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Original Article

Lifestyle and cognition: Separating the effects of average lifestyle and lifestyle changes based on the LIBRA score

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ABSTRACT

Background: The LIfestyle for BRAin Health (LIBRA) score, consisting of twelve factors, highlights individuals' potential for dementia risk reduction through lifestyle. The LIBRA score includes modifiable protective factors such as low to moderate alcohol consumption, and risk factors such as hypertension.
Objective: We studied whether LIBRA scores are longitudinally associated with cognition, and to what extent this is due to between-person differences or within-person changes in LIBRA scores.
Methods: Individuals were included from four Dutch community-based cohorts: Doetinchem Cohort Study (DCS; n = 4770), Maastricht Aging Study (MAAS; n = 1295), Longitudinal Aging Study Amsterdam (LASA; n = 2391) and the Rotterdam Study (RS; n = 5205). The number of available LIBRA components (range 7–11) and timepoints (range 3–9) differed per cohort. Outcomes were standardized processing speed (LDST), memory (15-word delayed recall of the verbal learning test (VLT)) and verbal fluency. Hybrid mixed models were fit for the association of 1) mean LIBRA score and 2) change in LIBRA between subsequent timepoints. Models were adjusted for age, sex, education and learning effects. Interactions of the mean LIBRA score with age, and change in LIBRA score with age were tested in two separate models.
Results: Higher (i.e., unhealthier) mean LIBRA scores were associated with worse cognitive speed (lower LDST z-score per 1-point higher LIBRA, range between cohorts: 0.039 – 0.0587), memory (VLT, 0.026 – 0.035), and fluency (0.020 – 0.033). Associations of mean LIBRA scores with cognitive function were stronger with older age (LDST: significant age-interaction, 2 out of 4 cohorts; VLT and fluency: 1 out of 4 cohorts). Relative to 65-year-old individuals with a mean LIBRA score at the 50th percentile, individuals at the 90th percentile of the LIBRA score showed an estimated 1.9–3.2 years more advanced cognitive ageing for LDST, 1.9 – 5.3 years for VLT and 1.4 – 1.7 years for fluency. Within-person change in LIBRA showed no consistent associations with cognitive decline.
Conclusions: An individual's mean LIBRA score, but not their change in LIBRA score over time, was longitudinally associated with cognitive functioning. In the general population, the investigated version of the LIBRA score is possibly not suitable to capture how cognition (as a proxy for dementia risk) changes with improvements in lifestyle.

1. Introduction

Due to population aging, the prevalence of dementia is expected to rise[1]. As there are currently limited disease-modifying treatments available, dementia risk reduction is crucial. It is estimated that 45 % of dementia cases are attributable to 14 modifiable factors including lifestyle behaviors [2].

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Dementia is often preceded by a long preclinical period of gradual cognitive decline[3]. The presence of modifiable risk and protective factors in midlife and older age, including lifestyle behaviors and health factors, may influence subsequent dementia risk [2,4]. For preventive purposes, more evidence is needed about whether changes (e.g., improvements) in modifiable factors in middle- and old-aged cognitively healthy individuals are associated with changes in cognitive scores as a proxy for later-life dementia risk. This knowledge could also provide insight into whether reductions in modifiable risk scores can be used as a surrogate marker for reduced dementia risk in lifestyle trials, which would shorten the needed follow-up period to demonstrate a difference in dementia incidence between intervention groups. There are several dementia risk scores based on modifiable factors, one of which is the LIfestyle for BRAin Health (LIBRA) score. The LIBRA score is a compound score consisting of 12 risk and protective factors, and has been developed based on literature review and expert feedback [5]. It has been validated in several cohort studies as predictive for the outcomes dementia and cognitive decline [6,7]. However, these studies only looked at baseline LIBRA scores, and did not analyze whether changes in LIBRA scores are associated with changes in cognition, and therefore do not yet show whether lifestyle changes in middle- to older-aged individuals can reduce cognitive decline.

The aim of our research was to longitudinally investigate the relationship of individuals' LIBRA scores with cognitive functioning over time. We distinguished the effects of average LIBRA scores, reflecting more general estimates of the associations of lifestyle behaviors with cognitive scores, from effects of changes in LIBRA scores over time, reflecting the effects of e.g. improvements of lifestyle behaviors on cognitive scores. We studied these objectives in data from four different population-based cohort studies.

2. Methods

2.1. Included cohorts

We included individuals from four population-based cohort studies, i.e., Doetinchem Cohort Study (DCS) [8,9], the Longitudinal Aging Study Amsterdam (LASA) [10,11], the Maastricht Aging Study (MAAS) [12] and the Rotterdam Study (RS) [13,14]. All cohort studies were approved by local ethical committees (DCS: external Medical Ethics Committee of The Netherlands Organization for Applied Scientific Research and Medical Ethics Committee of the University of Utrecht; LASA: medical ethics committee of the VU University Medical Center, IRB numbers: 92/138, 2002/141, 2012/361 and 2016.301; MAAS: ethics committee of Maastricht University Medical Centre; RS: Medical Ethics Committee of the Erasmus MC). All cohort studies respected the privacy of participants, and informed consent was obtained from all participants.

DCS started in 1987. The baseline round included 12,405 individuals from the city of Doetinchem (baseline age 20–59 years, baseline response rate: 62 %). Baseline participants were selected by a 5-year age-group and sex-stratified random sample from the municipality register of Doetinchem. Of the individuals who participated at baseline, 7769 were followed as a cohort every 5 years. DCS currently has seven complete rounds (remaining participants, approximately 3000, with the eighth round ongoing). The response rate per follow-up round varied between 75 and 79 %. Cognitive testing started halfway in the second round (1995 – 1997), and at the time of study conduct, cognitive data is available up and including the sixth round (2013–2017). In DCS, cognitive tests were only administered to individuals who are at least 45 years old. Individuals reached this age in different study rounds depending on their baseline age. We therefore transformed the cognitive data to timepoints, by taking the first round individuals have cognition as timepoint 0 (t0), the subsequent round as t5, etc. (see Supplementary Figure A.1).

LASA started in 1992, and included individuals from three regions in The Netherlands (around and including the cities of Zwolle, Oss and Amsterdam). The baseline measurement included 3107 individuals (baseline age 55–84, baseline response rate 62 %). Baseline participants were selected by random sampling from municipality registers of Amsterdam, with oversampling of oldest old and men. In 2002–2003, a refresher cohort of 1002 individuals aged 55–64 was added (baseline response rate 62 %), and in 2012–2013 a refresher cohort of 1023 individuals aged 55–64 (baseline response rate 63 %). Individuals have been followed-up about every 3 years. For our analyses, we included individuals from the original cohort (9 rounds: round C (completed in 1995 – 1996), D (1998 – 1999), E (2001 – 2002), F (2005 – 2006), G (2008 – 2009), H (2011 – 2012), I (2015–2016) and J (2018–2019)) and first refresher cohort (6 rounds: 2B (2002 – 2003), F, G, H, I and J).

MAAS started in 1993 as a prospective cohort study investigating normal and pathological cognitive aging. A random sample of 10,396 individuals was selected from the Registration Network Family Medicine (RNFM) of general practitioners in the south of The Netherlands [15]. From these individuals, a stratified random sample based on age, gender, and occupational level (low/high) took part in a longitudinal phase of the study (n = 1823, age range 24 to 82 years). Participants' medical status, lifestyle, anthropometric and neuropsychological measures were assessed at baseline (1993 – 1995), at 6 years and 12 years of follow-up. For our analyses, individuals aged ≥ 40 years at baseline were included.

