Abstract

Background and Objectives

Self-reflection (the active evaluation of ones thoughts, feelings and behaviours) can confer protection against adverse health outcomes. Its impact on markers sensitive to Alzheimer's disease (AD), however, is unknown. The primary objective of this cross-sectional study was to examine the association between self-reflection and AD-sensitive markers.

Methods

This study utilised baseline data from cognitively unimpaired older adults enrolled in the Age-Well clinical trial and older adults with subjective cognitive decline from the SCD-Well clinical trial. In both cohorts, self-reflection was measured via the reflective pondering subscale of the Rumination Response Scale, global cognition assessed via the Preclinical Alzheimer's Cognitive Composite 5, and a modified late-life Lifestyle-for-Brain-Health (LIBRA) index computed to assess health and lifestyle factors. In Age-Well, glucose metabolism and amyloid deposition were quantified in AD-sensitive grey matter regions via FDG- and AV45-PET scans, respectively. Associations between self-reflection and AD-sensitive markers (global cognition, glucose metabolism, and amyloid deposition) were assessed via unadjusted and adjusted regressions. Further, we explored whether associations were independent of health and lifestyle factors. To control for multiple comparisons in Age-Well, false discovery rate corrected *p*-values (p_{FDR}) are reported.

Results

A total of 134 (mean age 69.3 ± 3.8 years, 61.9% female) Age-Well and 125 (mean age 72.6 ± 6.9 years, 65.6% female) SCD-Well participants were included. Across unadjusted and adjusted analyses self-reflection was positively associated with global cognition in both cohorts (Age-Well: adjusted-β = 0.22, 95% confidence interval [CI] 0.05-0.40, p_{FDR} = 0.041; SCD-Well: adjusted-β = 0.18, 95% CI 0.03-0.33, p = 0.023) and with glucose metabolism in Age-Well after adjustment for all covariates (adjusted-β = 0.29, 95% CI 0.03-0.55, p_{FDR} =

0.041). Associations remained following additional adjustment for LIBRA but did not survive FDR correction. Self-reflection was not associated with amyloid deposition (adjusted-β = 0.13, 95% CI -0.07-0.34, p_{FDR} = 0.189).

Discussion

Self-reflection was associated with better global cognition in two independent cohorts and with higher glucose metabolism after adjustment for covariates. There was weak evidence that relationships were independent from health and lifestyle behaviours. Longitudinal and experimental studies are warranted to elucidate whether self-reflection helps preserve cognition and glucose metabolism, or whether reduced capacity to self-reflect is a harbinger of cognitive decline and glucose hypometabolism.

Trial Registration

Age-Well: NCT02977819; SCD-Well: NCT03005652.

Introduction

Alzheimer's disease (AD) has an extended preclinical phase whereby subtle changes in brain pathology and cognitive function occur decades before the clinical onset (1). In the absence of effective disease-modifying treatments, attention has shifted towards identifying risk and protective factors that might hasten or delay future AD.

Several studies have identified modifiable risk and protective factors for AD, with up to 40% of cases being attributable to modifiable factors (2,3). However, despite evidence pointing towards the importance of psychological factors in healthy ageing (4), relatively few studies have explored associations between modifiable psychological characteristics and AD risk. Existing research in this nascent field has primarily focussed upon negative psychological factors (eg, depression (5,6), anxiety (7), neuroticism (8)); but evidence suggests that some psychological characteristics may confer protection against AD. For example, purpose in life (9) and the personality characteristic conscientiousness (10) have been associated with markedly reduced AD incidence. Novel neuroimaging and clinicopathologic findings have demonstrated that purpose in life (11) and conscientiousness (12), amongst other psychological characteristics (eg, resilience to stress (13), optimism (14), trait mindfulness (15)), may bestow protective benefit. Specifically, higher levels of conscientiousness and trait mindfulness and greater resilience to stress have been associated with less amyloid deposition and/or tau aggregation (10,13,15). Further, although purpose in life has not been directly associated with AD pathology, it has been found to modify the association between a global measure of AD pathologic changes and cognition, with individuals reporting higher levels of purpose in life exhibiting better cognition despite greater AD pathology (11). Extant evidence therefore indicates that benefits of positive styles of thinking may be conferred by either reducing the deleterious effects of AD pathological changes on cognitive abilities (ie, resilience) or via the avoidance of pathology in the first place (ie, resistance) (16).

Self-reflection, the active evaluation of one's thoughts, feelings, and behaviours, is an introspective cognitive mechanism related to many positive psychological characteristics,

including purpose in life (11) and resilience to stress (17). Despite some conflicting evidence (eg, positive associations with depression and brooding (18)), self-reflection is primarily considered an adaptive characteristic, whereby engagement encourages awareness and evaluation of one's stress response (19). Indeed, studies have demonstrated that adopting a self-reflective thinking style yields more adaptive stress responses, that in turn lead to better short-term and longer-term biological and psychological outcomes (19). For instance, emerging evidence links self-reflection with reduced inflammatory responses to acute psychological stressors (eg, interleukin-6, cortisol) (17,20), better cardiovascular health (eg, reduced heart rate variability) (21) and improved mental health (eg, recovery from major depressive disorder) (22,23). Further, self-reflection has been associated with positive lifestyle factors, including greater engagement in health promoting behaviours (eg, lower alcohol consumption, greater physical exercise) (23,24) and high openness to experience (19), which is posited to promote more frequent and intensive engagement in stimulating leisure activities.

