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How to cite

IHLE, Andreas et al. The role of cognitive reserve accumulated in midlife for the relation between chronic diseases and cognitive decline in old age: A longitudinal follow-up across six years. In: Neuropsychologia, 2018, vol. 121, p. 37–46. doi: 10.1016/j.neuropsychologia.2018.10.013

This publication URL: https://archive-ouverte.unige.ch/unige:114187

Publication DOI: 10.1016/j.neuropsychologia.2018.10.013

The Role of Cognitive Reserve Accumulated in Midlife for the Relation between Chronic Diseases and Cognitive Decline in Old Age: A Longitudinal Follow-Up across Six Years

Andreas Ihle[1, 2, 3], PhD

Paolo Ghisletta[1, 3, 4], PhD

Nicola Ballhausen[1, 2, 3], PhD

Delphine Fagot[2, 3], PhD

Fanny Vallet[2, 3, 5], PhD

Marie Baeriswyl[2, 3], PhD

Julia Sauter[2, 3], MSc

Michel Oris[2, 3], PhD

Jürgen Maurer[3, 6], PhD

Matthias Kliegel[1, 2, 3], PhD

[1] Department of Psychology, University of Geneva, Geneva, Switzerland

[2] Center for the Interdisciplinary Study of Gerontology and Vulnerability, University of Geneva, Geneva, Switzerland

[3] Swiss National Centre of Competence in Research LIVES – Overcoming vulnerability: Life course perspectives, Lausanne and Geneva, Switzerland

[4] Distance Learning University Switzerland, Sierre, Switzerland

[5] Groupe de Recherche en Psychologie de la Santé, University of Geneva, Geneva, Switzerland

[6] Department of Economics, University of Lausanne, Lausanne, Switzerland

Correspondence: Andreas Ihle, CIGEV, University of Geneva,

Boulevard du Pont d'Arve 28, 1205 Geneva, Switzerland. E-mail: Andreas.Ihle@unige.ch

Phone: +41 22 37 98308

Abstract

Objectives: The present study set out to investigate relations of the number of chronic diseases (as a global indicator of individuals' multimorbidity) to cognitive status and cognitive decline over six years as measured by changes in Trail Making Test (TMT) completion time in old adults and whether those relations differed by key life course markers of cognitive reserve (education, occupation, and cognitively stimulating leisure activities).

Method: We analyzed data from 897 participants tested on TMT parts A and B in two waves six years apart. Mean age in the first wave was 74.33 years. Participants reported information on chronic diseases, education, occupation, and cognitively stimulating leisure activities.

Results: Latent change score modeling testing for moderation effects revealed that a larger number of chronic diseases significantly predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline). Notably, the detrimental relation of the number of chronic diseases to stronger increase in TMT completion time (i.e., cognitive performance decline) was significantly stronger in individuals with less engagement in cognitively stimulating leisure activities in midlife.

Discussion: Present data suggest that disease-related cognitive decline may be steeper in individuals who have accumulated less cognitive reserve in midlife. However, greater midlife activity engagement seemed to be associated with steeper cognitive decline in any case. Implications for current cognitive reserve and neuropsychological aging research are discussed.

Keywords: cognitive decline; multimorbidity; activities; life course; longitudinal study

1. Introduction

A major goal in current gerontological neuropsychology is to better understand how interindividual differences in cognitive health in old age emerge (Opdebeeck, Martyr, & Clare, 2016). In particular, with respect to an individual's potential for preserving cognitive functioning in old age, the cognitive reserve concept postulates that lifelong experiences, including educational and occupational attainment, and leisure activities in later life, stimulate brain development which increases the reserve capacity that may compensate for brain damage, neurological loss, and pathological decline such as dementia (Stern, 2002, 2017). Specifically, interindividual differences in the effective recruitment of neural networks and cognitive processes are hypothesized to explain differences in individuals' capacity to cope with or compensate for age-related decline or pathology (Stern, 2009, 2012; see also e.g. Barnett, Salmond, Jones, & Sahakian, 2006; Bartres-Faz & Arenaza-Urquijo, 2011; Perneczky et al., 2011; Sole-Padulles et al., 2009). In individuals with healthy cognitive functioning, these mechanisms contribute to the adaptation of brain activity when task difficulty level is increased and thereby enhance cognitive performance (Stern, 2012). Empirically corroborating the predictions of the cognitive reserve concept, evidence showed that greater cognitive stimulation throughout the life course such as longer education in early life, cognitively demanding jobs in midlife, and cognitively stimulating leisure activities in midlife and old age contributes to the accumulation of cognitive reserve over the life course and is related to better cognitive functioning such as memory and executive functioning in old age as well as a lower risk of developing dementia and later age at dementia onset (Adam, Bonsang, Grotz, & Perelman, 2013; Hertzog, Kramer, Wilson, & Lindenberger, 2008; Ihle et al., 2015; Karp et al., 2006; Paillard-Borg, Fratiglioni, Xu, Winblad, & Wang, 2012; see Opdebeeck et al., 2016, for a meta-analysis).

Cognitive reserve may particularly come into play when facing stressors that affect cognitive functioning such as suffering from chronic diseases (e.g., heart and vascular

diseases) that have been found to be related to lower cognitive functioning and faster cognitive decline in old age (Carmichael, 2014; Gasecki, Kwarciany, Nyka, & Narkiewicz, 2013; Reijmer et al., 2012). Specifically, from a more general conceptual perspective, following models of vulnerability (Spini, Bernardi, & Oris, 2017) and cognitive reserve (Stern, 2012), we argue that certain individuals are more vulnerable to impairments in human functioning such as cognition because of insufficient reserves accumulated over the life course such as cognitive reserve (Ihle, Oris, Sauter, Rimmele, & Kliegel, 2018). We further argue that because of their little reserves those vulnerable individuals consequently have greater difficulty to deal with stressors that affect their cognitive functioning (such as suffering from chronic diseases). On the other hand, less vulnerable individuals who have accumulated greater cognitive reserve over the life course should be able to better deal with the negative aftereffects of such stressors on cognitive functioning.

Therefore, we predict that cognitive reserve may modify the relation of chronic diseases to cognitive status and cognitive decline. Notably, in line with this conceptual view, recent empirical cross-sectional evidence suggests that in individuals with lower cognitive reserve (in terms of e.g. lower education, lower cognitive level of job, and less engagement in cognitively stimulating leisure activities) physiological stressors such as metabolic syndromes and chronic diseases (e.g., unfavorable blood fat level, obesity, and hypertension) are more strongly associated with poorer cognitive performance status (e.g., memory and executive functioning) than in individuals with greater cognitive reserve (Ihle, Gouveia et al., 2018; Ihle et al., 2016, 2017).

Yet, a longitudinal investigation of these patterns with respect to disease-related cognitive decline is missing so far. However, longitudinal research is needed to evaluate whether cognitive reserve not only modifies disease-related cognitive status but also disease-related cognitive decline. In addition, from a life course perspective further remaining open questions in this context include whether contributions to cognitive reserve in early, mid-, and

late-life phases are of equal importance or not. Therefore, to extend the literature we investigated relations of the number of chronic diseases (as a global indicator of individuals' multimorbidity) to cognitive status and cognitive decline over six years as measured by changes in Trail Making Test (TMT) completion time and whether those relations differed by key life course markers of cognitive reserve (education, occupation, and cognitively stimulating leisure activities).