RS started in 1990. It included 7893 inhabitants of Rotterdam (baseline age 55–106, baseline response rate 78 %), who were selected by random sampling of individuals aged 55 years or older from the municipal register. In 2000, 3011 individuals were added as an extension cohort (baseline age 55+, baseline response rate 67 %), and in 2006 a second extension cohort of 3932 individuals was added (baseline age 45–54, baseline response rate 63 %). Individuals were followed every 4–7 years. For the current analyses, individuals from the original cohort (3 rounds: RS-I-4 (2002 - 2004), RS-I-5 (2009 - 2011) and RS-I-6 (2014 - 2015)) and the first extension cohort (3 rounds: RS-II-2 (2004 - 2005), RS-II-3 (2011 - 2012), RS-II-4 (2015–2016)) were included.

An overview of selected rounds per cohort and availability of key variables (LIBRA score and cognitive scores) is presented in Supplementary Figure A.1.

2.2. Implementation of the LIBRA score in different datasets

The LIBRA score is a sum of modifiable individual risk and protective factors for dementia, of which the design and calculation has been described in detail elsewhere [5]. Briefly, based on a Delphi study and on literature research, 12 modifiable components for dementia were established: the protective factors low to moderate alcohol consumption, Mediterranean diet, and high cognitive activity (i.e., a high amount of time spent on cognitively stimulating activities such as reading), and the risk factors coronary heart disease, physical inactivity, renal dysfunction, diabetes, high cholesterol, smoking, obesity, hypertension and depression. The relative risks of dementia for these factors were extracted from existing meta-analyses and scaled to determine the weight of each factor [16]. The LIBRA score is computed by summing over the weights of each present risk or protective factor, resulting in a score ranging for the full LIBRA score from −5.9 (best possible score) to 12.7 (worst possible score). For each of the cohorts, we assessed whether we could include LIBRA components based on the following inclusion criteria: firstly, that the component was measured in at least three rounds of the cohort by study design, ensuring that changes in LIBRA scores can be appropriately modelled. Secondly, because we were interested in looking at changes in LIBRA scores, we required that the definition of each component was identical across timepoints – e.g., we excluded physical activity in RS because in some rounds it was based on a questionnaire, and in others on accelerometry. The number of available LIBRA components and their definitions differed across the cohorts (Supplementary Table A.1). Briefly, in DCS, 10 components could be included (all but diet and cognitive activity); in MAAS, 11 components (all but diet); in

LASA, 9 components (all but diet, cognitive activity and renal dysfunction) and in RS, 7 components (all but diet, cognitive activity, renal dysfunction, physical activity and coronary heart disease). For each individual, the LIBRA score was only calculated in rounds when they had no missing values in the LIBRA components (for information on missing values per component, see Supplementary Table A.2).

To make the LIBRA score more comparable between cohorts, we computed the LIBRA score based on factors that were available in at least two cohorts; therefore, high cognitive activity and diet were excluded. This resulted in different numbers of included components per cohort (DCS and MAAS: 10 components; LASA: 9 components; RS: 7 components). To make the model results more comparable between cohorts, we scaled the LIBRA scores to have the same possible range in all cohorts, using min-max normalization relative to the possible range of the 10-component score (−1 for the best possible to 12.7 for the worst possible score). Using these scaled scores as input to the statistical models has the advantage that the estimated regression coefficients, i.e., for a 1-point increase in the (scaled) LIBRA score, have a similar meaning across cohorts.

2.3. Cognitive scores in different datasets

Cognitive scores were included that reflect memory, processing speed and fluency (see Supplementary Table A.3). Cognitive testing procedures in the cohorts have been described in detail elsewhere (RS [17]).

For memory, in all cohorts, delayed recall on the 15-word verbal learning test (VLT) [18,19] was used. For processing speed, in DCS, MAAS and RS, the letter-digit substitution test (LDST) score was used [20,21], and in LASA, an adjusted version of the Alphabet Coding Task-15 [22]. For fluency, in DCS, LASA and RS, animal fluency was used [23,24]. Fluency test scores in MAAS were not used, because fewer than 3 timepoints were available.

Raw cognitive scores were Z-transformed relative to the mean and standard deviation of each cohort at baseline. In DCS, scores were Z-transformed relative to the first timepoint (the first round in which individuals had cognitive tests), as individuals in DCS only start cognitive testing when aged 45 years or older. For the analyses, cognitive scores were only included when there were no abnormalities during testing or physical or psychological limitations that could interfere with testing.

2.4. Covariates

In all cohorts, level of education was categorized into four levels: low (elementary education or less); medium-low (lower vocational education or pre-vocational secondary education), medium-high (secondary vocational education, senior general secondary education, pre-university education) and high (higher professional education, university education). Age was centered at 65 years in all cohorts. This centering age was chosen as it is included in the age range of all cohorts. To account for learning effects, the number of (re)tests was determined per person and per cognitive test, and categorized as 1 for the first cognitive test, and then incremented for each retest at a later round. In LASA and RS, to adjust for differences between cohorts that started at different times, it was dichotomized whether participants were from the original or expansion cohort.

2.5. Investigating within-person change in LIBRA scores

We studied the extent to which LIBRA scores change over time within the same individuals in DCS and MAAS, in which the full 10-component LIBRA scores could be determined. For visualization purposes, the LIBRA score was divided into 1-point intervals. Across all timepoints, we calculated the percentage of participants who stay in the same LIBRA interval between subsequent timepoints, who worsen, or who improve between timepoints. To capture how often, i.e. once or multiple times, individuals' LIBRA scores change over time, we also determined individual change patterns in LIBRA scores across all timepoints.

2.6. Statistical methods

2.6.1. Distinguishing between-person and within-person effects

Our aim was to separate the following effects of LIBRA scores on cognitive scores: 1) the overall difference in cognition between subjects with different LIBRA scores, based on all observations, and 2) the effects of changes in LIBRA scores on changes in cognition within the same individuals. A hybrid mixed model approach is suited to separate these between-person and within-person effects, as has been described and explained more extensively elsewhere [25]. In brief, for each individual, their mean (scaled) LIBRA scores were calculated across all time points. Next, for each individual and time point, deviations are calculated between that timepoint's LIBRA score and the person-specific mean. These two scores – the mean and deviations – are included simultaneously in a mixed model. The effect estimate of the person-specific mean, or 'between-person effect', then reflects the difference in cognitive scores over time between individuals with one unit difference in LIBRA scores. The effect estimate of the deviations, or 'within-person effect', then reflects the effect of a one unit change in LIBRA score over time on the change in cognitive scores, independent of the individual mean LIBRA score over time. Although the person-specific mean LIBRA score is time-invariant, both the person-specific mean (between-person effect) and deviations (within-person effect) reflect longitudinal associations with the repeated cognitive scores over time.

2.6.2. Models

We fit hybrid mixed models for the outcomes VLT delayed recall, LDST and fluency (all as Z-scores), to estimate the between- and within-person effect. All models were run separately per cohort to investigate if the findings are robust (i.e., validated across cohorts). All models included a random intercept for person and a random slope for age centered at 65 years. A series of models was fit: Model 1, adjusting for centered age, quadratic centered age (which improves model fit), sex, the number of retests (to adjust for learning effects), educational level and (expansion) cohorts recruited at different time points within the study for LASA and RS. Because prior research suggests the effect of lifestyle factors on cognition may differ depending on age [2], we also tested interactions between the LIBRA score and age in Models 2 and 3: Model 2 included an interaction between person-specific mean LIBRA score with age, to test whether the overall effect of lifestyle on cognition depended on age. Model 3 included an interaction between the LIBRA deviations and age, to test whether the effect of changes in lifestyle depend on age. Models 2 and 3 both built upon Model 1. The models were fit on all individuals without preselection based on the number of available measurements. This approach was chosen because mixed models are capable of dealing with missing values, and fitting the model on all individuals better adjusts for possible confounders.