Despite evidence that self-reflection can confer protection against adverse health outcomes, the association between self-reflection and AD-sensitive markers is unknown. To address this gap, we sought to: (i) determine the association between self-reflection and cognition and brain health; and (ii) explore whether any associations between self-reflection and AD-sensitive markers are independent of health and lifestyle factors.

Methods

Participants

Age-Well

Baseline data from 134 cognitively unimpaired older adults enrolled in the Age-Well randomised clinical trial, who completed an assessment of self-reflection, were included. All participants were recruited from the general population, aged 65 or older, native French speakers, retired for at least 1 year, received at least 7 years of education, had no evidence

of major neurological or psychiatric disorders, and performed within normal ranges on standardised cognitive tests. Detailed eligibility criteria have been previously described (26).

SCD-Well

Baseline data from 125 older adults enrolled in the SCD-Well randomised clinical trial, who completed an assessment of self-reflection, were included. Participants were recruited through memory clinics at four European centres (London, UK; Lyon, France; Cologne, Germany; and Barcelona, Spain), met published criteria for subjective cognitive decline (ie, self-perceived decline in cognitive capacity but normal performance on standardised cognitive tests used to classify mild cognitive impairment or prodromal AD (27)), were aged 60 or older, and had no evidence of major neurological or psychiatric disorders. Further eligibility criteria are reported elsewhere (28).

In both cohorts, age, sex, years of education, and country of residence were obtained from participants at baseline. In Age-Well, participants also provided a blood sample for APOE genotyping (see eMethods in the Supplement), with ε4 carriers collapsed into one category.

Standard Protocol Approvals, Registrations, and Patient Consents

Both trials were approved by local ethics committees and were registered on ClinicalTrials.gov (Age-Well: NCT02977819; SCD-Well: NCT03005652). All participants provided written informed consent prior to participation.

Behavioural Measures

Self-reflection

Participants completed the full 22-item Rumination Response Scale (RRS), with scores from the 5-item reflective pondering subscale used to assess self-reflection levels (22). A 4-point Likert scale ranging from 1 (*almost never*) to 4 (*almost always*) was used for each item. Item scores were summed to yield a total score for each participant (possible range: 5 – 20), with higher scores indicating greater self-reflection levels. The RRS is widely used in clinical

psychology and psychopathology research (29), has previously been administered to older adult populations, and has displayed adequate psychometric properties (22,30).

Psychological Distress

Brooding (ie, passive and judgmental thoughts about one's mood) was assessed via the brooding subscale of the RRS (possible range: 5 – 20) (22). Depressive symptoms were measured using the Geriatric Depression Scale (possible range: 0 – 15) (31).

Health and Lifestyle

The late-life 'Lifestyle-for-Brain-health' (LIBRA) composite (32) is a poly-environmental risk score for cognitive functioning and dementia risk (33). It typically comprises 10 health and lifestyle factors (ie, depression, coronary heart disease, diabetes, hypercholesterolemia, smoking, physical inactivity, renal disease, low-to-moderate alcohol use, high cognitive activity, and healthy diet), which receive weights based on their relative risk (34). Self-reflection is commonly confounded with psychological distress (35); we therefore removed depression and calculated a nine-item modified LIBRA index (34), so analyses could be adjusted for psychological distress (ie, depression and brooding; see above). In both cohorts, weights of the remaining nine factors were summed to yield LIBRA scores (possible range: −5.9 – 7.4), with higher scores indicating poorer health and lifestyle behaviours. See eTable1 in the Supplement for detailed definitions and weights attributed to each factor.

Cognition

The Preclinical Alzheimer's Cognitive Composite 5 (PACC5) is a validated global cognitive composite sensitive to detecting and tracking pre-clinical AD-related decline (36). The PACC5 includes two measures of episodic memory and executive function, and one measure of global cognition. In Age-Well, all measures were available. SCD-Well only had four (a single measure of episodic memory), therefore an abridged version of the PACC5 ($PACC5_{Abridged}$) was created. The specific measures included in the PACC5/ $PACC5_{Abridged}$ are provided in Table1. Briefly, PACC5/$PACC5_{Abridged}$ scores were computed in Age-Well and

SCD-Well separately by converting each measure into a z-score and then taking the unweighted average (see eMethods in the Supplement for further details).

Neuroimaging Measures

Age-Well participants were scanned at the Cyceron Center (Caen, France) on the same PET (Discovery RX VCT 64 PET-CT; General Electric Healthcare) and MRI (Philips Achieva 3.0T scanner; used for PET pre-processing only) scanners. Detailed acquisition and pre-processing procedures have previously been published and are available in the eMethods in the Supplement (26).

Participants (N=131) underwent a florbetapir (AV45, Amyvid) PET scan to assess amyloid deposition, and a subset (N=92) also underwent an FDG (Glucotep) PET scan to assess brain glucose metabolism. Standard uptake value ratios (SUVR) were obtained from a pre-determined AD-sensitive neocortical mask for amyloid burden and the temporo-parietal regions for FDG-PET, as previously defined (37) (see also eMethods in the Supplement). FDG-PET analyses only were performed on images corrected for partial volume effects using the 3-compartmental voxelwise Müller-Gartner method (38).