2. Methods

2.1 Participants

Data come from the two waves of the Vivre-Leben-Vivere (VLV) survey (Ihle et al., 2015; Ludwig, Cavalli, & Oris, 2014), which is a part of the research program LIVES on vulnerability processes across the life course. Respondents were first interviewed during 2011 (Wave 1; W1) using a face-to-face computer-assisted personal interview method (CAPI) and questionnaires. The main sample in W1 included 3080 participants who were randomly selected in the cantonal Swiss administrations' records and stratified by age (65-69, 70-74, 75-79, 80-84, 85-89, and 90+), sex, and canton (Basel, Bern, Geneva, Ticino, and Valais). A subsample of 1059 participants from four cantons (Basel, Bern, Geneva, and Valais) was interviewed again during 2017 (Wave 2; W2). Present analyses were based on 897 participants with data on TMT parts A and B as these were the outcome variables in the present study. Among these respondents, mean age was 74.33 years (SD = 6.50, range 65-96) in W1.

With respect to the longitudinal study design, we acknowledge that our sample is clearly a survival sample. From the participants initially tested in W1, the participants who were analyzed in the present study were slightly younger (M = 74.33 years in W1, SD = 6.50) than the individuals who were lost at follow-up in W2 (M = 80.00 years in W1, SD = 8.60; p < .001). However, importantly, we still had a considerable number of respondents in the two highest age categories of 85 years and older (24.5% among the participants who were

analyzed in the present study; in comparison, 25.7% among the participants initially tested in W1). The participants who were analyzed in the present study (51.4% men) did not differ from the individuals who were lost at follow-up in W2 (51.9% men) with regard to sex (p = .811). The participants who were analyzed in the present study (43.2% with low education, 30.0% with a low cognitive level of the first job, and 15.9% with a low cognitive level of the last job) slightly differed from the individuals who were lost at follow-up in W2 (58.9% with low education, 46.0% with a low cognitive level of the first job, and 31.1% with a low cognitive level of the last job) with regard to education and cognitive level of job (ps < .001). However, importantly, they were in a similar range as the overall sample initially tested in W1 (53.6% with low education, 39.9% with a low cognitive level of the first job, and 24.2% with a low cognitive level of the last job), suggesting that we still had a considerable number of respondents in low education and job categories. The participants who were analyzed in the present study had pursued slightly more leisure activities (at age 45: M = 11.73, SD = 2.66; in W1: M = 9.94, SD = 2.82) than the individuals who were lost at follow-up in W2 (at age 45: M = 10.76, SD = 3.03; in W1: M = 7.31, SD = 3.44; ps < .001). However, importantly, we still had a considerable number of respondents in the lower range of leisure activity participation (23.6% individuals with seven or fewer activities among the participants who were analyzed in the present study; in comparison, 42.6% among the participants initially tested in W1). The participants who were analyzed in the present study had slightly fewer chronic diseases in W1 (M = 1.90, SD = 1.56) than the individuals who were lost at follow-up in W2 (M = 2.49, SD = 2.10; p < .001). However, importantly, we still had a relatively large proportion of respondents with three or more chronic diseases (46.3% among the participants who were analyzed in the present study; in comparison, 43.9% among the participants initially tested in W1), suggesting sufficient heterogeneity of multimorbidity in the study sample (see e.g. Aartsen, Smits, van Tilburg, Knipscheer, & Deeg, 2002, for a comparable maintenance of the initial sample stratification distribution over six years in the Longitudinal Aging Study

Amsterdam; see e.g. Hultsch, Hertzog, Small, & Dixon, 1999, for a similar follow-up of participants over six years in the Victoria Longitudinal Study; see e.g. Lifshitz-Vahav, Shrira, & Bodner, 2017, for a similar follow-up of participants over four years in the Survey of Health, Ageing and Retirement in Europe).

All participants gave their written informed consent for inclusion before they participated in the study. The present study was conducted in accordance with the Declaration of Helsinki, and the protocol had been approved by the ethics commission of the Faculty of Psychology and Social Sciences of the University of Geneva (project identification codes: CE_FPSE_14.10.2010 and CE_FPSE_05.04.2017).

2.2 Materials

2.2.1 Trail Making Test Completion Time

We administered in both waves the Trail Making Test part A (TMT A; Reitan, 1958). After one exercise trail (connecting the numbers from 1 to 8), participants had to connect the numbers from 1 to 25 as fast as possible and without error in ascending order. The TMT A completion time was the time in seconds needed to correctly connect the 25 numbers.

In addition, we administered in both waves the Trail Making Test part B (TMT B; Reitan, 1958). After one exercise trail (connecting 1-A-2-B-3-C-4-D), participants had to connect the numbers 1 to 13 in ascending order and the letters A to L in alphabetic order while alternating between numbers and letters (i.e., 1-A-2-B-3-C ... 12-L-13) as fast as possible and without error. The TMT B completion time was the time in seconds needed to correctly connect the 25 numbers / letters.

2.2.2 Multimorbidity of Chronic Diseases

We interviewed participants in both waves regarding the chronic diseases they suffered from such as heart diseases of ischemic or organic pathogenesis, primary arrhythmias, pulmonary heart diseases, hypertension, and peripheral vascular diseases. Participants reported in W1 and W2 the chronic diseases they currently suffered from at that

time, respectively. To gain a long-term-effect perspective, we analyzed the overall number of those chronic diseases participants suffered from in both W1 and W2 as a global indicator of individuals' multimorbidity (see, e.g., Rozzini et al., 2002, for a similar approach).

2.2.3 Markers of Cognitive Reserve

Education. We asked participants in W1 to indicate their highest educational level attained. For analyses, low versus high education were distinguished according to the two categories of low educational attainment (i.e., primary and inferior secondary school levels) and apprenticeship graduation, both leading mainly to blue collar and/or unskilled jobs versus higher (advanced) educational attainment (i.e., superior secondary school level, technical college or superior vocational college, and university degree), typically leading to white collar jobs (Gabriel, Oris, Studer, & Baeriswyl, 2015).

Cognitive level of job. We asked participants in W1 to indicate the first profession they had practiced after education had been completed as well as the last profession they had practiced before retirement. For analyses, low versus high cognitive level of job regarding individuals' first profession and the last profession practiced were distinguished according to the two categories of lower cognitive demands (i.e., blue collar or unskilled jobs such as factory work, plumbing, carpentry, farming, etc.) versus higher cognitive demands (i.e., white collar jobs such as teacher, clerical work, lawyer, medical practice, etc.; see e.g. Kesse-Guyot et al., 2013; Opdebeeck et al., 2016, for similar ratings reflecting the degree of intellectual involvement at work as marker of cognitive reserve).

Leisure activities. We interviewed participants in W1 regarding their engagement in cognitively stimulating leisure activities such as going to the cinema, going to conferences, journeys, artistic activities, table games, and municipality activities. Participants reported in W1 the activities they currently carried out (within the last months) at that time and those activities they had carried out at age 45. For analyses, we calculated the overall number of

leisure activities participants carried out in W1 and the overall number of midlife leisure activities participants had carried out at age 45.

2.3 Statistical Analyses

We conducted latent change score modeling (McArdle, 2009) using the R package lavaan (Rosseel, 2012). The specification of our latent change score model is illustrated in Fig. 1. Specifically, we modeled latent cognitive factors of TMT completion time in W1 (constructed from scores in TMT parts A and B in W1) and W2 (constructed from scores in TMT parts A and B in W2) as well as a latent change variable regarding change in TMT completion time from W1 to W2. We enforced strong factorial invariance on the factor loadings, with intercepts of all indicators being fixed to zero to assure that the same cognitive factor was assessed at both waves (Meredith & Teresi, 2006). We included several covariates that predicted latent change and were correlated to the latent cognitive factor in W1: age, sex, the number of chronic diseases, the markers of cognitive reserve, and the interactions of the markers of cognitive reserve with the number of chronic diseases. We also included interrelations of all covariates and interaction terms.