Interaction terms were considered significant at a two-sided p-value < 0.1; all other effects were considered significant at a two-sided p-value < 0.05.

2.6.3. Visualization of the hybrid mixed model results

For visualization purposes, we expressed the between- and within-person effects of LIBRA scores as age-related decline in cognitive scores, by plotting prediction lines for different mean LIBRA levels and LIBRA change levels: middle (50th percentile), low (10th percentile) and high (90th percentile). Confidence intervals for the prediction lines were generated using parametric bootstrapping with 500 iterations. In short, a parametric bootstrap keeps the model coefficients (for the mean LIBRA and LIBRA change) constant, while residuals from the model fit are sampled at random and added to the model coefficients. From these bootstrapped values, a 95 % confidence interval was calculated and added to the prediction lines.

2.7. Sensitivity analyses

To test whether any of the LIBRA components drove the associations, a leave-one-out analysis was performed in DCS and MAAS, in which the most complete LIBRA scores could be determined. For this analysis, we constructed distinct LIBRA scores while leaving out one component, and repeated the hybrid mixed models.

Next, because in RS fewer components could be included, we constructed LIBRA scores with the identical 7 components in the remaining cohorts (alcohol consumption; diabetes; cholesterol; smoking; obesity; hypertension; depression), and tested whether results remained similar as when the complete scores were used in DCS, MAAS and LASA.

Finally, we tested if associations remained similar when using an identical age range across cohorts (60- to 85-years old). For this purpose, cognitive scores were Z-scored relative to the mean and standard deviation of 60- to 85-year-olds at the baseline round of the study. Next, hybrid mixed model fitting was repeated while selecting only 60- to 85-year-olds.

2.8. Software and packages

All analyses were conducted with R version 4.3.2 or higher. LIBRA scores were transformed into person-specific mean scores and deviation scores with *parameters* version 0.21.6, and hybrid mixed models were fit with *nlme* version 3.1–165 or higher. Sankey diagrams were constructed with *networkD3* version 0.4.

3. Results

3.1. Baseline demographics

Jointly, the four cohorts contributed information on 13,661 participants, of whom 53 % were women. Individuals in RS and LASA were on average older than in DCS and MAAS (Supplementary Table A.4). The proportion of individuals with a low education was higher in LASA compared to the other cohorts.

3.2. LIBRA components and scores

Average scaled LIBRA scores were higher in LASA and RS than in DCS and MAAS (Supplementary Table A.5, Supplementary Figure A.2). The most prevalent unhealthy LIBRA components at baseline were: high cholesterol (DCS (31.3 %), RS (22.5 %)), hypertension (LASA (73.9 %) and RS (80.9 %)), poor physical activity (DCS (44.3 %), LASA (55.1 %), MAAS (38.5 %)), diabetes (RS (17.3 %)), and smoking (DCS (23.8 %), LASA (23.3 %), MAAS (25.8 %), RS (15.8 %)) (Supplementary Table A.5).

Fig. 1 displays change between consecutive timepoints for the LIBRA score divided into 1-point intervals for visualization purposes. Averaged across all timepoints, about a third of the participants stay in the same LIBRA interval between two subsequent timepoints (DCS: 36 %, MAAS: 28 %), a third to half of the participants worsen (DCS: 38 %, MAAS: 45 %), and a quarter improves (DCS: 26 %, MAAS: 26 %). Of individuals whose score changed between timepoints, approximately half changed more than one point (for worsened scores: DCS 48 % and MAAS 63 %; for improved scores: DCS 42 % and MAAS 50 %). The majority of individuals changed in LIBRA score at least once over time (of individuals with at least two timepoints, DCS: more than 66 % changed; in MAAS, more than 74 % changed) (see full characterization in Supplementary Table A.6).

3.3. Associations of the LIBRA score with cognitive scores

Next, we distinguished the overall (i.e., mean) effect of the LIBRA score from changes in the LIBRA score. Higher overall LIBRA scores were consistently and statistically significantly associated with lower cognitive scores in all cohorts (i.e., between-person effect): individuals with worse average LIBRA scores had poorer cognitive scores after adjustment for age, sex, education, learning effects, and cohort effects (Table 1, model 1; Supplementary Figures A.3 – A.5). The strongest between-person effect was observed for LDST: a 1-point worse average LIBRA score was associated with 0.039 to 0.059 SD lower LDST, depending on the cohort.

For the within-person effects of LIBRA scores, after adjustment for age, sex, education, learning effects and cohort effects, only a few statistically significant associations were found with VLT delayed recall and LDST. In DCS, a one-point increase of LIBRA scores over 5 years was associated with 0.0177 SD decreased VLT Z-scores (p-value < 0.01). In DCS and MAAS, a one-point increase of LIBRA score over 5 years (DCS) or 6 years (MAAS), was associated with 0.0079 to 0.022 SD decreased LDST score, respectively (both with p-value < 0.05). These associations were however not consistent between cohorts.(Table 1) To investigate whether the lack of consistent within-person effects changes was due to differences in levels of change in individuals with higher or lower average LIBRA scores, we visualized the level of change for different average LIBRA score quartiles. Except for the lowest (healthiest) quartile, which showed less variability in LIBRA score changes over time, the other quartiles had largely similar levels of LIBRA score changes over time (Supplementary Figure A.6).

The between-person effect showed interactions with age on LDST scores in two of four cohorts (DCS and MAAS), all with stronger effects with older age; on VLT recall Z-scores in one cohort (DCS); and on fluency in one cohort (RS) (Table 1, model 2). The within-person effect showed no interactions with age on any cognitive score (Table 1, model 3).

3.4. Visualizing the effect of LIBRA scores as age-related decline

Figs. 2–4 visualize the cognitive trajectories for 65-year-old individuals with different levels of average LIBRA score or change in LIBRA scores, for LDST (Fig. 2), VLT (Fig. 3) and fluency (Fig. 4). For the between-person effect of LIBRA, compared to 65-year-olds at the 50th percentile, those at the 90th percentile showed 1.9 – 3.2 years more advanced cognitive ageing for LDST, 1.9 – 5.3 years for VLT and 1.4 – 1.7 years (excluding LASA's estimate which fell outside of the observed age range) for fluency, depending on the cohort.

For the within-person effect, the estimated trajectories of age-related decline in cognitive scores for different levels of change in LIBRA scores overlapped (Figs. 2–4).

3.5. Sensitivity analyses

Compared to individuals who dropped out prior to the end of follow-up, those who remained for the entire follow-up duration were younger, more highly educated, and had better LIBRA scores and cognitive scores (Supplementary Table A.7).