Statistical Analyses

Differences between cohorts and the associations between self-reflection and potential confounds (ie, demographic characteristics and psychological distress) were investigated. Non-parametric tests (ie, Spearman's rho and Kruskal-Wallis) were utilised where data were not normally distributed.

To determine associations between self-reflection and AD-sensitive markers, we performed a series of linear regression models with each marker as the dependent variable (ie, global cognition, glucose metabolism and amyloid deposition), in Age-Well and SCD-Well separately. Model-1 was unadjusted, model-2 was adjusted for relevant demographic characteristics (ie, age, sex, education and [in SCD-Well] country of residence), and model-3

was adjusted for demographic characteristics and psychological distress (ie, depressive symptoms and brooding levels). For analyses where glucose metabolism and amyloid deposition were the dependent variables, APOE ε4 status was also included as a covariate in models-2 and -3.

In exploratory analyses we tested whether the presence of amyloid pathology altered associations between self-reflection and global cognition and glucose metabolism by including a self-reflection-by-amyloid deposition interaction. Further, in Age-Well where APOE data was available, we included APOE ε4 status as an additional covariate in models-2 and -3, when assessing the association between self-reflection and cognition.

Finally, to explore the potential mechanism linking self-reflection with AD-sensitive markers, we examined the relationship between self-reflection and LIBRA in a series of unadjusted and adjusted regressions (ie, model-1, -2, and -3). In further exploratory analyses, LIBRA was then added as an additional covariate in analyses investigating associations between self-reflection and each AD-sensitive marker (ie, model-4: demographic characteristics, psychological distress, and LIBRA).

There is an ongoing debate surrounding the utility of correcting for multiple comparisons (39,40). We therefore report the number of analyses performed and provide both unadjusted and adjusted p-values to facilitate interpretations regarding the strength of evidence. Specifically, Benjamini-Hochberg adjusted p-values, which control the false discovery rate (FDR), are reported for the Age-Well analyses. All analyses were conducted using R, version 4.0.2, and used 2-tailed hypothesis tests with $\alpha = .05$.

Data Availability

The Age-Well and SCD-Well study protocols, including summary statistical analysis plans, have previously been published (26,28). The Material can be mobilized, under the conditions and modalities defined in the Medit-Ageing Charter by any research team belonging to an Academic, for carrying out a scientific research project relating to the scientific theme of

mental health and well-being in older people. The Material may also be mobilized by non-academic third parties, under conditions, in particular financial, which will be established by separate agreement between Inserm and the said third party.

Results

Participant Characteristics

Demographic characteristics for each cohort are provided in Table 2. Participants in Age-Well were younger (W = 6016, $P < 0.001$), had better cognition (t[264.70] = 5.07, $P < 0.001$), and lower levels of brooding (W = 7190, $P = 0.047$) relative to SCD-Well participants. In both cohorts, self-reflection was positively associated with brooding levels (Age-Well: $r_s[134] = 0.49$, $P < 0.001$; SCD-Well: $r_s[125] = 0.36$, $P < 0.001$) and depressive symptoms (Age-Well: $r_s[134] = 0.22$, $P = 0.011$; SCD-Well: $r_s[125] = 0.21$, $P = 0.021$). Self-reflection was additionally positively associated with age ($r_s[134] = -0.25$, $P = 0.004$) and education ($r_s[134] = 0.19$, $P = 0.027$) in Age-Well, and country of residence (H[3] = 9.81, $P = 0.020$; with levels higher in Germany relative to all the countries) in SCD-Well.

Associations between self-reflection and AD-sensitive markers

Results from the multiple linear regressions between self-reflection and AD-sensitive markers are presented in Figure 1 and Table 3, and described below.

Global Cognition

In Age-Well, self-reflection was positively associated with PACC5 in the unadjusted model (model-1: standardised estimate = 0.28, 95% CI 0.12 to 0.45, $P = <0.001$; $P_{FDR} = 0.003$), and following adjustment for demographic characteristics (model-2: standardised estimate = 0.16, 95% CI 0.00 to 0.32, $P = 0.044$; $P_{FDR} = 0.111$); although the latter association did not survive multiple comparison correction. Following additional adjustment for psychological distress, a positive association, which survived multiple comparison correction, was observed (model-3: standardised estimate = 0.22, 95% CI 0.05 to 0.40, $P = 0.014$, P_{FDR} =

0.041). There was no evidence that psychological distress levels were associated with global cognition (*P's* > 0.25; eTable2 in the Supplement). In exploratory analyses neither the inclusion of APOE ε4 status as an additional covariate or a self-reflection-by-amyloid deposition interaction affected results (eTable3 in the Supplement).

The associations between self-reflection and global cognition were replicated in SCD-Well. Specifically, self-reflection was positively associated with $PACC5_{Abridged}$ in unadjusted (model-1: standardised estimate = 0.23, 95% CI 0.05 to 0.40, *P* = 0.012) and adjusted analyses (model-2: standardised estimate = 0.15, 95% CI 0.01 to 0.29, *P* = 0.042; model-3: standardised estimate = 0.18, 95% CI 0.03 to 0.33, *P* = 0.023). Further, there was no evidence that psychological distress levels contributed to model-3 (*P's* > 0.17; see eTable2 in the Supplement).