We obtained parameter estimates using maximum likelihood (ML) estimation. To evaluate model fit, we used the following criteria: χ^2 test (good models: p value > .10), Comparative Fit Index (good models: CFI > .95), Incremental Fit Index (good models: IFI > .95), Root Mean Square Error of Approximation (good models: $RMSEA$ < .06), and Standardized Root Mean Square Residual (good models: $SRMR$ < .08; Hu & Bentler, 1999). Significance testing of the effects of the covariates on latent change and of the associations of the covariates to the latent cognitive factor in W1 was based on likelihood ratio tests. Specifically, we compared the unconstrained model in which the parameter of interest (e.g., a covariate predicting latent change) was estimated freely with a constrained model in which this parameter was fixed to zero. For this purpose, we statistically tested the difference in model fit between the unconstrained model and the constrained model ($\Delta\chi^2$), including testing

for significance. In case the constrained model would have a significantly worse fit than the unconstrained model, that would mean that the parameter of interest was significant (e.g., the covariate significantly predicted latent change).

For analyses, we standardized markers of cognitive reserve that have big scales, i.e. number of midlife leisure activities and number of W1 leisure activities so that the reported raw estimates (*b*) can be interpreted in terms of *SD*s. We did not standardize the number of chronic diseases because it allowed interpreting the reported raw estimates in terms of effects 'for each additional chronic disease'. We did not standardize completion time in TMT A or TMT B so that the reported raw estimates can be interpreted in terms of seconds.

3. Results

3.1 Descriptive Statistics

Table 1 shows descriptive statistics for completion time in TMT A and TMT B in W1 and W2, the number of chronic diseases, the markers of cognitive reserve, age, and sex in terms of means, standard deviations, skewness, and kurtosis as well as sample proportions. Comparing both waves, on average there was no difference in completion time in TMT A nor TMT B (*p*s > .145).

With respect to first-order correlations, a larger number of chronic diseases was significantly related to longer completion time in both TMT A and TMT B in W2 (but not in W1). Higher education was significantly related to shorter completion time in TMT B (but not in TMT A) in both waves. Higher cognitive level of first job was significantly related to shorter completion time in TMT A in W2 (but not in W1) as well as in TMT B in both waves. Higher cognitive level of last job was significantly related to shorter completion time in TMT A in both waves as well as in TMT B in W2 (but not in W1). A larger number of midlife leisure activities was significantly related to shorter completion time in TMT A in both waves as well as in TMT B in W1 (but not in W2). A larger number of W1 leisure activities was significantly related to shorter completion time in both TMT A and TMT B in both waves.

Older age was significantly related to longer completion time in both TMT A and TMT B in both waves. In women completion time in TMT A in W2 was significantly shorter than in men. Besides that, TMT completion time did not differ by sex. A larger number of W1 leisure activities was significantly related to fewer chronic diseases (see Table 2 for the full correlation matrix).

3.2 Latent Change Score Modeling

Appendix A shows all parameter estimates of the latent change score model before the covariates being entered. Appendix B shows all parameter estimates of the latent change score model after the covariates being entered. This latent change score model provided a very good statistical account of the data (χ^2 = 30.73, *df* = 23, *p* = .130, *CFI* > .99, *IFI* > .99, *RMSEA* = .02, *SRMR* = .01). In this model, the covariates predicted 27.7% of variance in latent change in TMT completion time. Specifically, older age significantly predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline, *b* = 4.37, $\Delta\chi^2$ = 31.01, Δdf = 1, *p* < .001). Sex (*b* = -2.01, $\Delta\chi^2$ = 2.17, Δdf = 1, *p* = .141) did not predict change in TMT completion time. A larger number of chronic diseases significantly predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline, *b* = 1.99, $\Delta\chi^2$ = 11.57, Δdf = 1, *p* < .001). Education (*b* = 1.03, $\Delta\chi^2$ = 0.47, Δdf = 1, *p* = .494), cognitive level of first job (*b* = -2.15, $\Delta\chi^2$ = 1.34, Δdf = 1, *p* = .247), and cognitive level of last job (*b* = -2.39, $\Delta\chi^2$ = 1.11, Δdf = 1, *p* = .292) did not predict change in TMT completion time. A larger number of midlife leisure activities significantly predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline, *b* = 3.14, $\Delta\chi^2$ = 7.93, Δdf = 1, *p* = .005). A larger number of W1 leisure activities significantly predicted less increase in TMT completion time (i.e., less cognitive performance decline, *b* = -3.08, $\Delta\chi^2$ = 13.07, Δdf = 1, *p* < .001). There was a significant interaction of the number of midlife leisure activities with the number of chronic diseases. Specifically, the relation of a larger number of chronic diseases to stronger increase in TMT completion time (i.e., cognitive performance decline) was significantly stronger in

individuals with a smaller number of midlife leisure activities (b = -1.23, $\Delta\chi^2$ = 4.77, Δdf = 1, p = .029; cf. Fig. 2). Besides that, no other interactions of the markers of cognitive reserve with chronic diseases on latent change in TMT completion time were observed.

With respect to correlations between the latent cognitive factor in W1 and the covariates, older age significantly correlated with longer TMT completion time (i.e., lower cognitive performance status, r = .32, $\Delta\chi^2$ = 57.93, Δdf = 1, p < .001). Sex (r = .00, $\Delta\chi^2$ = 0.01, Δdf = 1, p = .907) and the number of chronic diseases (r = .01, $\Delta\chi^2$ = 0.01, Δdf = 1, p = .905) did not correlate with TMT completion time. Higher education (r = -.14, $\Delta\chi^2$ = 10.12, Δdf = 1, p = .001), higher cognitive level of first job (r = -.15, $\Delta\chi^2$ = 12.69, Δdf = 1, p < .001), higher cognitive level of last job (r = -.10, $\Delta\chi^2$ = 5.21, Δdf = 1, p = .022), a larger number of midlife leisure activities (r = -.13, $\Delta\chi^2$ = 9.72, Δdf = 1, p = .002), and a larger number of W1 leisure activities (r = -.27, $\Delta\chi^2$ = 41.66, Δdf = 1, p < .001) significantly correlated with shorter TMT completion time (i.e., better cognitive performance status).[1]

4. Discussion

The present study set out to investigate relations of the number of chronic diseases to cognitive status and cognitive decline over six years as measured by changes in TMT completion time and whether those relations differed by key life course markers of cognitive reserve. With respect to first-order correlations, a larger number of chronic diseases was related to longer completion time in both TMT A and TMT B in W2. Latent change score modeling showed that a larger number of chronic diseases predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline). This finding confirms prior evidence that chronic diseases are a major antecedent of lower cognitive functioning and faster cognitive decline in old age (Carmichael, 2014; Gasecki et al., 2013; Reijmer et al., 2012). We also found that a larger number of leisure activities in old age was related to fewer chronic diseases. This result is consistent with the view that markers of cognitive reserve are associated with a lower risk for developing chronic diseases in old age (Ihle, Oris, Fagot et al.,

2018; see also e.g. Batty, Deary, Benzeval, & Der, 2010; Hart et al., 2004; Kilander, Nyman, Boberg, & Lithell, 1997).