A leave-one-out analysis showed that most LIBRA components did not drive the association: for most components, constructing a LIBRA score without the component only led to slight attenuation or a small strengthening of some effects (Supplementary Table A.8). Exclusion of hypertension from the score had more effect: the within-person effect on VLT was no longer significant, and the between-person effect on LDST was somewhat attenuated (both in DCS). Excluding depression attenuated effects on all cognitive scores in DCS and MAAS, and led to loss of statistical significance for various cognitive scores of the LIBRA score's between-person effects (i.e., for the LDST and VLT score in MAAS, and fluency scores in DCS), and within-person effects (i.e., for the LDST score in DCS). For the within-person effect on LDST Z-score in DCS, excluding several components (diabetes, a history of CVD, poor physical activity, smoking, poor mental health or poor kidney function) led to loss of statistical significance.

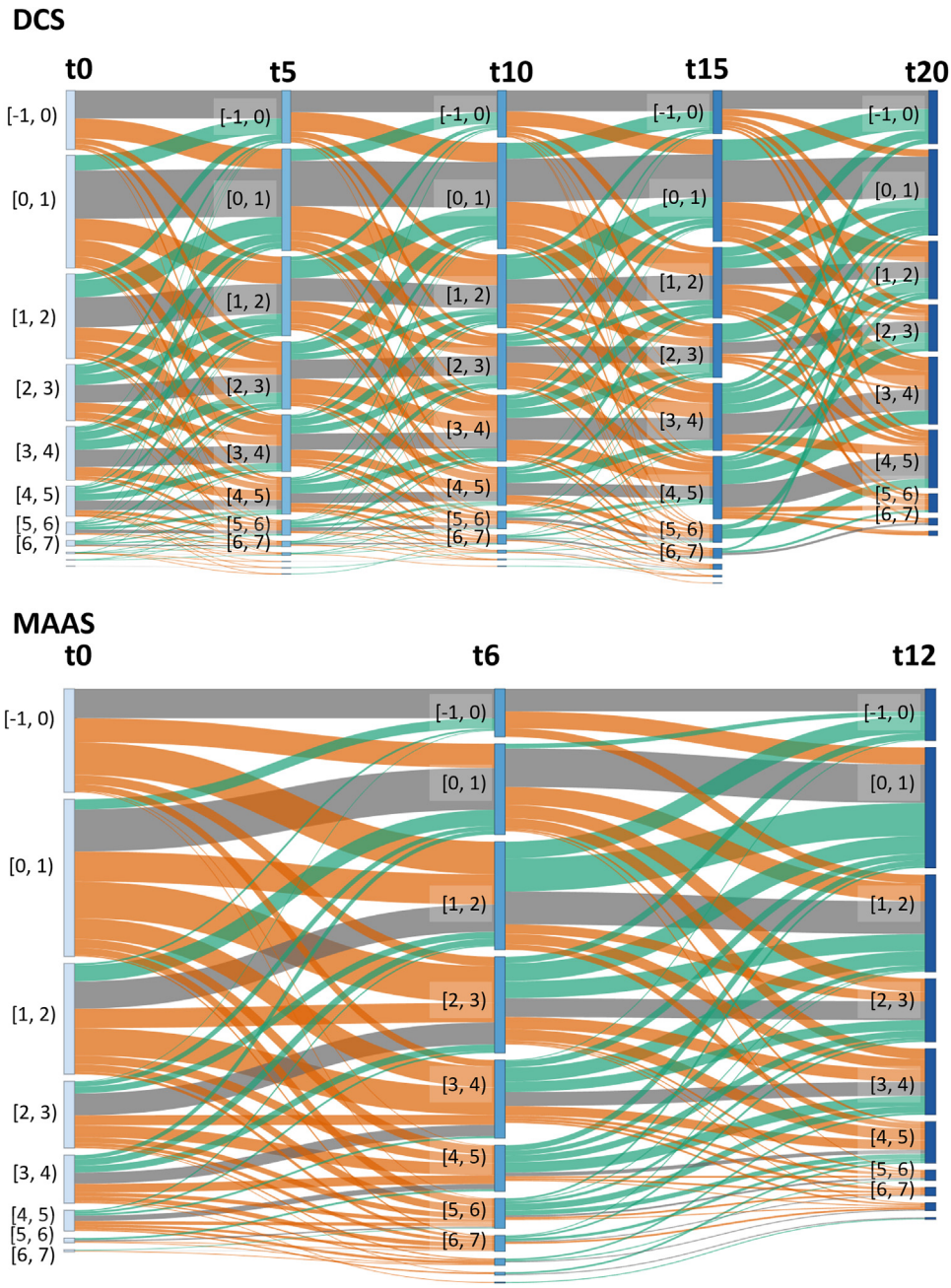

Fig. 1. Change in LIBRA scores across time in DCS and MAAS.
Figure subscript: Each column displays LIBRA values for a timepoint, separated into 1-point intervals (rectangles). The height of the interval is proportional to the number of individuals falling within that interval. Lines between columns indicate proportions of individuals that stay in the same LIBRA interval between adjacent timepoints (grey color), or that change to a higher or lower LIBRA interval (red vs. green color, respectively). LIBRA intervals and lines have been scaled relative to the number of individuals who remain in the cohort at the next timepoint.
Abbreviations: DCS, Doetinchem Cohort Study; MAAS, Maastricht Aging Study; t0, first measurement; t5, follow-up measurement (5 years later); t10, follow-up measurement (10 years later), etc.

Because in RS fewer components could be included, we constructed LIBRA scores with the identical 7 components in the remaining cohorts (alcohol consumption; diabetes; cholesterol; smoking; obesity; hypertension; depression). Results remained similar for the between-person effects, but the within-person effect of LDST in DCS was no longer significant (Supplementary Table A.9).

Finally, we tested if associations remained similar when using an identical age range across cohorts. When we tested associations for individuals who were 60- to 85-years old, the between-person effects remained significant for LDST, VLT recall and fluency in most cohorts (DCS, LASA, RS), but the within-person effects were no longer significant. (Supplementary Table A.10, Supplementary Figure A.7 – A.9).

4. Discussion

In this study, we investigated whether change in LIBRA scores is associated with changes in cognition in four Dutch population-based cohorts. Individuals with higher LIBRA scores had worse cognition over time. However, individual improvement or worsening of the LIBRA score was not consistently associated with changes in cognition. In the general population, the investigated version of the LIBRA score may not be suitable to assess how cognition may change with improved lifestyle.

4.1. Between-person but no within-person effects on cognition

We found that the between-person effect (reflecting differences between individuals in average LIBRA score), but not the within-person effect (reflecting changes in LIBRA score within individuals), was consistently associated with cognitive scores (Table 1, Model 1). These results imply that worse average LIBRA over time is associated longitudinally with worse cognitive scores over time. Comparing these results with the literature, no studies have yet separated between- and within-person effects of LIBRA scores on cognitive scores over time; however, several studies have investigated whether (mostly baseline values of)

Table 1
Association of average LIBRA score and change in LIBRA score with cognitive scores over time.

