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## Association of Accelerated Multi-Morbidity and Age-Related Cognitive Decline in Older, Non-Demented Participants from the Baltimore Longitudinal Study of Aging

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### Abstract

**Objectives**—To explore the association between the rate of physical health deterioration, operationalized as rising multi-morbidity overtime, and the longitudinal decline in cognitive function in non-demented older adults.

**Design**—Longitudinal Study (Baltimore Longitudinal Study of Aging, BLSA)

**Setting**—Community

**Participants**—756 BLSA participants, aged 65 or older, followed for an average of 3 years and free of dementia or mild cognitive impairment both at baseline and follow-ups.

**Measurements**—Standardized neurocognitive tests evaluating mental status, memory, executive function, processing speed and verbal fluency were administered. Multi-morbidity was assessed at each visit as number of diagnosed chronic diseases from a pre-defined list. Faster accumulation of chronic diseases was defined as upper quartile of rate of change in number of diseases over time ( 0.25 diseases/year).

**Results**—Faster accumulation of chronic diseases was significantly associated with greater rate of decline in Category and Letter Fluency Tests ( $P=.015$  and  $P=.013$  respectively). Similar trends were also found for Trail Making Tests A and B ( $P<0.1$ ), while no association was found with rate of change in visual and verbal memory.

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**Author Contributions:** All authors contributed to this paper.

**Conclusion**—Although further investigations are required to validate our results and fully understand the underlying mechanisms, these findings suggest that accelerated deterioration of physical health is associated with accelerated decline with aging in specific cognitive domains in non-demented older adults.

### Keywords

multimorbidity; cognition; cognitive decline; aging; older adults

## INTRODUCTION

Multi-morbidity, the co-occurrence of multiple chronic diseases, affects roughly 3 in 4 individuals aged 65 years and older, and has been recognized as the most common “chronic medical condition” in older persons<sup>1</sup>.

From a gerontological perspective, the rising burden of multi-morbidity with aging can be interpreted as the clinical manifestation of progressive loss of resilience and homeostatic dysregulation in multiple organs and systems, which characterize aging itself. In fact, when a certain threshold of dysfunction is reached, the multisystem effect of aging becomes evident as multi-morbidity<sup>2</sup>. Noteworthy, especially in the context of longitudinal studies, the complexity of multisystem effect of aging has been partially resolved and clustered in discrete domains or aging phenotypes<sup>3</sup>. In particular, neurodegeneration, whose main expression is cognitive decline, is considered one of the typical aging phenotypes. Therefore, if we assumed that multi-morbidity is a proxy measure of age-related multisystem failures, it is reasonable to hypothesize an association between burden of multi-morbidity and cognitive decline.

In addition, at a population level, multi-morbidity presents new challenges to clinical decision making in clinical practice and health care organizations, which tend to be organized around specific disease diagnoses<sup>4-6</sup>. The co-occurrence of multiple chronic conditions, in fact, is a well-known risk factor for hospital admission, longer hospital stays, polypharmacy, physical function decline and premature death<sup>7</sup>. Besides, it is a common clinical observation that older patients with accelerated accumulation of multi-morbidity tend to have an accelerated worsening of their cognition, including slight chronic cognitive decline accompanying multiple chronic diseases and episodes of acute delirium. This cognitive deterioration may not evolve to frank dementia and may even improve if the underlying diseases are successfully controlled. However, whether deterioration of physical health, operationalized as rising multi-morbidity, can be one of the multiple pathways leading to cognitive decline in older adults has not been fully investigated. Previous studies examining the influence of co-morbidities on clinical progression of dementia provided contradictory results and only one attempt to explore the effect of incident medical conditions on cognitive function in a normal adult population was reported<sup>8-13</sup>. However, in this study, cognitive assessment was limited solely to verbal memory and psychomotor speed<sup>13</sup>. Therefore, while previous literature largely explored the effect of single chronic diseases, such as, for example, diabetes<sup>14</sup>, congestive heart failure<sup>15</sup>, COPD<sup>16</sup> and chronic kidney disease<sup>17</sup> on cognition, knowledge about neuropsychological deficits associated with

the co-presence of multiple medical conditions is still limited. Indeed, understanding whether the accumulation of multiple chronic diseases, independent of their type, accelerates the decline of cognitive performance, even in non-demented older adults, may help to better understand pathological mechanisms leading to cognitive deterioration in older adults and to develop preventive strategies.