Moreover, we found that higher values in several markers of cognitive reserve (in terms of education, cognitive level of the first job and the last job, and cognitively stimulating leisure activities in midlife and old age) were related to shorter TMT completion time (i.e., better cognitive performance status). This finding confirms the conceptual view that cognitive stimulation throughout the life course may be associated with cognitive reserve, thereby being related to better cognitive functioning in old age (Hertzog et al., 2008; Opdebeeck et al., 2016; Stern, 2012). With respect to cognitive decline across six years, we observed only few associations with markers of cognitive reserve. Education as well as cognitive level of the first job and the last job did not predict change in TMT completion time. This result corroborates prior studies reporting that education was only related to better cognitive status but not to cognitive decline (Köhncke et al., 2016; Tucker-Drob, Johnson, & Jones, 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008). Yet, a larger number of leisure activities pursued in old age predicted less increase in TMT completion time (i.e., less cognitive performance decline). Thus, importantly, present findings also support those studies that observed relations of greater activity engagement in old age to reduced cognitive decline (e.g., Wang et al., 2013). Hence, findings seem to suggest a dissociation between cognitive reserve effects of early brain stimulation (education) mainly affecting cognitive status only and adulthood stimulation (leisure activities) affecting both status and decline.

With respect to midlife leisure activities, we found that a larger number of midlife leisure activities predicted stronger increase in TMT completion time (i.e., steeper cognitive performance decline). Notably, and most importantly, we observed an interaction between midlife leisure activities and chronic diseases. Specifically, the detrimental relation of the number of chronic diseases to stronger increase in TMT completion time (i.e., steeper cognitive performance decline) was stronger in individuals with less compared to those with

greater engagement in cognitively stimulating leisure activities in midlife. However, greater midlife activity engagement seemed to be associated with steeper cognitive decline in any case (see Figure 2), while those not so active in midlife were favored for some reason. On first glance this finding may sound counterintuitive. Yet, this pattern is actually in line with the prediction of the cognitive reserve concept (Stern, 2002, 2009): Individuals with higher cognitive reserve can tolerate more pathology, i.e. they can still maintain cognitive functioning for a longer time (though pathology is advancing). Cognitive functioning will begin to decline later in time, after more pathology has accumulated. But, once it starts to decline the cognitive system rapidly collapses and will then decline at a steeper rate given that pathology is already highly advanced (Stern, 2002, 2009). Yet, empirical research on this conceptual prediction is mixed. While some studies found steeper decline in individuals with higher cognitive reserve such as with higher educational and occupational attainment and with greater activity engagement (e.g., Hall et al., 2007; Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007; Scarmeas, Albert, Manly, &Stern, 2006; Thorvaldsson, Skoog, & Johansson, 2017), other studies found the opposite pattern, i.e. less rapid decline in individuals with higher education and greater engagement in stimulating activities in old age (e.g., Schneeweis, Skirbekk, & Winter-Ebmer, 2014; Wang et al., 2013). Notably, in our data the difference in cognitive decline between individuals with greater and those with less leisure activity engagement in midlife was largely gone once individuals suffered from chronic diseases. This pattern of results suggests that presence/absence of chronic diseases may (at least partly) explain the inconsistencies across findings on cognitive reserve and cognitive decline. Given that we did not observe such patterns neither for education, nor for the first or the last profession practiced before retirement, nor for leisure activities in old age, but mainly for midlife leisure activities, present findings suggest a particularly important role of active reserve build-up in midlife for cognitive decline in old age.

This is conceptually important, as with respect to life course models on the development of vulnerability (e.g., Spini et al., 2017) and cognitive reserve (Stern, 2012), present differential results contrasting midlife activities versus activities in old age suggest that the investigated markers of cognitive reserve - depending on the specific life course phase they concern - may differentially affect cognitive decline (see a recent conceptual proposal on the development of reserves over the life course; Cullati, Kliegel, & Widmer, 2018). Moreover, steeper cognitive decline associated with higher cognitive reserve as a result of pathology-related processes has so far typically been reported in the context of Alzheimer's disease (e.g., Hall et al., 2007; Helzner et al., 2007; Scarmeas et al., 2006; Stern, 2002, 2009). However, the preclinical phase of Alzheimer's disease is known to be up to 15 years and more before the development of clinical symptoms and the diagnosis of dementia, which calls for a long-term perspective (Dubois et al., 2016; see also e.g. Amieva et al., 2014). Therefore, present results on cognitive decline over six years may also be related to early pathology-related cognitive decline among healthy older adults that were so far not diagnosed. Thus, with the help of future long-term cognitive reserve studies the cognitive reserve concept will have to be further specified with respect to the detailed neuropsychological pathways underlying the interplay between chronic diseases and cognitive reserve in relation to cognitive decline observed (see also e.g. Nilsson & Lövdén, 2018, for a recent discussion on future directions for the cognitive reserve concept).

We acknowledge that the present correlative study does not allow drawing causal inferences. Moreover, we acknowledge that we can only draw conclusions regarding the time period and time scale captured in the present study since interindividual differences in cognitive performance at any given point in time are the result of previous changes. Thus, we cannot draw conclusions regarding a time period or time scale that was not captured in the present study. We acknowledge that therefore future longitudinal studies encompassing much broader phases of individuals' aging trajectories will have to investigate whether present

observations hold over a broader time frame. Furthermore, we acknowledge that the current study is limited by a relatively short assessment of cognitive performance. The battery of cognitive tests in the present study contained only TMT parts A and B. Thus, future studies will have to examine whether the present pattern of results holds also for a larger set of cognitive abilities such as episodic memory, working memory, and a broader range of executive functions and thereby apply to the broader domain of cognitive functioning. Moreover, we acknowledge that the present sample contained only a relatively small proportion of individuals who had worked in unskilled professions or who had only a very low education such as primary school level. Therefore, future research will have to investigate in more detail the association of cognitive decline with physiological and psychological stressors, vulnerability, and very low levels of reserves also with respect to very low socio-economic status.

Footnotes

[1] We additionally repeated all analyses using maximum likelihood estimation with robust standard errors (MLR), which revealed the same pattern of results. Moreover, we additionally repeated all analyses with calculating bootstrapped standard errors (based on 1000 bootstrap draws), which again revealed the same pattern of results.

Acknowledgements

This publication benefited from the support of the Swiss National Centre of Competence in Research LIVES – Overcoming vulnerability: Life course perspectives, which is financed by the Swiss National Science Foundation (grant number: 51NF40-160590). The authors are grateful to the Swiss National Science Foundation for its financial assistance. The authors also thank the participants of the Vivre-Leben-Vivere (VLV) study, as well as all members of the LIVES project IP213 and LINK institute who contributed to the realization of the VLV study.

Conflict of interest

We declare that there is no conflict of interest.

References

Aartsen, M. J., Smits, C. H. M., van Tilburg, T., Knipscheer, K. C. P. M., & Deeg, D. J. H. (2002). Activity in older adults: Cause or consequence of cognitive functioning? A longitudinal study on everyday activities and cognitive performance in older adults. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 57*, 153-162. doi: 10.1093/geronb/57.2.P153

Adam, S., Bonsang, E., Grotz, C., & Perelman, S. (2013). Occupational activity and cognitive reserve: implications in terms of prevention of cognitive aging and Alzheimer's disease. *Clinical Interventions in Aging, 8*, 377-390. doi: 10.2147/Cia.S39921

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., ... Dartigues, J. F. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. *Brain, 137*, 1167-1175. doi: 10.1093/brain/awu035

Barnett, J. H., Salmond, C. H., Jones, P. B., & Sahakian, B. J. (2006). Cognitive reserve in neuropsychiatry. *Psychological Medicine, 36*, 1053-1064. doi: 10.1017/S0033291706007501

Bartres-Faz, D. & Arenaza-Urquijo, E. M. (2011). Structural and Functional Imaging Correlates of Cognitive and Brain Reserve Hypotheses in Healthy and Pathological Aging. *Brain Topography, 24*, 340-357. doi: 10.1007/s10548-011-0195-9