			Model 1: age+age^2+sex+ mean LIBRA+ LIBRA deviations+ measurement number+ education + Cohort (RS/LASA)		**Model 2: Model 1+ interaction mean LIBRA*age**			**Model 3: Model 1+ interaction LIBRA deviations*age**		
Study	**Observations (n)**	**Individuals (n)**	**Between-person effect: estimate±SE**	**Within-person effect: estimate±SE**	**Between-person effect: estimate±SE**	**Within-person effect: estimate±SE**	**Interaction: estimate±SE**	**Between-person effect: estimate±SE**	**Within-person effect: estimate±SE**	**Interaction: estimate±SE**
LDST Z-score										
DCS	11,881	4610	**−0.0587 ± 0.00689*****	**−0.0079 ± 0.00392***	**−0.0716 ± 0.00744*****	−0.00641 ± 0.00393	**−0.00209 ± 0.000455*****	**−0.0587 ± 0.00689*****	−0.00661 ± 0.0043	0.000357 ± 0.000488
LASA	7456	2194	**-0.0497 ± 0.0086*****	-0.00695 ± 0.00524	**-0.0479 ± 0.00939*****	-0.00677 ± 0.00526	-0.000271 ± 0.000585	**-0.0497 ± 0.0086*****	-0.00762 ± 0.00685	9.21e-05 ± 0.000608
MAAS	2539	1231	**−0.0394 ± 0.0136****	**−0.022 ± 0.00832****	**−0.043 ± 0.0137****	**−0.0196 ± 0.00841***	**−0.00156 ± 0.000869#**	**−0.0392 ± 0.0136****	**−0.0234 ± 0.00874****	−0.00041 ± 0.000801
RS	9516	4831	**−0.0451 ± 0.00577*****	−0.00156 ± 0.00514	**−0.0402 ± 0.0074*****	−0.00141 ± 0.00514	−0.000558 ± 0.00053	**−0.0451 ± 0.00577*****	0.00531 ± 0.00866	−0.000818 ± 0.000828
VLT recall Z-score										
DCS	11,877	4606	**−0.0257 ± 0.00721*****	**−0.0177 ± 0.00602****	**−0.0327 ± 0.00803*****	**−0.0168 ± 0.00604****	**−0.00121 ± 0.000613***	**−0.0259 ± 0.00721*****	**−0.0144 ± 0.00659***	0.000908 ± 0.000743
LASA	7453	2204	**-0.0347 ± 0.00891*****	-0.00208 ± 0.007	**-0.0402 ± 0.00973*****	-0.0028 ± 0.00702	0.00106 ± 0.000748	**-0.0346 ± 0.00891*****	0.00278 ± 0.00918	-0.000665 ± 0.000812
MAAS	2521	1228	**−0.0329 ± 0.0144***	−0.019 ± 0.0134	**−0.0344 ± 0.015***	−0.0185 ± 0.0135	−0.000386 ± 0.00116	**−0.0327 ± 0.0144***	−0.0203 ± 0.0141	−0.000381 ± 0.00128
RS	9053	4755	**−0.0299 ± 0.00628*****	−0.00942 ± 0.00732	**−0.0273 ± 0.00861****	−0.00934 ± 0.00732	−0.00031 ± 0.000698	**−0.0299 ± 0.00628*****	−0.00794 ± 0.0123	−0.000174 ± 0.00116
Fluency Z-score										
DCS	11,929	4622	**−0.0204 ± 0.00699****	−0.00567 ± 0.00628	**−0.023 ± 0.00763****	−0.00528 ± 0.0063	−0.000509 ± 0.00061	**−0.0202 ± 0.00699****	−0.00855 ± 0.00685	−0.000818 ± 0.000773
LASA	2499	1141	**-0.0332 ± 0.0117****	-0.00588 ± 0.0152	-0.0292 ± 0.0196	-0.00582 ± 0.0152	-0.000376 ± 0.00149	**-0.0333 ± 0.0117****	-0.0377 ± 0.0315	0.00279 ± 0.00243
RS	9520	4836	**−0.0267 ± 0.00625*****	0.00388 ± 0.00709	−0.0119 ± 0.00869	0.00421 ± 0.00709	**−0.00167 ± 0.000679***	**−0.0267 ± 0.00625*****	0.00277 ± 0.012	0.000128 ± 0.00111

Table subscript: Hybrid mixed models were fit with a random intercept for person and a random slope for age. The mean LIBRA score is a person's mean LIBRA score across time, and LIBRA deviations are person-specific changes in LIBRA score relative to their mean LIBRA over time. These predictors were modelled concomitantly with cognitive scores (without lag). Age terms in the model were centered at 65 years. LIBRA between estimates were derived from the term for average LIBRA score, and within estimates from the term for change in LIBRA score. *, p-value < 0.05; **, p-value < 0.01; ***, p-value < 0.001; #, p-value < 0.1 (interactions only).

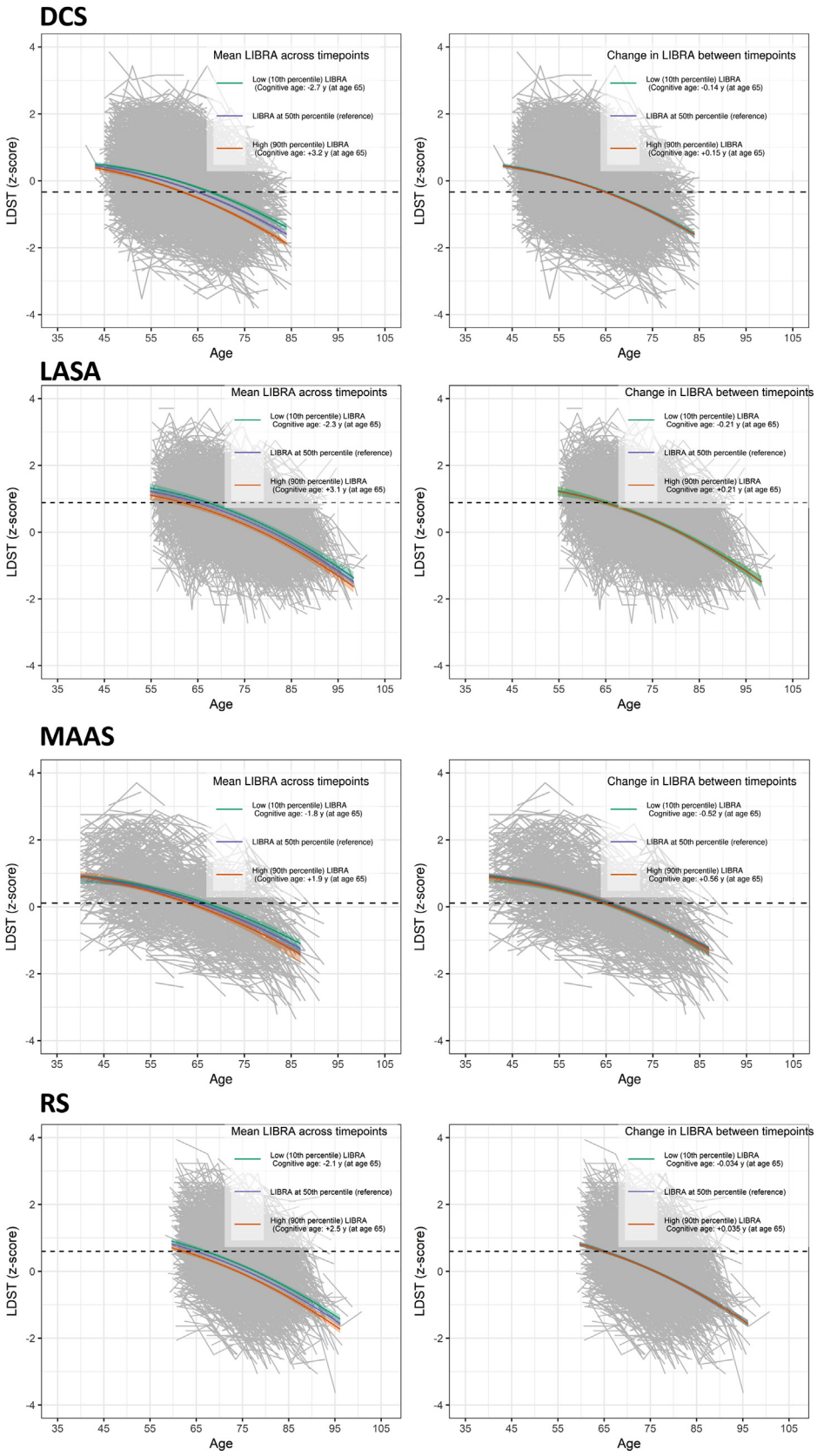

Fig. 2. Effect of average LIBRA score and change in LIBRA score on age-related decline in LDST scores.