Using data from the Baltimore Longitudinal Study of Aging (BLSA), including participants aged 65 years or older and free of diagnosis of mild cognitive impaired (MCI) or dementia, we explored the relationship between the rate of change in number of chronic diseases and rate of change in cognitive performance. In particular, the aims of the present study were (1) to test whether participants with accelerated deterioration of physical health, operationalized as faster accumulation of chronic diseases over time, experience concurrent accelerated longitudinal decline in cognitive performance compared to the rest of the population and independent of potential confounders, and (2) to determine whether specific cognitive domains are differentially affected by faster accumulation of chronic diseases over time.

## METHODS

### Study design and setting

The BLSA is a study of human aging established in 1958 and conducted by the National Institute on Aging (NIA) Intramural Research Program. A general description of the study population and enrollment procedures and criteria has been previously reported<sup>18</sup>. Briefly, the BLSA continuously enrolls healthy volunteers aged 20 and older who are followed for life regardless of changes in health and functional status. Presently, participants are examined over three days of testing at the NIA Clinical Research Unit in Baltimore at intervals of 1 to 4 years, with more frequent follow up visits for older ages. Certified nurse practitioners and certified technicians administer all assessments according to standardized protocols.

### Participants

The sample for the current study consisted of 756 participants, aged 65 or older, who attended their first visit between May 2005 and September 2013 and were followed for an average of 3 years (range 0-8 years). Of these, 515 (68.12%) underwent at least one follow up visit. The number of participants by length of follow up and the number of observations by follow up time (years) are also provided in TableS1a and TableS1b, respectively. All data used in these analyses were from participants who were considered cognitively non-impaired and non-demented both at baseline and at follow up visits. Visits after the onset of symptoms of cognitive impairment indicative of MCI or prevalent or incident dementia defined by standardized consensus criteria procedures for the BLSA, were excluded from analysis<sup>19-20</sup>.

### Measurements

**Cognitive assessment**—At each study visit, standard neuropsychological tests were administered by highly trained psychometricians. The *Mini Mental State Examination* (MMSE;  $n = 702$ ) assessed global cognitive function. *Letter Fluency* ( $n = 652$ ) and

**Category Fluency** ( $n = 652$ ) examined phonemic and semantic fluency, respectively. The **Benton Visual Retention Test** (BVRT;  $n = 749$ ) evaluated short term visual memory and visuo-constructional skills. The **California Verbal Learning Test** (CVLT), including **Learning and Immediate Free Recall** ( $n = 684$ ), **Short Delay Free Recall** ( $n = 683$ ) and **Long Delay Free Recall** ( $n = 679$ ), measured verbal learning and memory. The **Digit Span Forward** ( $n = 750$ ), **Backward** ( $n = 750$ ) and **Digit Symbol Substitution Test** ( $N = 697$ ) tests assessed attention and working memory. The **Trail Making Test Part A** ( $n = 653$ ) and **Part B** ( $n = 647$ ) evaluated psychomotor speed, attention, and executive functions. The **Card Rotations Test** ( $n = 715$ ) measured spatial ability.

For BVRT and the Trail Making Test, worse performance was indicated by higher scores. For all other neuropsychological measures, worse performance was indicated by lower scores.