Batty, G. D., Deary, I. J., Benzeval, M., & Der, G. (2010). Does IQ predict cardiovascular disease mortality as strongly as established risk factors? Comparison of effect estimates using the West of Scotland Twenty-07 cohort study. *European Journal of Cardiovascular Prevention & Rehabilitation, 17*, 24-27. doi: 10.1097/HJR.0b013e328321311b

Carmichael, O. (2014). Preventing Vascular Effects on Brain Injury and Cognition Late in Life: Knowns and Unknowns. *Neuropsychology Review, 24,* 371-387. doi: 10.1007/s11065-014-9264-7

Cullati, S., Kliegel, M., & Widmer, E. (2018). Development of reserves over the life course and onset of vulnerability in later life. *Nature Human Behaviour, 2,* 551-558. doi: 10.1038/s41562-018-0395-3

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., ... Jack, C. R. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimers & Dementia, 12,* 292-323. doi: 10.1016/j.jalz.2016.02.002

Gabriel, R., Oris, M., Studer, M., & Baeriswyl, M. (2015). The persistence of social stratification? A life course perspective on old-age poverty in Switzerland. *Swiss Journal of Sociology, 41*, 465-487.

Gasecki, D., Kwarciany, M., Nyka, W., & Narkiewicz, K. (2013). Hypertension, Brain Damage and Cognitive Decline. *Current Hypertension Reports, 15,* 547-558. doi: 10.1007/s11906-013-0398-4

Hall, C. B., Derby, C., LeValley, A., Katz, M. J., Verghese, J., & Lipton, R. B. (2007). Education delays accelerated decline on a memory test in persons who develop dementia. *Neurology, 69*, 1657-1664. doi: 10.1212/01.wnl.0000278163.82636.30

Hart, C. L., Taylor, M. D., Smith, G. D., Whalley, L. J., Starr, J. M., Hole, D. J., ... Deary, I. J. (2004). Childhood IQ and cardiovascular disease in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *Social Science & Medicine, 59,* 2131-2138. doi: 10.1016/j.socscimed.2004.03.016

Helzner, E. P., Scarmeas, N., Cosentino, S., Portet, F., & Stern, Y. (2007). Leisure activity and cognitive decline in incident Alzheimer disease. *Archives of Neurology, 64,* 1749-1754. doi: 10.1001/archneur.64.12.1749

Hertzog, C., Kramer, A. F., Wilson, R. S., & Lindenberger, U. (2008). Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *Psychological Science in the Public Interest, 9*, 1-65. doi: 10.1111/j.1539-6053.2009.01034.x

Hu, L. & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling, 6*, 1-55. doi: 10.1080/10705519909540118

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging, 14*, 245-263. doi: 10.1037//0882-7974.14.2.245

Ihle, A., Gouveia, É. R., Gouveia, B. R., Freitas, D. L., Jurema, J., Machado, F. T., & Kliegel, M. (2018). The Relation of Hypertension to Performance in Immediate and Delayed Cued Recall and Working Memory in Old Age: The Role of Cognitive Reserve. *Journal of Aging and Health, 30*, 1171-1187. doi: 10.1177/0898264317708883

Ihle, A., Gouveia, É. R., Gouveia, B. R., Freitas, D. L., Jurema, J., Tinôco, M. A., & Kliegel, M. (2017). High-Density Lipoprotein Cholesterol Level Relates to Working Memory, Immediate and Delayed Cued Recall in Brazilian Older Adults: The Role of Cognitive Reserve. *Dementia and Geriatric Cognitive Disorders, 44*, 84-91. doi: 10.1159/000477846

Ihle, A., Mons, U., Perna, L., Oris, M., Fagot, D., Gabriel, R., & Kliegel, M. (2016). The Relation of Obesity to Performance in Verbal Abilities, Processing Speed, and Cognitive Flexibility in Old Age: The Role of Cognitive Reserve. *Dementia and Geriatric Cognitive Disorders, 42*, 117-126. doi: 10.1159/000448916

Ihle, A., Oris, M., Fagot, D., Baeriswyl, M., Guichard, E., & Kliegel, M. (2015). The Association of Leisure Activities in Middle Adulthood with Cognitive Performance in Old Age: The Moderating Role of Educational Level. *Gerontology, 61*, 543-550. doi: 10.1159/000381311

Ihle, A., Oris, M., Fagot, D., Chicherio, C., van der Linden, B. W. A., Sauter, J., & Kliegel, M. (2018). Associations of educational attainment and cognitive level of job with old age verbal ability and processing speed: The mediating role of chronic diseases. *Applied Neuropsychology: Adult, 25*, 356-362. doi: 10.1080/23279095.2017.1306525

Ihle, A., Oris, M., Sauter, J., Rimmele, U., & Kliegel, M. (2018). Cognitive Reserve and Social Capital Accrued in Early and Midlife Moderate the Relation of Psychological Stress to Cognitive Performance in Old Age. *Dementia and Geriatric Cognitive Disorders, 45*, 190-197. doi: 10.1159/000488052

Karp, A., Paillard-Borg, S., Wang, H. X., Silverstein, M., Winblad, B., & Fratiglioni, L. (2006). Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders, 21*, 65-73. doi: 10.1159/000089919

Kesse-Guyot, E., Andreeva, V. A., Lassale, C., Ferry, M., Jeandel, C., Hercberg, S., ... SU.VI.MAX 2 Research Group (2013). Mediterranean diet and cognitive function: A French study. *American Journal of Clinical Nutrition, 97*, 369-376. doi: 10.3945/ajcn.112.047993

Kilander, L., Nyman, H., Boberg, M., & Lithell, H. (1997). Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. *Journal of Internal Medicine, 242*, 313-321. doi: 10.1046/j.1365-2796.1997.00196.x

Köhncke, Y., Laukka, E. J., Brehmer, Y., Kalpouzos, G., Li, T. Q., Fratiglioni, L., ... Lövdén, M. (2016). Three-year changes in leisure activities are associated with concurrent changes in white matter microstructure and perceptual speed in individuals aged 80 years and older. *Neurobiology of Aging, 41*, 173-186. doi: 10.1016/j.neurobiolaging.2016.02.013

Lifshitz-Vahav, H., Shrira, A., & Bodner, E. (2017). The reciprocal relationship between participation in leisure activities and cognitive functioning: the moderating effect of self-rated literacy level. *Aging & Mental Health, 21*, 524-531. doi: 10.1080/13607863.2015.1124838

Ludwig, C., Cavalli, S., & Oris, M. (2014). "Vivre/Leben/Vivere": An interdisciplinary survey addressing progress and inequalities of aging over the past 30 years in Switzerland. *Archives of Gerontology and Geriatrics, 59*, 240-248. doi: 10.1016/j.archger.2014.04.004

McArdle, J. J. (2009). Latent variable modeling of differences and changes with longitudinal data. *Annual Review of Psychology, 60*, 577-605. doi: 10.1146/annurev.psych.60.110707.163612

Meredith, W. & Teresi, J. A. (2006). An essay on measurement and factorial invariance. *Medical Care, 44*, 69-77. doi: 10.1097/01.mlr.0000245438.73837.89

Nilsson, J. & Lövdén, M. (2018). Naming is not explaining: future directions for the "cognitive reserve" and "brain maintenance" theories. *Alzheimers Research & Therapy, 10*: 34. doi: 10.1186/s13195-018-0365-z

