4.6)
Education, years	11.6 (4.2)	13.8 (3.4)	10.0 (3.5)	12.4 (3.9)	14.6 (3.7)	11.1 (4.9)
Current smoker	172 (12.0)	60 (15.2)	64 (10.1)	2 (3.2)	13 (12.5)	33 (13.8)
Cardiovascular Risk Factors						
Obesity status						
Normal weight	378 (26.5)	141 (36.1)	162 (25.8)	25 (41.0)	50 (48.1)	0 (0.0)
Overweight	578 (40.6)	165 (42.2)	278 (44.3)	28 (45.9)	34 (32.7)	73 (30.4)
Obesity	468 (32.9)	85 (21.7)	188 (29.9)	8 (13.1)	20 (19.2)	167 (69.6)
Hypertension	959 (67.5)	153 (39.2)	496 (78.7)	59 (95.2)	38 (36.5)	211 (87.9)
Diabetes status						
Normal glycaemia	558 (39.4)	214 (54.5)	143 (22.7)	16 (32.0)	84 (80.8)	101 (42.1)
Prediabetes	627 (44.3)	157 (39.9)	374 (59.5)	30 (60.0)	9 (8.7)	57 (23.8)
Diabetes	231 (16.3)	22 (5.8)	112 (17.8)	4 (8.0)	11 (10.8)	82 (34.2)
Dyslipidemia	692 (49.0)	147 (37.4)	336 (54.9)	8 (12.7)	42 (40.4)	159 (66.2)
Lifestyle Risk Factors						
Adherence to a healthy diet						
Low	415 (29.1)	112 (28.4)	100 (15.9)	47 (78.3)	45 (43.3)	111 (46.2)
Medium	706 (49.5)	149 (37.8)	499 (79.5)	10 (16.7)	37 (36.0)	99 (41.2)
High	304 (21.3)	133 (33.8)	116 (18.5)	3 (5.0)	22 (21.2)	30 (12.5)
Physical activity						
Sedentary	288 (20.8)	74 (19.2)	126 (20.2)	8 (26.6)	8 (7.7)	72 (30.0)
Modestly active	445 (32.2)	149 (37.8)	165 (26.4)	11 (39.3)	45 (43.3)	99 (41.2)
Active	401 (29.0)	101 (26.2)	215 (34.4)	9 (32.1)	32 (30.9)	44 (18.3)
Very active	249 (18.0)	86 (22.3)	119 (19.0)	0 (0.0)	19 (18.3)	25 (10.4)
Alcohol consumption						
Abstain	201 (14.1)	64 (16.2)	82 (13.1)	0 (0.0)	12 (11.5)	43 (17.9)
Low risk	987 (69.2)	242 (61.4)	499 (79.5)	36 (60.0)	65 (62.5)	145 (60.4)
High risk	238 (16.7)	88 (22.3)	47 (7.5)	24 (40.0)	27 (26.0)	52 (21.7)
Depression symptoms	208 (14.8)	25 (6.4)	120 (19.8)	8 (12.7)	5 (4.8)	50 (20.8)
Dementia risk indices						
CAIDE score (5 items)	8.5 (2.3)	6.9 (2.0)	9.2 (1.8)	7.3 (1.8)	6.7 (2.0)	10.2 (2.0)
LIBRA index score (9 items)	1.3 (2.0)	0.3 (1.0)	1.4 (1.9)	1.0 (1.5)	0.3 (1.7)	2.9 (1.9)
Cognition						
MMSE total score	27.9 (2.0)	29.1 (1.0)	26.7 (2.1)	27.7 (1.5)	29.0 (1.3)	28.4 (1.7)

*Results reported as Mean (SD); otherwise as N (%).

2. Intensity on dementia risk

- Generalized additive models (GAMs) were used to assess the association of intervention intensity with annualized LIBRA change and the odds of a meaningful LIBRA reduction, overall and by baseline risk.
- Higher intensity was non-linearly associated with greater annualized LIBRA reductions (**Figure 3A**), primarily in higher-risk participants (**Figure 3B**).
- Intervention intensity was also non-linearly associated with increased odds of meaningful LIBRA decrease (**Figure 3C**), showing distinct patterns by baseline risk group (**Figure 3D**).

Figure 3. Association between multimodal intensity and LIBRA change using generalized additive models (GAM). Effect on annualized LIBRA change (continuous) for all participants (A) and by baseline risk group (B). Effect on odds of meaningful LIBRA decrease (dichotomous) for all participants (C) and by baseline risk group (D).



3. Intensity on global cognition

- Linear mixed effects models were used to examine the association between intervention intensity and changes in global cognition evaluated with the MMSE.
- Intervention intensity significantly predicted MMSE trajectories over time ($p = 0.012$): higher intensity was associated with greater cognitive improvement (**Figure 4A**).
- A parallel trend was observed for LIBRA change ($p = 0.056$): greater reductions in dementia risk score were associated with better cognitive trajectories over time, suggesting that lifestyle improvements may translate into cognitive benefit (**Figure 4B**).

Figure 4. Predicted MMSE trajectories by multimodal exercise intensity (A) and annualized LIBRA risk (B).

Cognitive Response to Multimodal Interventions