Figure subscript: Prediction lines of age-related decline in LDST scores are shown for different levels of the mean LIBRA score (left) and change in LIBRA score (right): the 10th percentile for a low mean LIBRA score, 90th percentile for a high mean LIBRA score, and 50th percentile as reference, keeping all other parameters constant. The dashed horizontal line indicates the reference level of LDST score predicted for 65-year-olds with a 50th percentile of the mean LIBRA score or change in LIBRA score. The difference in cognitive age is estimated by determining the age at which individuals with high or low LIBRA score reach the same LDST score as the reference group. Prediction lines for the change in LIBRA score overlap. Predictions are based on model 2, which includes age, quadratic age, sex, mean LIBRA score, the number of (re)tests, education, cohort effects (in case of RS and LASA), and an interaction of the mean LIBRA score with age. 95 % confidence intervals were calculated using parametric bootstrapping of model residuals.

Abbreviations: DCS, Doetinchem Cohort Study; LASA, Longitudinal Aging Study Amsterdam; MAAS, Maastricht Aging Study; RS, Rotterdam Study.

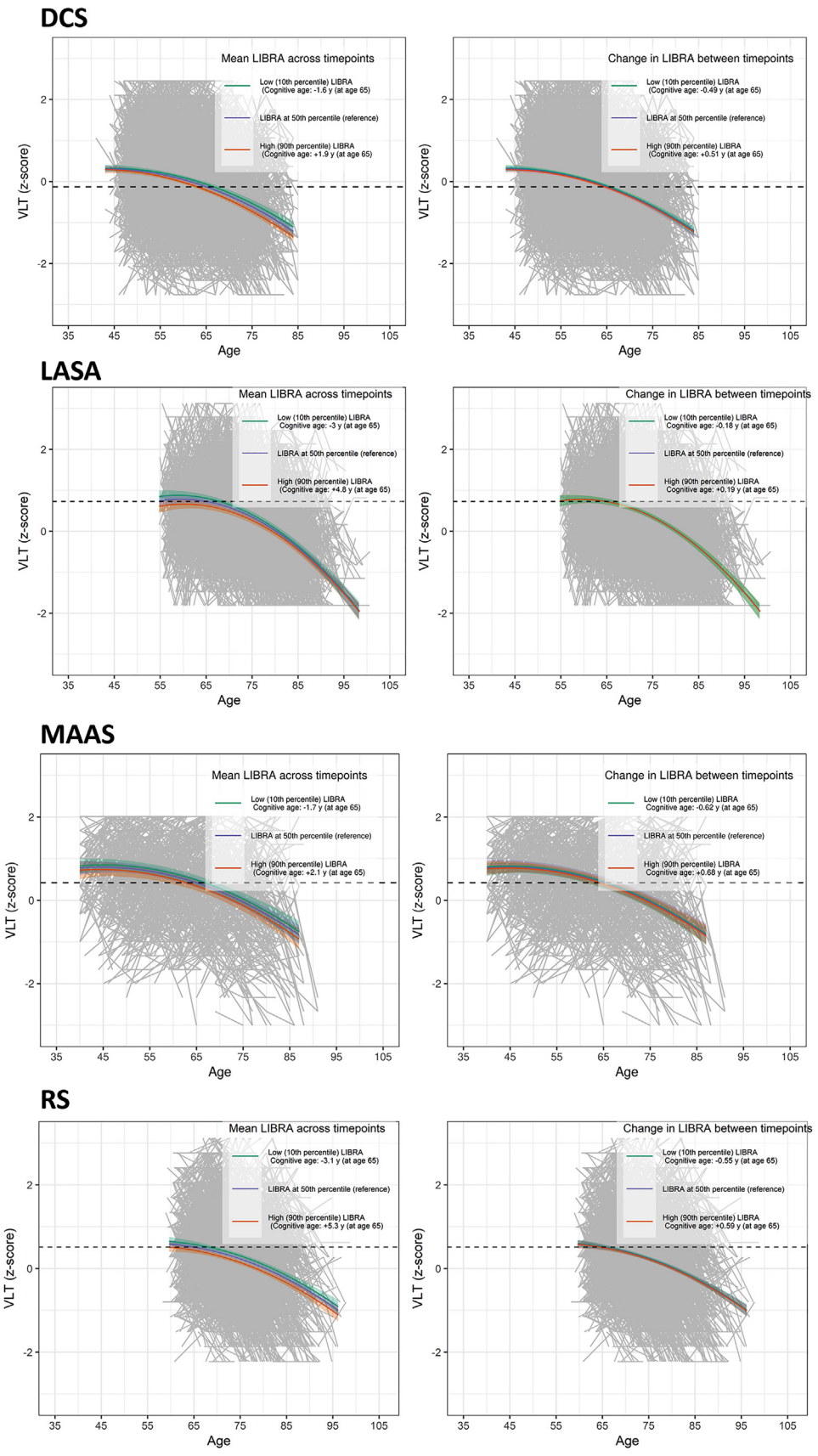

Fig. 3. Effect of average LIBRA score and change in LIBRA score on age-related decline in VLT scores.

Figure subscript: Prediction lines of age-related decline in VLT scores are shown for different levels of the mean LIBRA score (left) and change in LIBRA score (right): the 10th percentile for a low mean LIBRA score, 90th percentile for a high mean LIBRA score, and 50th percentile as reference, keeping all other parameters constant. The dashed horizontal line indicates the reference level of VLT score predicted for 65-year-olds with a 50th percentile of the mean LIBRA score or change in LIBRA score. The difference in cognitive age is estimated by determining the age at which individuals with high or low LIBRA score reach the same VLT score as the reference group. Prediction lines for the change in LIBRA score overlap. Predictions are based on model 2, which includes age, quadratic age, sex, mean LIBRA score, the number of (re)tests, education, cohort effects (in case of RS and LASA), and an interaction of the mean LIBRA score with age. 95 % confidence intervals were calculated using parametric bootstrapping of model residuals.

Abbreviations: DCS, Doetinchem Cohort Study; LASA, Longitudinal Aging Study Amsterdam; MAAS, Maastricht Aging Study; RS, Rotterdam Study.