Opdebeeck, C., Martyr, A., & Clare, L. (2016). Cognitive reserve and cognitive function in healthy older people: a meta-analysis. *Aging, Neuropsychology, and Cognition, 23*, 40-60. doi: 10.1080/13825585.2015.1041450

Paillard-Borg, S., Fratiglioni, L., Xu, W. L., Winblad, B., & Wang, H. X. (2012). An Active Lifestyle Postpones Dementia Onset by More than One Year in Very Old Adults. *Journal of Alzheimers Disease, 31*, 835-842. doi: 10.3233/Jad-2012-120724

Perneczky, R., Alexopoulos, P., Schmid, G., Sorg, C., Forst, H., Diehl-Schmid, J., & Kurz, A. (2011). Cognitive reserve and its relevance for the prevention and diagnosis of dementia. *Nervenarzt, 82*, 325-+. doi: 10.1007/s00115-010-3165-7

Reijmer, Y. D., van den Berg, E., Dekker, J. M., Nijpels, G., Stehouwer, C. D. A., Kappelle, L. J., & Biessels, G. J. (2012). Development of Vascular Risk Factors over 15 Years in Relation to Cognition: The Hoorn Study. *Journal of the American Geriatrics Society, 60*, 1426-1433. doi: 10.1111/j.1532-5415.2012.04081.x

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Perceptual and Motor Skills, 8*, 271-276.

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software, 48*, 1-36.

Rozzini, R., Frisoni, G. B., Ferrucci, L., Barbisoni, P., Sabatini, T., Ranieri, P., ... Trabucchi, M. (2002). Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. *Age and Ageing, 31*, 277-285. doi: 10.1093/ageing/31.4.277

Scarmeas, N., Albert, S. M., Manly, J. J., & Stern, Y. (2006). Education and rates of cognitive decline in incident Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*, 308-316. doi: 10.1136/jnnp.2005.072306

Schneeweis, N., Skirbekk, V., & Winter-Ebmer, R. (2014). Does education improve cognitive performance four decades after school completion? *Demography, 51*, 619-643. doi: 10.1007/s13524-014-0281-1

Sole-Padulles, C., Bartres-Faz, D., Junque, C., Vendrell, P., Rami, L., Clemente, I. C., ... Molinuevo, J. L. (2009). Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiology of Aging, 30*, 1114-1124. doi: 10.1016/j.neurobiolaging.2007.10.008

Spini, D., Bernardi, L., & Oris, M. (2017). Toward a Life Course Framework for Studying Vulnerability. *Research in Human Development, 14*, 5-25. doi: 10.1080/15427609.2016.1268892

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8*, 448-460. doi: 10.1017/S1355617702813248

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*, 2015-2028. doi: 10.1016/j.neuropsychologia.2009.03.004

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurology, 11*, 1006-1012. doi: 10.1016/S1474-4422(12)70191-6

Stern, Y. (2017). An approach to studying the neural correlates of reserve. *Brain Imaging and Behavior, 11*, 410-416. doi: 10.1007/s11682-016-9566-x

Thorvaldsson, V., Skoog, I., & Johansson, B. (2017). IQ as Moderator of Terminal Decline in Perceptual and Motor Speed, Spatial, and Verbal Ability: Testing the Cognitive Reserve Hypothesis in a Population-Based Sample Followed From Age 70 Until Death. *Psychology and Aging, 32*, 148-157. doi: 10.1037/pag0000150

Tucker-Drob, E. A., Johnson, K. E., & Jones, R. N. (2009). The Cognitive Reserve Hypothesis: A Longitudinal Examination of Age-Associated Declines in Reasoning and Processing Speed. *Developmental Psychology, 45*, 431-446. doi: 10.1037/a0014012

Van Dijk, K. R. A., Van Gerven, P. W. M., Van Boxtel, M. P. J., Van der Elst, W., & Jolles, J. (2008). No protective effects of education during normal cognitive aging: Results from the 6-year follow-up of the Maastricht aging study. *Psychology and Aging, 23*, 119-130. doi: 10.1037/0882-7974.23.1.119

Wang, H. X., Jin, Y. L., Hendrie, H. C., Liang, C. K., Yang, L. L., Cheng, Y. B., ... Gao, S. J. (2013). Late Life Leisure Activities and Risk of Cognitive Decline. *Journals of Gerontology Series a: Biological Sciences and Medical Sciences, 68*, 205-213. doi: 10.1093/gerona/gls153

Table 1

Descriptive statistics of measures

Variable	*M* (*SD*) / sample proportions	skewness	kurtosis
1. TMT A completion time (W1) [seconds]	55.23 (24.40)	1.60	6.45
2. TMT A completion time (W2) [seconds]	56.03 (24.37)	1.67	7.44
3. TMT B completion time (W1) [seconds]	115.13 (44.80)	1.16	4.37
4. TMT B completion time (W2) [seconds]	108.90 (45.40)	0.98	4.63
5. Number of chronic diseases [number]	1.26 (1.22)	1.16	4.61
6. Education	low: 43.2% high: 56.8%		
7. Cognitive level first job	low: 30.0% high: 70.0%		
8. Cognitive level last job	low: 15.9% high: 84.1%		
9. Midlife leisure activities [number]	11.73 (2.66)	-.23	2.60
10. W1 leisure activities [number]	9.94 (2.82)	-.19	2.80
11. Age (W1) [years]	74.33 (6.50)	0.58	2.61
12. Sex	men: 51.4% women: 48.6%		

Note: Descriptive statistics for completion time in TMT A and TMT B in W1 and W2, the number of chronic diseases, the markers of cognitive reserve, age, and sex in terms of means (standard deviations are given in parentheses), skewness, and kurtosis as well as sample proportions.

Table 2

Full correlation matrix of measures

Variable	1	2	3	4	5	6	7	8	9	10	11
1. TMT A completion time (W1)	---										
2. TMT A completion time (W2)	.38***	---									
3. TMT B completion time (W1)	.55***	.38***	---								
4. TMT B completion time (W2)	.35***	.63***	.49***	---							
5. Number of chronic diseases	-.02 ns	.11**	.02 ns	.17***	---						
6. Education (0 = low; 1 = high)	-.08 ns	-.05 ns	-.10*	-.10*	-.01 ns	---					
7. Cognitive level first job (0 = low; 1 = high)	-.08 ns	-.12***	-.14***	-.23***	.00 ns	.39***	---				
8. Cognitive level last job (0 = low; 1 = high)	-.09*	-.08*	-.07 ns	-.17***	-.06 ns	.36***	.51***	---			
9. Midlife leisure activities	-.11**	-.08*	-.08*	-.07 ns	.01 ns	.04 ns	.07*	.06 ns	---		
10. W1 leisure activities	-.20***	-.28***	-.18***	-.25***	-.12***	.09**	.09**	.08*	.53***	---	
11. Age (W1)	.19***	.34***	.27***	.40***	.11***	.01 ns	-.08*	.01 ns	-.09**	-.33***	---
12. Sex (0 = men; 1 = women)	.00 ns	-.07*	-.01 ns	.03 ns	.06 ns	-.06 ns	.19***	-.03 ns	.07*	.00 ns	-.06 ns

Note: First-order correlations between completion time in TMT A and TMT B in W1 and W2, the number of chronic diseases, the markers of cognitive reserve, age, and sex. *** $p < .001$; ** $p < .01$; * $p < .05$; ns = non-significant, $p > .05$.