Brain Glucose Metabolism

There was no evidence of an association between self-reflection and glucose metabolism in either the unadjusted model or the model adjusted for demographic characteristics (*P's* > 0.101). However, following adjustment for psychological distress, a positive relationship between self-reflection and glucose metabolism emerged (model-3: standardised estimate = 0.29, 95% CI 0.03 to 0.55, *P* = 0.027, P_{FDR} = 0.041). Whilst there was no evidence that depressive symptoms contributed to the model, brooding was negatively associated with glucose metabolism (standardised estimate = -0.26, 95% CI -0.51 to -0.01, *P* = 0.045 [eTable 2 in the Supplement]). The association between brooding and glucose metabolism, however, did not survive correction for multiple comparisons (P_{FDR} = 0.135). Inclusion of a self-reflection-by-amyloid deposition interaction did not affect results (eTable4).

Amyloid Deposition

We found no evidence of a relationship between self-reflection and amyloid deposition in any analyses (*P's* > 0.10). Results did not change when utilising florbetapir-PET images corrected for partial volume effects.

Health and Lifestyle

In both cohorts, self-reflection was negatively associated with LIBRA in all unadjusted and adjusted analyses (*P's* < 0.02; eTable4 in the Supplement). Inclusion of LIBRA as an additional covariate (model-4; eTable2 in the Supplement) did not alter associations between self-reflection and either global cognition (Age-Well: standardised estimate = 0.21, 95% CI 0.02 to 0.39, *P* = 0.028; SCD-Well: standardised estimate = 0.17, 95% CI 0.01 to 0.32, *P* = 0.033) or glucose metabolism (standardised estimate = 0.27, 95% CI 0.01 to 0.54, *P* = 0.046). Associations in Age-Well, however, did not survive correction for multiple comparisons (global cognition: P_{FDR} = 0.069; glucose metabolism: P_{FDR} = 0.069).

Discussion

The present study examined the relationship between self-reflection and markers sensitive to AD. We found that higher levels of self-reflection were associated with better global cognition in two independent cohorts of cognitively unimpaired older adults. Further, we found evidence of a relationship between self-reflection and glucose metabolism in AD-sensitive neocortical regions. We did not observe associations with amyloid deposition.

Self-reflection has been associated with openness to experience and posited to promote intellectual curiosity, both of which are thought to lead to a lifetime of stimulating activities and learning of new information (41,42). Prior investigations have demonstrated that factors promoting greater lifetime cognitive activity (eg, occupational complexity) and openness to experience can bestow cognitive advantages later in life (43,44). Comparable cognitive advantages have also been reported for positive psychological characteristics, including optimism (14) and trait mindfulness (15). In the present study, self-reflection was associated with better global cognition, as measured via a cognitive composite sensitive to tracking AD-related decline (ie, PACC5) (36). Whilst we propose that engagement in self-reflection helps preserve cognition, the converse relationship must also be acknowledged. Self-reflection

involves high-level cognitive functions (eg, problem-solving), thus individuals with better cognitive ability may be more able to engage in self-reflection.

Self-reflection was also positively associated with brain glucose metabolism. Further, we observed a negative association between brooding and glucose metabolism. This aligns with literature reporting associations between neuropsychiatric symptoms and glucose hypometabolism in cognitively normal older adults (45). Taken together, these opposing associations support the differentiation of self-reflection and brooding as adaptive and maladaptive ruminative styles, respectively (22). To expand, self-reflection (ie, the active evaluation of one's thoughts, feelings, and behaviours), but not brooding (ie, circular, non-purposeful, judgemental thinking), is generally considered adaptive due to its association with increased resilience to stress (46) and markers of good mental health (eg, well-being (47), recovery from depression (23)). However, it is important to note that although extant literature typically supports an adaptive conceptualisation of self-reflection, contrary findings have been reported (eg, associations with greater suicidal ideation) (18). There is currently no clear explanation to account for these conflicting findings, but it seems likely that the relative adaptiveness of self-reflection may depend on other individual state or trait characteristics (eg, depression severity) (41). In particular, research has assessed the impact of brooding on the adaptiveness of self-reflection. Despite being distinct constructs associated with markedly different outcomes, self-reflection and brooding commonly co-occur (18,20,22,41). Notably, engaging in self-reflection has been found to predict brooding (but not vice versa), with previous research suggesting that self-reflection becomes brooding when attempts to find solutions to problems are unsuccessful (41). It has therefore been proposed that a failure to account for brooding in analyses may result in the positive function of self-reflection being masked (22). In agreement with the above, we found that self-reflection and brooding were positively correlated in both cohorts, and a positive association between self-reflection and glucose metabolism was only observed following adjustment for brooding and depressive symptoms (ie, psychological distress). These findings highlight that

the relative adaptiveness of the self-reflective process can be easily hampered in the presence of (even sub-clinical) psychological distress levels. Important avenues for future research include investigating under what circumstances self-reflection turns to brooding, and whether the associations we observed between self-reflection and AD-sensitive markers are present in psychiatric populations.