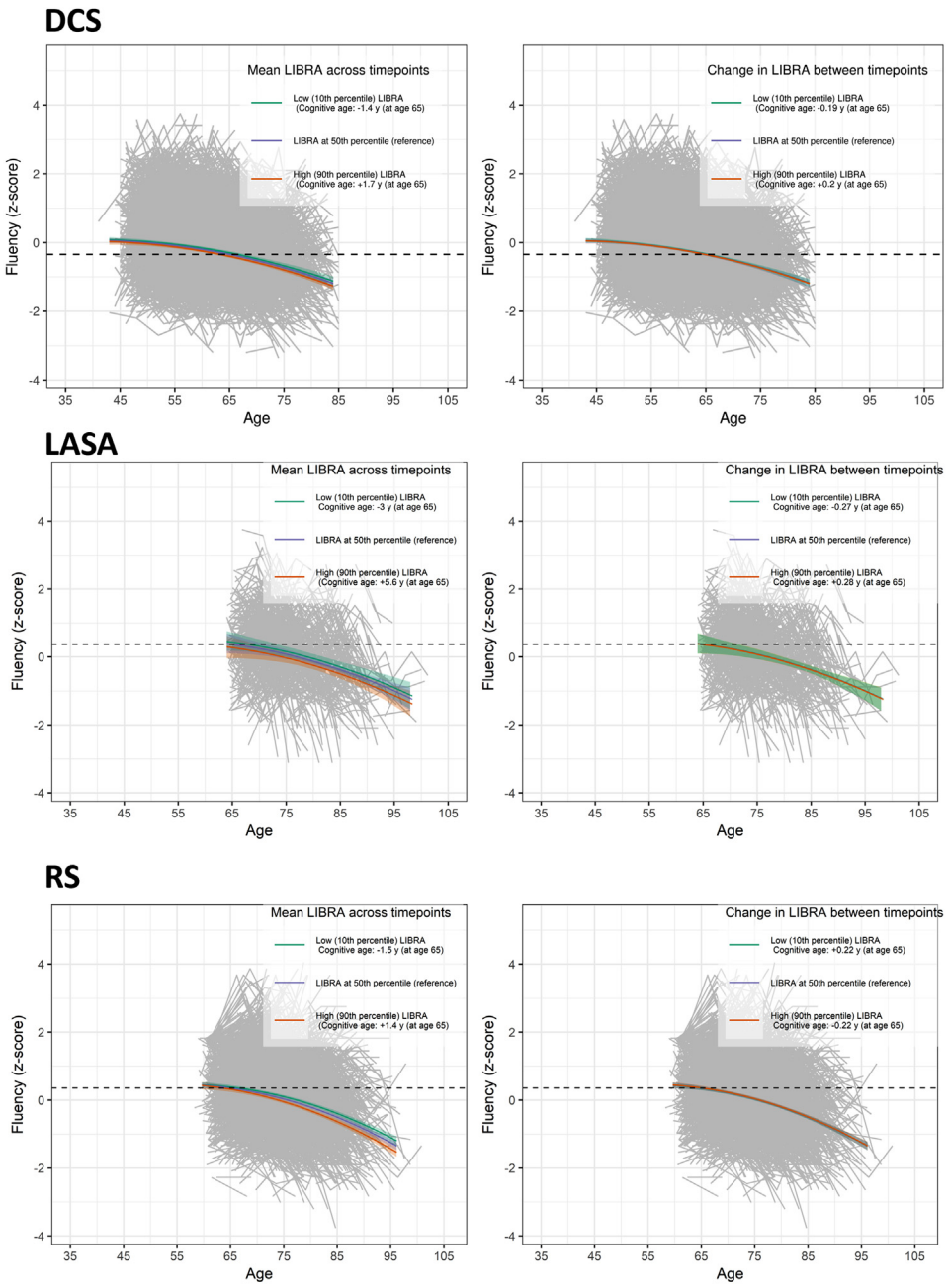

Fig. 4. Effect of average LIBRA score and change in LIBRA score on age-related decline in fluency scores.

Figure subscript: Prediction lines of age-related decline in fluency scores are shown for different levels of the mean LIBRA score (left) and change in LIBRA score (right): the 10th percentile for a low mean LIBRA score, 90th percentile for a high mean LIBRA score, and 50th percentile as reference, keeping all other parameters constant. The dashed horizontal line indicates the reference level of fluency score predicted for 65-year-olds with a 50th percentile of the mean LIBRA score or change in LIBRA score. The difference in cognitive age is estimated by determining the age at which individuals with high or low LIBRA score reach the same fluency score as the reference group. Prediction lines for the change in LIBRA score overlap. Predictions are based on model 2, which includes age, quadratic age, sex, mean LIBRA score, the number of (re)tests, education, cohort effects (in case of RS and LASA), and an interaction of the mean LIBRA score with age. 95 % confidence intervals were calculated using parametric bootstrapping of model residuals.

Abbreviations: DCS, Doetinchem Cohort Study; LASA, Longitudinal Aging Study Amsterdam; MAAS, Maastricht Aging Study; RS, Rotterdam Study.

LIBRA scores are longitudinally associated with cognitive scores. One study investigated baseline LIBRA scores with longitudinal cognitive scores in data from the Wisconsin Registry for Alzheimer's Prevention. They found that baseline LIBRA scores were longitudinally associated with cognitive function, regardless of APOE-e4 status or amyloid positivity[26]. In a French cohort followed for up to 17 years, worse baseline LIBRA scores were associated with worse global cognition at baseline[27]. Another study investigating a New Zealand cohort reported that baseline LIBRA scores were longitudinally associated with cognitive scores over 2 years of follow-up[28]. Overall, these previous studies have reported that (mostly baseline values of) the LIBRA score are longitudinally associated with cognitive scores, which is mostly in line with our findings. We extend upon previous studies of associations of the LIBRA score with cognitive scores by separating between-person and within-person effects. Of note, one study investigated between- and within-person effects of single lifestyle factors (i.e., BMI, waist-hip ratio, diet and physical activity) on cognition across 5 years of follow-up [29]. Our results are largely in line with this study, as they also reported stronger between-person than within-person effects on cognitive scores. These results could suggest that comparing individuals, having on average a better or worse lifestyle may have a stronger effect on cognition than changing lifestyle behaviors within individuals. However, this study looked at a few single lifestyle factors, so research on the combined effect of risk scores incorporating multiple modifiable factors for dementia, such as the LIBRA score, are needed. Even though we observed the association of between-person differences in LIBRA scores and cognition robustly across cohorts, the question remains how to interpret these findings. With the available data, we cannot establish whether the associations of the between-persons effect reflect the effect of long-term lifestyle behaviors (longer 'exposure' to healthy or unhealthy lifestyle which may have more impact than changes over a shorter period), or residual confounding, without additional long-term studies that follow individuals' lifestyle and cognition over time with detailed information on confounding factors.

4.2. Interactions of the between-persons effect with age

We observed that the between-persons effect, but not the within-persons effect of LIBRA scores on cognitive scores over time was stronger with older age for several cognitive scores with older age, particularly for LDST (in 2/4 cohorts), with less evidence for VLT recall and fluency (both only in 1/4 cohorts, Table 1, Model 2). This implies that for some cognitive outcomes (although with heterogeneity depending on the cohort), worse LIBRA scores were also associated with faster age-related cognitive decline. This could be because we included relatively young individuals in our study – i.e., individuals in their forties and fifties, where cognition in most remains relatively stable. However, when we restricted our analyses to older individuals (60- to 85-year-olds), results were similar to those across the entire age range, arguing against this possibility. An alternative and more speculative explanation could be that cognitive health is more sensitive to the effects of lifestyle at some life stages than others. This is in line with the model presented by Livingston [2], in which at different life stages, distinct modifiable factors are related to later developing dementia (e.g., midlife hypertension, vs. late-life social isolation). Comparing the literature, some previous studies also reported that LIBRA scores were associated with a faster cognitive decline: in one study, less worsening of LIBRA scores over time was associated with slower episodic memory decline, but this occurred only in participants who were aged 60+ and not in those aged 40+ at baseline[30]. In individuals followed up to 17 years, worse baseline LIBRA scores were also associated with a faster global cognitive decline[27]. Another study with a 2-year follow-up period found that baseline LIBRA scores were not associated with a faster cognitive decline, which may have been due in part to the relatively short follow-up period[28]. Regarding the heterogeneity in our results for the interactions of between-persons effects with age for different cognitive tests, most interactions of average LIBRA scores with age were observed in DCS (LDST and VLT Z-scores), with the remainder in MAAS (LDST Z-score) and RS (Fluency Z-score). A potential explanation of this heterogeneity relates to the different age distributions between cohorts (with LASA and RS having on average older included ages), as there is evidence that LIBRA scores may be less suitable in those aged 75+ [31]. Alternatively, it may be related to the different LIBRA score distributions (with worse baseline LIBRA scores in LASA and RS, reducing the potential for worsening of the scores in these cohorts).