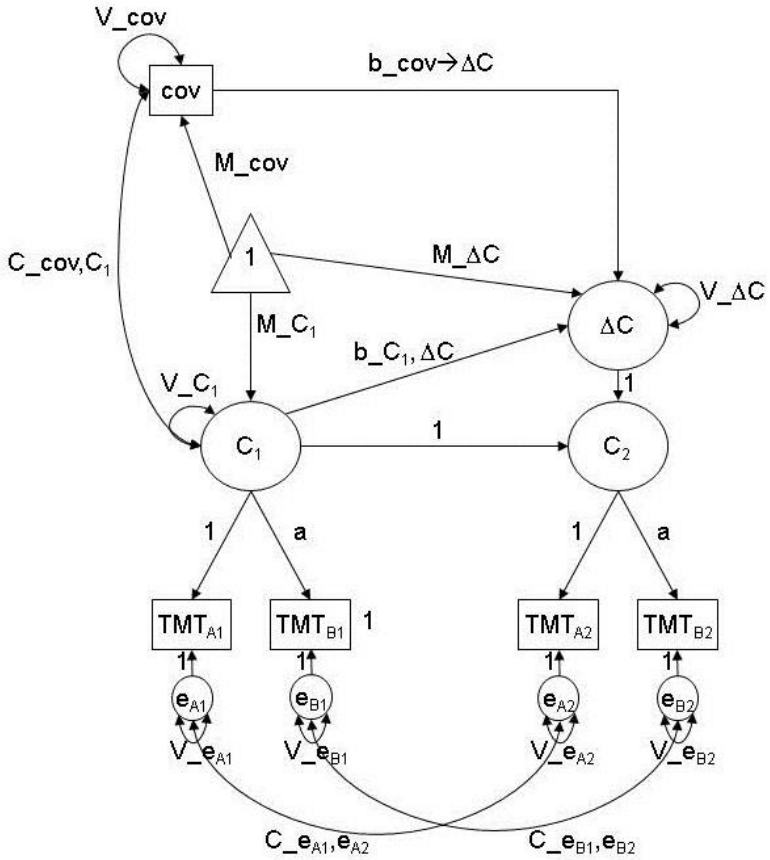

Fig. 1. Specification of the tested latent change score model. C_1 and C_2 represent the latent cognitive factors of Trail Making Test (TMT) completion time in Wave 1 (W1; constructed from scores in TMT parts A and B in W1) and Wave 2 (W2; constructed from scores in TMT parts A and B in W2), respectively. ΔC represents the latent change variable regarding change in TMT completion time from W1 to W2. Note that for clarity purposes the illustration is simplified. We enforced strong factorial invariance on the factor loadings, with intercepts of all indicators being fixed to zero to assure that the same cognitive factor was assessed at both waves. For simplification purposes, arrows from the triangle to the observed indicator variables (TMT A and B) that would indicate that intercepts of all indicators being fixed to zero are not displayed. cov represents all covariates that predicted latent change and were correlated to the latent cognitive factor in W1: age, sex, the number of chronic diseases, the markers of cognitive reserve, and the interactions of the markers of cognitive reserve with the number of chronic diseases (including interrelations of all covariates and interaction terms, which are not displayed here for a better overview).

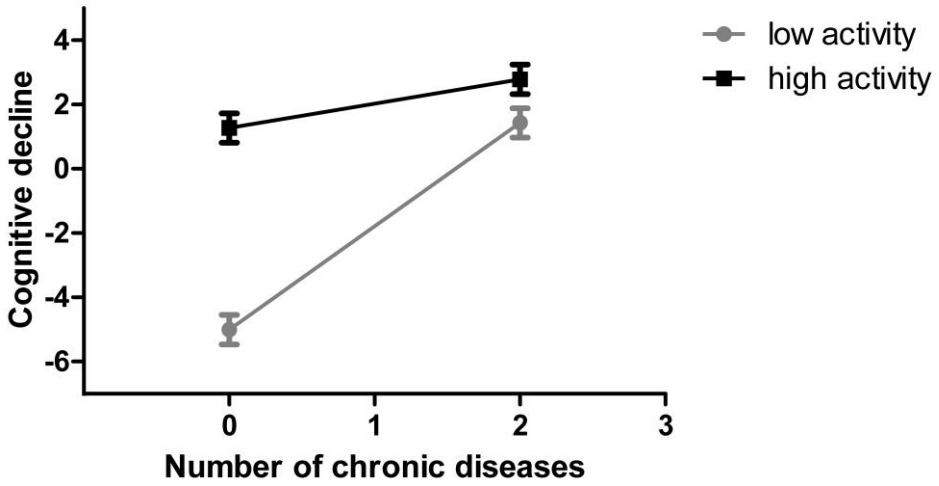

Fig. 2. Estimated mean increase in Trail Making Test (TMT) completion time (i.e., cognitive performance decline in seconds) at a low and a high number of chronic diseases (i.e., 0 and 2 diseases, respectively) as a function of midlife leisure activities (at a low and a high number, i.e. -1 and +1 *SD*, respectively). Bars represent standard errors.

Appendices

Appendix A

Parameter estimates of the latent change score model before the covariates being entered

Parameter (lavaan syntax)			Raw estimate	Standardized estimate	*p*-value
Loadings of latent variables:					
TMT factor W1	=~	TMT A W1	1.00	0.72	NA
TMT factor W1	=~	TMT B W1	2.11	0.80	< .001
TMT factor W2	=~	TMT A W2	1.00	0.82	NA
TMT factor W2	=~	TMT B W2	2.11	0.85	< .001
TMT change	=~	TMT factor W2	1.00	0.82	NA
Regressions:					
TMT factor W2	~	TMT factor W1	1.00	0.87	NA
TMT change	~	TMT factor W1	-0.29	-0.31	< .001
Covariances:					
TMT A W1	~~	TMT A W2	2.30	0.01	.896
TMT B W1	~~	TMT B W2	205.69	0.29	.015
Intercepts:					
TMT A W1	~1		0.00	0.00	NA
TMT B W1	~1		0.00	0.00	NA
TMT A W2	~1		0.00	0.00	NA
TMT B W2	~1		0.00	0.00	NA
TMT factor W1	~1		55.09	3.18	< .001
TMT factor W2	~1		0.00	0.00	NA
TMT change	~1		16.51	1.01	< .001
Variances:					
TMT factor W1	~~	TMT factor W1	300.99	1.00	< .001
TMT factor W2	~~	TMT factor W2	0.00	0.00	NA
TMT change	~~	TMT change	242.54	0.91	< .001
TMT A W1	~~	TMT A W1	284.69	0.49	< .001
TMT B W1	~~	TMT B W1	768.12	0.36	< .001
TMT A W2	~~	TMT A W2	198.24	0.33	< .001
TMT B W2	~~	TMT B W2	670.86	0.28	< .001

Note: Parameter estimates of the latent change score model before the covariates being entered. Specifically, we modeled latent cognitive factors of Trail Making Test (TMT) completion time in Wave 1 (W1; constructed from scores in TMT parts A and B in W1) and Wave 2 (W2; constructed from scores in TMT parts A and B in W2) as well as a latent change variable regarding change in TMT completion time from W1 to W2. We enforced strong factorial invariance on the factor loadings, with intercepts of all indicators being fixed to zero to assure that the same cognitive factor was assessed at both waves. NA: *p*-value not available because the respective parameter was fixed in the model specification.