Notably, in the current study, self-reflection was not related to fibrillar amyloid, as measured by PET imaging. Prior studies have reported complementary findings; for example, whilst purpose in life has been shown to reduce the negative impact of AD pathology on cognition, direct associations with AD pathology (ie, amyloid and tau) have not been observed (11). Interestingly, the ability to find purpose in life and a developed sense of direction requires engagement in self-reflective practices (11,48). Taken together, it is conceivable that, instead of preventing the accumulation of pathologic changes (ie, providing resistance (16)), self-reflection may contribute to the development of efficient neural systems that allow one to maintain cognition even in the face of accumulating amyloid pathology (ie, resilience (16)). Indeed, in our exploratory analyses', associations between self-reflection and global cognition and glucose metabolism remained largely unchanged following inclusion of self-reflection-by-amyloid deposition interactions.

The systematic self-reflection model of resilience-strengthening proposes that everyday stressors are pertinent to the development of resilient capacities when scaffolded in self-reflective practices (19). For example, initial responses to stressors may increase distress levels. However, engagement in self-reflection can facilitate the search for better coping strategies. Upon re-exposure to similar stressors, an individual's resilience, developed through self-reflection, may then promote better psychological and physiological outcomes (19). Although relatively little data is available on the association between self-reflection and physiological outcomes, emerging evidence indicates that self-reflection is associated with important health-related biomarkers. For example, self-reflection has been negatively associated with cortisol (17) and interleukin-6 levels (20) in older adults. Further, self-

reflection has been associated with better cardiovascular health (21), recovery from psychological ill-health (22,23) and healthier lifestyles (25). Stress responses, health and lifestyle factors are associated with AD-risk (2); thus, self-reflection may affect AD-sensitive markers via one of these pathways. To this end, we investigated the association between self-reflection and health and lifestyle behaviours which have been associated with cognitive functioning and AD risk (ie, LIBRA) and in exploratory analyses assessed whether self-reflection affects AD-sensitive markers independently of these behaviours (32,34). Aligning with existing literature, self-reflection was associated with better health and lifestyle behaviours in both cohorts. Interestingly, associations between self-reflection and cognition and glucose metabolism remained even after LIBRA was included as an additional covariate. Self-reflection, however, may affect AD-sensitive markers via other factors (eg, associations with other psychological constructs, stress response, neuroendocrine functions, inflammatory markers), which we were not able to test in the current study. Future studies, powered to conduct mediation analyses, are required to determine whether health and lifestyle behaviours and/or other factors mediate associations between self-reflection and AD-sensitive markers.

Strengths, Limitations and Perspectives

This study has some notable strengths. We replicated the association between self-reflection and global cognition in two independent cohorts of cognitively unimpaired older adults, including one multi-centric study; and additionally characterised these associations using multimodal neuroimaging in the other study. Further, we explored a potential mechanism that might link self-reflection with AD-sensitive markers.

We must also acknowledge the limitations. First, despite replicating findings in two separate cohorts that differed in recruitment population, age, cognition, and brooding levels, the selective nature of the Age-Well and SCD-Well cohorts may limit the generalizability of our findings – participants were highly educated and were screened for the absence of serious

physical and mental illnesses. Research conducted in more diverse samples is therefore required to assess the generalizability of our findings. Further, it would be reasonable to surmise that individuals with higher self-reflection levels would be more likely to participate in clinical trials which include a meditation-based intervention such as Age-Well and SCD-Well. However, self-reflection levels in both cohorts do not appear to be higher than those commonly reported in the literature (49,50). Second, although the association between self-reflection and brain glucose metabolism survived (an albeit liberal) correction for multiple comparisons, the association was assessed in one cohort (ie, Age-Well) only. Further, exploratory analyses in Age-Well assessing whether associations between self-reflection and AD-sensitive markers are independent of health and lifestyle factors did not survive correction. The exploratory analyses in particular should be interpreted cautiously, with studies including larger sample sizes required to confirm (or refute) our findings. Third, whilst we adjusted for a wide array of potential confounders (including psychological distress), other variables (eg, brain atrophy, vascular disease) known to influence our AD-sensitive outcomes were not examined. Finally, the cross-sectional design precludes us from determining causality. For example, while we propose that engagement in self-reflection helps preserve cognitive function and glucose metabolism, the opposite may also be true – preclinical AD alterations and/or symptoms could lead to reduced capacity for self-reflection. Investigations using data from longitudinal cohorts or intervention studies targeting self-reflection would help address this issue. Crucially, evidence suggests that self-reflection is modifiable and that improvement in self-reflection is associated with better health-related outcomes. For example, an intervention designed to promote self-reflection in older adults demonstrated sustained improvements in positive affect, perceived resilience, and physiological stress responses (46). The majority of adults can engage in self-reflection to some degree (eg, irrespective of socio-economic status, physical health); thus, interventions that focus on promoting self-reflection could be conducted in a large swathe of the population and have wide-reaching positive effects. Both Age-Well and SCD-Well are randomised clinical trials that include meditation interventions and comprehensive AD

marker assessments (26,28). Findings from these studies will indicate whether meditation interventions can promote self-reflection and whether greater engagement in self-reflective practices are associated with changes in AD-sensitive markers.

Self-reflection is associated with cognition and brain health, which may provide protection against AD. The identification of factors that protect against or delay the onset of AD may help combat the large and rapidly increasing public health challenge that this disease possesses. Whilst it is not yet known whether promoting self-reflection could reduce AD risk, the findings here indicate that this is an avenue worth exploring.