4.3. Mechanisms and timing of lifestyle's impact on cognition

There are several potential explanations for why lifestyle change was not associated with cognitive scores in our study, one of which relates to the mechanism of how lifestyle influences cognition. It is possible that the strongest influence of lifestyle factors on cognition already occurred before the observations in our data began. For example, research in the UK Biobank shows that poorer early-life environments were associated with worse later-life cognition [32]. There is evidence that some lifestyle factors impact cognition and particularly the build-up of cognitive reserve already in childhood and adolescence, such as a healthy diet, physical activity and education (reviewed more extensively elsewhere [33]). These early-life impacts and changes during this period could be important, but as our cohorts start mostly from middle age onwards, this part of lifestyle's effect on cognition is outside our view.

4.4. Methodological explanations of the lack of within-person effects on cognition

Other possible explanations of the lack of within-person effects of LIBRA scores on cognitive scores relate to methodological issues, both with regard to our study population and to difficulties with capturing change well. First, because we used general population cohorts, very few individuals had very poor LIBRA scores or low cognitive scores. It is possible that the effects of changes in LIBRA scores are restricted to individuals with very poor lifestyle or other forms of increased risk (e.g., due to a family history of dementia). For example, our finding seems to contradict the FINGER trial, a 2-year multidomain lifestyle intervention trial for prevention of dementia which found that improving lifestyle was associated with a subtle improvement in cognition. However, this trial included individuals with an increased dementia risk due to below-average baseline cognitive scores or lifestyle, which may therefore be more likely to demonstrate improvements in cognitive scores in middle- and old-aged individuals [34], and improving LIBRA scores [35]. Our analyses should be repeated in population representative individuals with poorer lifestyle scores to test whether changing the LIBRA score has more effect in this group.

Second, the dynamics of within-individual changes over time may make it difficult to capture the effects of lifestyle changes on cognition. In our study, the majority of individuals have changing LIBRA scores over time, with a large proportion changing multiple times across the study duration (Supplementary Table A.6). The effect of such highly time-variant lifestyle behaviors on cognition may be difficult to determine, especially when scores fluctuate around an average, and different modeling approaches may be needed (perhaps capturing changes over longer periods of time). Future studies could investigate the associations with different models that, rather than change between timepoints, reflect change across the entire follow-up period, e.g., to test if those who have a stable trajectory, worsen or improve in LIBRA scores across the entire follow-up period differ in cognitive trajectories.

Third, it is possible that the within-person effect, capturing changes in LIBRA scores over time, is more sensitive to effects of attrition bias than the between-person effect, capturing the mean effect over time. This may have attenuated the within-person effects.

Fourth, the LIBRA score may not yet be optimal to capture change. In part, this may be because we were unable to include the modifiable factors diet and high cognitive activity into the LIBRA score, because of limited data availability in our cohorts. It is possible that the excluded protective factors diet and high cognitive activity could have influenced the results. There is evidence that diet and various cognitive activities are associated with cognitive outcomes (such as dementia, mild cognitive impairment and change in cognitive performance), as shown in an umbrella review, albeit with heterogeneous results (68 % of consistent results between meta-analyses and systematic reviews for high cognitive activity and 56 % for diet)[36]. In the future, this may be addressed by follow-up studies that collect the LIBRA score with as many components as possible. Another issue is that not all components in the LIBRA score are equally subject to change: e.g., physical activity is highly variable [37,38] whereas smoking behavior is largely stable [37,38]. For some components, there is also discussion whether they are modifiable [36], and it has been argued that the LIBRA score contains several factors that once present are irreversible [39] (e.g., history of cardiovascular disease). Additionally, as the components are dichotomous, not all changes within the measured components are captured, e.g., large changes further away from the cutoff may be invisible but could still be relevant for influencing cognition[39]. Modified and improved versions of the LIBRA score may be needed. Recently, three novel components (hearing impairment, social contact and sleep) were added to an updated version of the LIBRA score [36]. In follow-up studies, modified versions of the LIBRA score should be constructed based on novel risk and protective factors as new evidence emerges, while also incorporating either smaller change categories or using continuous LIBRA scores (as e.g. in [39]), to test whether these modified LIBRA scores have an improved capacity to capture the change in cognitive scores over time.

4.5. LIBRA score as a surrogate marker for dementia in clinical trials

The LIBRA score has been proposed as a potential surrogate marker for developing dementia in lifestyle trials, although it remains unknown whether the LIBRA score is optimally suited for this. The LIBRA score has been included in several trials including non-demented individuals

who are at risk of cognitive decline (i.e., FINGER, MAPT, preDIVA and HATICE)[35,39]. The intervention led to (slight) reductions in LIBRA score in some of these trials (preDIVA [39] and FINGER [35], but not in MAPT or HATICE [39]). To be used as a surrogate marker for dementia in lifestyle trials, it was also necessary to investigate whether changes in the LIBRA score result in changes in cognition over time. Because we found no consistent associations of changes in LIBRA score with changes in cognition, our results do not lend support to the use of the current version of the LIBRA score as a surrogate marker of dementia risk, especially for lifestyle trials targeting the general population.

Limitations of our study are that not all LIBRA components could be determined in all cohorts, and that operationalization differed despite efforts to harmonize. Our study also suffers from common limitations of cohort studies – selection bias as individuals who participate are often healthier than the general population, and survival bias because healthier individuals remain longer in the cohort. The included cohorts have relatively few participants who belong to the lowest income or non-Dutch ancestry groups, potentially limiting the generalizability of our results, and our analyses should be repeated in cohorts where these groups are better represented. Strengths are that we performed analyses in four longitudinal cohort studies with long follow-up to test the robustness of our findings, and that we used a methodology to distinguish between- and within-person effects of the LIBRA score on cognition.

4.6. Conclusion

In conclusion, in the general population, we studied the associations of LIBRA scores based on up to ten modifiable components with cognition over time. We found that individuals with worse LIBRA scores showed poorer cognitive function, while no consistent associations were found between *changes in* LIBRA scores with changes in cognitive scores. In the general population, the investigated version of the LIBRA score is possibly not suitable to capture how cognition (as a proxy for dementia risk) changes with improvements in lifestyle.

Data availability

The analyzed datasets are not publicly available due to restrictions related to the informed consent of study participants.

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.

CRediT authorship contribution statement

KEJ Wesenhagen: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **K Deckers:** Resources. **HSJ Picavet:** Resources. **ML Rietman:** Data curation. **AAL Kok:** Supervision. **S Köhler:** Resources. **MA Ikram:** Resources. **FJ Wolters:** Resources, Data curation. **M Huisman:** Supervision, Project administration. **WMM Verschuren:** Supervision, Project administration, Resources.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100159.

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