Appendix B

Parameter estimates of the latent change score model after the covariates being entered

Parameter (lavaan syntax)			Raw estimate	Standardized estimate	*p*-value
Loadings of latent variables:					
TMT factor W1	=~	TMT A W1	1.00	0.71	NA
TMT factor W1	=~	TMT B W1	2.12	0.81	< .001
TMT factor W2	=~	TMT A W2	1.00	0.80	NA
TMT factor W2	=~	TMT B W2	2.12	0.86	< .001
TMT change	=~	TMT factor W2	1.00	0.83	NA
Regressions:					
TMT factor W2	~	TMT factor W1	1.00	0.89	NA
TMT change	~	TMT factor W1	-0.43	-0.46	< .001
TMT change	~	age	4.37	0.27	< .001
TMT change	~	sex	-2.01	-0.06	.141
TMT change	~	diseases	1.99	0.15	< .001
TMT change	~	education	1.03	0.03	.494
TMT change	~	first job	-2.15	-0.06	.247
TMT change	~	last job	-2.39	-0.05	.292
TMT change	~	midlife activities	3.14	0.19	.005
TMT change	~	W1 activities	-3.08	-0.19	< .001
TMT change	~	interaction midlife activities X diseases	-1.23	-0.14	.029
Covariances:					
TMT factor W1	~~	TMT change	0.00	0.00	NA
TMT A W1	~~	TMT A W2	16.48	0.06	.325
TMT B W1	~~	TMT B W2	122.35	0.19	.121
TMT factor W1	~~	age	5.53	0.32	< .001
TMT factor W1	~~	sex	0.04	0.00	.907
TMT factor W1	~~	diseases	0.11	0.01	.905
TMT factor W1	~~	education	-1.16	-0.14	.001
TMT factor W1	~~	first job	-1.21	-0.15	< .001
TMT factor W1	~~	last job	-0.63	-0.10	.022
TMT factor W1	~~	midlife activities	-2.28	-0.13	.002
TMT factor W1	~~	W1 activities	-4.67	-0.27	< .001
TMT factor W1	~~	interaction midlife activities X diseases	-3.63	-0.11	.008
TMT factor W1	~~	interaction W1 activities X diseases	-6.72	-0.20	< .001
age	~~	sex	-0.03	-0.06	.057
age	~~	diseases	0.14	0.12	< .001
age	~~	education	0.01	0.02	.645
age	~~	first job	-0.04	-0.08	.014
age	~~	last job	0.00	0.00	.889
age	~~	midlife activities	-0.09	-0.09	.008
age	~~	W1 activities	-0.33	-0.33	< .001
age	~~	interaction midlife activities X diseases	-0.13	-0.07	.045

age	~~	interaction W1 activities X diseases	-0.47	-0.24	< .001
sex	~~	diseases	0.04	0.06	.091
sex	~~	education	-0.02	-0.06	.070
sex	~~	first job	0.04	0.19	< .001
sex	~~	last job	-0.01	-0.03	.321
sex	~~	midlife activities	0.03	0.07	.042
sex	~~	W1 activities	0.00	0.00	.938
sex	~~	interaction midlife activities X diseases	0.05	0.06	.092
sex	~~	interaction W1 activities X diseases	-0.04	-0.04	.282
diseases	~~	education	0.00	-0.01	.842
diseases	~~	first job	0.00	0.00	.890
diseases	~~	last job	-0.03	-0.06	.107
diseases	~~	midlife activities	0.02	0.02	.597
diseases	~~	W1 activities	-0.15	-0.12	< .001
diseases	~~	interaction midlife activities X diseases	0.04	0.02	.585
diseases	~~	interaction W1 activities X diseases	-0.37	-0.16	< .001
education	~~	first job	0.09	0.39	< .001
education	~~	last job	0.07	0.36	< .001
education	~~	midlife activities	0.02	0.04	.199
education	~~	W1 activities	0.05	0.09	.006
education	~~	interaction midlife activities X diseases	0.03	0.03	.306
education	~~	interaction W1 activities X diseases	0.07	0.07	.037
first job	~~	last job	0.09	0.51	< .001
first job	~~	midlife activities	0.03	0.06	.057
first job	~~	W1 activities	0.04	0.09	.012
first job	~~	interaction midlife activities X diseases	0.03	0.03	.340
first job	~~	interaction W1 activities X diseases	0.03	0.03	.315
last job	~~	midlife activities	0.02	0.06	.062
last job	~~	W1 activities	0.03	0.07	.031
last job	~~	interaction midlife activities X diseases	0.01	0.01	.734
last job	~~	interaction W1 activities X diseases	0.02	0.03	.416
midlife activities	~~	W1 activities	0.53	0.53	< .001
midlife activities	~~	interaction midlife activities X diseases	1.33	0.73	< .001
midlife activities	~~	interaction W1 activities X diseases	0.63	0.33	< .001
W1 activities	~~	interaction midlife activities X diseases	0.64	0.35	< .001
W1 activities	~~	interaction W1 activities X diseases	1.41	0.73	< .001
interaction midlife activities X diseases	~~	interaction W1 activities X diseases	1.40	0.40	< .001
Intercepts:					
TMT A W1	~1		0.00	0.00	NA
TMT B W1	~1		0.00	0.00	NA
TMT A W2	~1		0.00	0.00	NA
TMT B W2	~1		0.00	0.00	NA

TMT factor W1	~1		54.89	3.15	< .001
TMT factor W2	~1		0.00	0.00	NA
TMT change	~1		25.54	1.58	< .001
age	~1		0.00	0.00	> .999
sex	~1		0.49	0.97	< .001
diseases	~1		1.27	1.04	< .001
education	~1		0.57	1.15	< .001
first job	~1		0.70	1.53	< .001
last job	~1		0.84	2.31	< .001
midlife activities	~1		0.00	0.00	.986
W1 activities	~1		0.00	0.00	.993
interaction midlife activities X diseases	~1		0.02	0.01	.804
interaction W1 activities X diseases	~1		-0.15	-0.08	.023
Variances:					
TMT factor W1	~~	TMT factor W1	302.82	1.00	< .001
TMT factor W2	~~	TMT factor W2	0.00	0.00	NA
TMT change	~~	TMT change	189.34	0.72	< .001
age	~~	age	1.00	1.00	< .001
sex	~~	sex	0.25	1.00	< .001
diseases	~~	diseases	1.50	1.00	< .001
education	~~	education	0.25	1.00	< .001
first job	~~	first job	0.21	1.00	< .001
last job	~~	last job	0.13	1.00	< .001
midlife activities	~~	midlife activities	1.00	1.00	< .001
W1 activities	~~	W1 activities	1.00	1.00	< .001
interaction midlife activities X diseases	~~	interaction midlife activities X diseases	3.36	1.00	< .001
interaction W1 activities X diseases	~~	interaction W1 activities X diseases	3.76	1.00	< .001
TMT A W1	~~	TMT A W1	293.52	0.49	< .001
TMT B W1	~~	TMT B W1	718.19	0.35	< .001
TMT A W2	~~	TMT A W2	219.94	0.36	< .001
TMT B W2	~~	TMT B W2	591.45	0.26	< .001

Note: Parameter estimates of the latent change score model after the covariates being entered. Specifically, we modeled latent cognitive factors of Trail Making Test (TMT) completion time in Wave 1 (W1; constructed from scores in TMT parts A and B in W1) and Wave 2 (W2; constructed from scores in TMT parts A and B in W2) as well as a latent change variable regarding change in TMT completion time from W1 to W2. We enforced strong factorial invariance on the factor loadings, with intercepts of all indicators being fixed to zero to assure that the same cognitive factor was assessed at both waves. We included several covariates that predicted latent change and were correlated to the latent cognitive factor in W1: age, sex, the number of chronic diseases, the markers of cognitive reserve, and the interactions of the markers of cognitive reserve with the number of chronic diseases (note that only significant interactions were included in the final model for sake of parsimony and simplicity). We also included interrelations of all covariates and interaction terms. NA: *p*-value not available because the respective parameter was fixed in the model specification.