References

1. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, *et al.* (2011): Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 7: 280–292.
2. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al.* (2020): Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet* 396: 413–446.
3. Silva MVF, Loures C de MG, Alves LCV, de Souza LC, Borges KBG, Carvalho M das G (2019): Alzheimer's disease: risk factors and potentially protective measures. *Journal of Biomedical Science* 26: 33.
4. Steptoe A, Deaton A, Stone AA (2015): Psychological wellbeing, health and ageing. *Lancet* 385: 640–648.
5. Cherbuin N, Kim S, Anstey KJ (2015): Dementia risk estimates associated with measures of depression: a systematic review and meta-analysis. *BMJ Open* 5: e008853.
6. Holmquist S, Nordström A, Nordström P (2020): The association of depression with subsequent dementia diagnosis: A Swedish nationwide cohort study from 1964 to 2016. *PLOS Medicine* 17: e1003016.
7. Gimson A, Schlosser M, Huntley JD, Marchant NL (2018): Support for midlife anxiety diagnosis as an independent risk factor for dementia: a systematic review. *BMJ Open* 8: e019399.
8. Terracciano A, Stephan Y, Luchetti M, Albanese E, Sutin AR (2017): Personality traits and risk of cognitive impairment and dementia. *J Psychiatr Res* 89: 22–27.
9. Sutin AR, Stephan Y, Terracciano A (2018): Psychological well-being and risk of dementia. *International Journal of Geriatric Psychiatry* 33: 743–747.
10. Low L-F, Harrison F, Lackersteen SM (2013): Does Personality Affect Risk for Dementia? A Systematic Review and Meta-Analysis. *The American Journal of Geriatric Psychiatry* 21: 713–728.

11. Boyle PA, Buchman AS, Wilson RS, Yu L, Schneider JA, Bennett DA (2012): Effect of Purpose in Life on the Relation Between Alzheimer Disease Pathologic Changes on Cognitive Function in Advanced Age. *Arch Gen Psychiatry* 69: 499–505.
12. Yoon B, Baker SL, Korman D, Tennant VR, Harrison TM, Landau S, Jagust WJ (2020): Conscientiousness is associated with less amyloid deposition in cognitively normal aging. *Psychol Aging* 35: 993–999.
13. Arenaza-Urquijo EM, Przybelski SA, Machulda MM, Knopman DS, Lowe VJ, Mielke MM, *et al.* (2020): Better stress coping associated with lower tau in amyloid-positive cognitively unimpaired older adults. *Neurology* 94: e1571–e1579.
14. Gawronski KAB, Kim ES, Langa KM, Kubzansky LD (2016): Dispositional Optimism and Incidence of Cognitive Impairment in Older Adults. *Psychosom Med* 78: 819–828.
15. Strikwerda-Brown C, Ozlen H, Pichet Binette A, Chapleau M, Marchant NL, Breitner JCS, Villeneuve S (2022): Trait Mindfulness Is Associated With Less Amyloid, Tau, and Cognitive Decline in Individuals at Risk for Alzheimer's Disease. *Biological Psychiatry Global Open Science*. https://doi.org/10.1016/j.bpsgos.2022.01.001
16. Arenaza-Urquijo EM, Vemuri P (2018): Resistance vs resilience to Alzheimer disease. *Neurology* 90: 695–703.
17. Crane MF, Kangas M, Karin E, Searle B, Chen D (2020): Leveraging the experience of stressors: the role of adaptive systematic self-reflection. *Anxiety, Stress, & Coping* 33: 231–247.
18. Miranda R, Nolen-Hoeksema S (2007): Brooding and reflection: Rumination predicts suicidal ideation at one-year follow up in a community sample. *Behav Res Ther* 45: 3088–3095.
19. Crane MF, Searle BJ, Kangas M, Nwiran Y (2019): How resilience is strengthened by exposure to stressors: the systematic self-reflection model of resilience strengthening. *Anxiety, Stress, & Coping* 32: 1–17.

20. Woody A, Figueroa WS, Benencia F, Zoccola PM (2016): Trait reflection predicts interleukin-6 response to a social-evaluative stressor. *Brain, Behavior, and Immunity* 52: 27–31.

21. Ayduk Ö, Kross E (2008): Enhancing the Pace of Recovery: Self-Distanced Analysis of Negative Experiences Reduces Blood Pressure Reactivity. *Psychol Sci* 19: 229–231.

22. Treynor W, Gonzalez R, Nolen-Hoeksema S (2003): Rumination Reconsidered: A Psychometric Analysis. *Cognitive Therapy and Research* 27: 247–259.

23. Arditte KA, Joormann J (2011): Emotion Regulation in Depression: Reflection Predicts Recovery from a Major Depressive Episode. *Cogn Ther Res* 35: 536–543.

24. Leal CKN, Faria GGB de, DeSouza ML (2019): Private Self-consciousness, Self-reflection, Insight and Alcohol Consumption Among Young People and Adults. *Psico-USF* 24: 633–644.

25. Pitkethly AJ, Lau PWC, Maddison R (2019): Investigating the association of self-regulated learning skills and physical activity in Hong Kong Chinese and Scottish adolescents. *International Journal of Sport and Exercise Psychology* 17: 670–684.

26. Poisnel G, Arenaza-Urquijo E, Collette F, Klimecki OM, Marchant NL, Wirth M, *et al.* (2018): The Age-Well randomized controlled trial of the Medit-Ageing European project: Effect of meditation or foreign language training on brain and mental health in older adults. *Alzheimers Dement (N Y)* 4: 714–723.

27. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, *et al.* (2014): A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement* 10: 844–852.

28. Marchant NL, Barnhofer T, Klimecki OM, Poisnel G, Lutz A, Arenaza-Urquijo E, *et al.* (2018): The SCD-Well randomized controlled trial: Effects of a mindfulness-based intervention versus health education on mental health in patients with subjective cognitive decline (SCD). *Alzheimers Dement (N Y)* 4: 737–745.

29. Nolen-Hoeksema S, Wisco BE, Lyubomirsky S (2008): Rethinking Rumination. *Perspect Psychol Sci* 3: 400–424.

30. Schlosser M, Demnitz-King H, Whitfield T, Wirth M, Marchant NL (2020): Repetitive negative thinking is associated with subjective cognitive decline in older adults: a cross-sectional study. *BMC Psychiatry* 20: 500.

31. Sheikh JI, Yesavage JA (1986): Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health* 5: 165–173.

32. Deckers K, Barbera M, Köhler S, Ngandu T, van Boxtel M, Rusanen M, *et al.* (2020): Long-term dementia risk prediction by the LIBRA score: A 30-year follow-up of the CAIDE study. *Int J Geriatr Psychiatry* 35: 195–203.

33. Deckers K, Boxtel MPJ van, Schiepers OJG, Vugt M de, Sánchez JLM, Anstey KJ, *et al.* (2015): Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *International Journal of Geriatric Psychiatry* 30: 234–246.

34. Franchini F, Musicco M, Ratto F, Storti G, Shofany J, Caltagirone C, Di Santo SG (2019): The LIBRA Index in Relation to Cognitive Function, Functional Independence, and Psycho-Behavioral Symptoms in a Sample of Non-Institutionalized Seniors at Risk of Dementia. *Journal of Alzheimer's Disease* 72: 717–731.

35. Stein D, Grant AM (2014): Disentangling the Relationships Among Self-Reflection, Insight, and Subjective Well-Being: The Role of Dysfunctional Attitudes and Core Self-Evaluations. *The Journal of Psychology* 148: 505–522.

36. Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC (2017): Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. *Alzheimers Dement (N Y)* 3: 668–677.

37. Besson FL, La Joie R, Doeuvre L, Gaubert M, Mézenge F, Egret S, *et al.* (2015): Cognitive and Brain Profiles Associated with Current Neuroimaging Biomarkers of Preclinical Alzheimer's Disease. *J Neurosci* 35: 10402–10411.

38. Müller-Gärtner HW, Links JM, Prince JL, Bryan RN, McVeigh E, Leal JP, *et al.* (1992): Measurement of Radiotracer Concentration in Brain Gray Matter Using Positron Emission Tomography: MRI-Based Correction for Partial Volume Effects. *J Cereb Blood Flow Metab* 12: 571–583.

39. Perneger TV (1998): What's wrong with Bonferroni adjustments. *BMJ* 316: 1236–1238.

40. Rothman KJ (1990): No Adjustments Are Needed for Multiple Comparisons. *Epidemiology* 1: 43–46.

41. Takano K, Tanno Y (2009): Self-rumination, self-reflection, and depression: Self-rumination counteracts the adaptive effect of self-reflection. *Behaviour Research and Therapy* 47: 260–264.

42. Trapnell PD, Campbell JD (1999): Private Self-Consciousness and the Five-Factor Model of Personality: Distinguishing Rumination From Reflection. *Journal of Personality* 76: 284–304.

43. Sharp ES, Reynolds CA, Pedersen NL, Gatz M (2010): Cognitive Engagement and Cognitive Aging: Is Openness Protective? *Psychol Aging* 25: 60–73.

44. Karp A, Andel R, Parker MG, Wang H-X, Winblad B, Fratiglioni L (2009): Mentally Stimulating Activities at Work During Midlife and Dementia Risk After Age 75: Follow-Up Study From the Kungsholmen Project. *The American Journal of Geriatric Psychiatry* 17: 227–236.

45. Krell-Roesch J, Ruider H, Lowe VJ, Stokin GB, Pink A, Roberts RO, *et al.* (2016): FDG-PET and Neuropsychiatric Symptoms among Cognitively Normal Elderly Persons: The Mayo Clinic Study of Aging. *J Alzheimers Dis* 53: 1609–1616.

46. Crane MF, Kho M, Kangas M, Griffin B, Karin E, Earl JK, Harris CB (2020): Strengthening resilience in over 50's: a nested clustered-randomized controlled trial of adaptive systematic self-reflection. *Anxiety, Stress, & Coping* 33: 623–641.

47. Bucknell KJ, Kangas M, Crane MF (2022): Adaptive self-reflection and resilience: The moderating effects of rumination on insight as a mediator. *Personality and Individual Differences* 185: 111234.

48. Czyżowska N, Gurba E (2021): Does Reflection on Everyday Events Enhance Meaning in Life and Well-Being among Emerging Adults? Self-Efficacy as Mediator between Meaning in Life and Well-Being. *Int J Environ Res Public Health* 18: 9714.

49. Stewart TM, Hunter SC, Rhodes SM (2019): Reflective pondering is associated with executive control for emotional information: An adolescent prospective study. *Journal of Behavior Therapy and Experimental Psychiatry* 65: 101486.

50. Satyshur MD, Layden EA, Gowins JR, Buchanan A, Gollan JK (2018): Functional connectivity of reflective and brooding rumination in depressed and healthy women. *Cogn Affect Behav Neurosci* 18: 884–901.

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Table 1. Cognitive tests used to compute the PACC5/PACC5$_{Abridged}$

	SCD-Well (PACC5$_{Abridged}$)	**Age-Well (PACC5)**
Global memory	Dementia Rating Scale-2 (total score)	Dementia Rating Scale-2 (total score)
Executive function	Wechsler Adult Intelligence Scale-IV Coding (raw score)	Wechsler Adult Intelligence Scale-IV Coding (raw score)
Episodic memory	Rey Auditory Verbal Learning Test (delayed recall score)	California Verbal Learning Test (delayed free recall score)
Episodic memory	–	Logical Memory Test (delayed recall score)
Semantic memory	Category Fluency (1 x 2 minute [number of correct animals stated])	Category Fluency (1 x 2 minute [number of correct animals stated])

Abbreviations: PACC5, Preclinical Alzheimer's Cognitive Composite 5.

Table 2. Demographic, clinical and biological characteristics of the SCD-Well and Age-Well cohorts

Characteristics	SCD-Well (N = 125)	Age-Well (N = 134)
Demographics		
Age, y	72.6 (6.9)	69.3 (3.8)
Sex (Female), No. (%)	82 (65.6%)	83 (61.9%)
Education, y	13.5 (3.8)	13.1 (3.1)
Ethnicity (White), No. (%)	121 (96.8%)	-
APOE ε4 carriers, No. (%)	-	35 (26.7%)[b]
Trial site, No. (%)		
Caen, France	-	134 (100.0%)
Barcelona, Spain	40 (32.0%)	-
Cologne, Germany	21 (16.8%)	-
London, UK	28 (22.4%)	-
Lyon, France	36 (28.8%)	-
Self-reflection		
RRS reflective pondering score	8.5 (2.8)	8.9 (3.2)
Psychological distress		
RRS brooding score	8.7 (2.6)	8.1 (2.3)
GDS depression score	2.6 (2.3)	1.3 (1.7)
Global cognition		
$PACC5_{Abridged}$ / PACC5	0.0 (1.0)	0.0 (1.0)
Neuroimaging AD markers		
Global glucose metabolism, FDG SUVR	-	1.2 (0.1)[c]
Global amyloid, Florbetapir SUVR	-	1.2 (0.2)[d]
Amyloid positive, No. (%)	-	28 (21.1%)[d]
Health and lifestyle		
LIBRA	-0.82 (2.5)[a]	-0.41 (1.9)

Data are presented as mean (standard deviation) of participants unless otherwise indicated. Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; FDG, fluorodeoxyglucose; GDS, Geriatric Depression Scale; LIBRA, 'Lifestyle for Brain health'; MMSE, Mini-Mental State Examination; PACC5, Preclinical Alzheimer's Cognitive Composite; RRS, Rumination Response Scale; SUVR, standard uptake value ratio.

[a] N = 113; [b] N = 131; [c] N = 92; [d] N = 133

Table 3. Association between self-reflection and AD-sensitive markers in SCD-Well and Age-Well

	SCD-Well		**Age-Well**								
	Global cognition (N = 125)		**Global cognition (N = 134)**			**Glucose metabolism (N = 92)[a]**			**Amyloid deposition (N = 133)[b]**		
	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	P_{FDR}	Coefficient (95% CI)	*P*	P_{FDR}	Coefficient (95% CI)	*P*	P_{FDR}
Model-1	0.23 (0.05 to 0.40)	0.012	0.28 (0.12 to 0.45)	<0.001	0.003	0.17 (-0.03 to 0.37)	0.101	0.152	0.06 (-0.11 to 0.23)	0.479	0.479
Model-2	0.15 (0.01 to 0.29)	0.042	0.16 (0.00 to 0.32)	0.044	0.111	0.18 (-0.04 to 0.40)	0.111	0.111	0.15 (-0.03 to 0.33)	0.104	0.111
Model-3	0.18 (0.03 to 0.33)	0.023	0.22 (0.05 to 0.40)	0.014	0.041	0.29 (0.03 to 0.55)	0.027	0.041	0.13 (-0.07 to 0.34)	0.189	0.189

Abbreviations: CI, confidence interval.
Model-1: Unadjusted.
Model-2: Adjusted for age, sex, education and [in SCD-Well] country of residence. For glucose metabolism and amyloid deposition analyses APOE ε4 status was included as an additional covariate.
Model-3: Adjusted for depressive symptoms and brooding levels along with all model 2 covariates.
[a] N = 89 included in models-2, and -3; [b] N = 130 included in models-2, and -3.

Figure 1. Association between self-reflection and global cognition and glucose metabolism in SCD-Well and Age-Well

Associations between self-reflection and a) global cognition in SCD-Well, b) global cognition in Age-Well and c) glucose metabolism in Age-Well. The illustrated associations are derived from model-3 adjusted linear regression and represent estimates for the average participant in each cohort (eg, SCD-Well: female participant from the Barcelona site with mean values for age [72.6], education [13.5], depression symptoms [2.6] and brooding levels [8.7]; Age-Well: female participant, with mean values for age [69.3], education [13.1], depression symptoms [1.3] and brooding levels [8.1]).