### Multi-morbidity

In recent years, the study of multi-morbidity has gained considerable interest in the literature although no standard and widely acknowledged operational definition of multi-morbidity has emerged. One of the most common approaches is to define multi-morbidity as a count of number of diseases<sup>21</sup>. For this purpose, Fortin et al suggested considering (at least) the 12 most prevalent chronic diseases with high impact or burden in a given population<sup>22</sup>. Following these recommendations, we selected “a priori” a list of 13 candidate chronic conditions that could be reliably adjudicated based on the data available that are known to have high prevalence and associated with high disability and mortality risk in older adults. Most of these conditions (hypertension, diabetes, coronary artery disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, cancer, Parkinson’s disease, history of hip fracture and lower extremities joint disease) were defined using standard criteria and algorithms similar to those used in the Women’s Health and Aging Study<sup>23</sup>. In addition, anemia was defined as hemoglobin  $< 12\text{g/dl}$  in women and  $< 13\text{ g/dl}$  in men<sup>24</sup>; chronic kidney disease was defined as glomerular filtration rate estimated using the MRDR equation  $< 60\text{ ml/l}^{25}$ ; peripheral arterial disease was defined as ankle-brachial index measured by Doppler stethoscope  $< 0.9$ <sup>26</sup>. The presence of each chronic condition was ascertained at baseline and follow-ups. Details about the diagnostic criteria for each condition and their prevalence in our study population are also presented in TableS2. As in previous studies, we operationalized multi-morbidity as *number of diagnosed diseases* according to standard clinical criteria<sup>27</sup>.

### Covariates

Baseline age and education were assessed in years. Binary covariates included sex (male = 1; female = 0) and race (white = 1; nonwhite = 0). Baseline number of diseases, among those included in the definition of multi-morbidity presented above, was treated as an ordinal variable (range 0-8). Depression was defined as a score of 16 or greater on the Center for Epidemiologic Studies-Depression (CES-D) Scale<sup>28</sup>. Current and former smokers were ascertained by self-reported questionnaire. Alcohol use was ascertained by self-reported questionnaire as number of drink per week.

## Statistical analyses

Summary statistics of the population at the baseline are presented as mean  $\pm$  standard deviation (SD) or percentage. Baseline prevalence of each disease was also calculated and presented in Supplemental Materials.

Linear mixed models were used to explore the longitudinal association between rising multi-morbidity and decline in cognitive performance overtime. First of all, using linear mixed models, we estimated individual longitudinal rate of change (or slopes) in multi-morbidity, operationalized as number of diagnosed chronic diseases. Multi-morbidity was used as dependent variable while intercept and time (of follow up) were used both as fixed effects and random effects. Unstructured covariance structure was assumed on the random effects. Secondly, linear mixed models were used again with each longitudinal cognitive measure as outcome to explore association between changes in multi-morbidity and changes in cognition. In particular, person-specific rates of change overtime in number of diseases, which were estimated from the first step, were used as predictors of rate of change overtime in cognitive tests scores. The individual slopes of rising multi-morbidity overtime were ranked and dichotomized as “group with faster accumulation of multi-morbidity” versus the rest of the population. Group with faster accumulation of multi-morbidity was defined as rate of accumulation greater or equal to the upper quartile cut-off of the sample population ( 0.25 diseases/year). Main predictors included group with faster accumulation of multi-morbidity, time and group with faster accumulation of multi-morbidity\*time. We also included the following covariates baseline age, sex, race, education and baseline number of chronic diseases and their interactions with time. We also included the following covariates baseline age, sex, race, education and baseline number of chronic diseases and their interactions with time. Results are presented as  $\beta$  coefficients and P values corresponding to “group with faster accumulation of multi-morbidity \*time” interactions for all the neuropsychological tests. Baseline age and education were used as continuous covariates and centered on the average value. The other covariates were used as binary/ordinal variables.

Moreover, actual annual changes in cognitive tests scores were also calculated, according to group with faster accumulation of multi-morbidity versus the rest of the population, in order to verify whether the statistical models appropriately fitted the crude data. In particular, we firstly calculated crude changes per year as individual difference between last visit and first visit scores, divided by number of years of follow up. Then, the crude changes were adjusted by baseline age and sex, weighted on length of follow up and presented as means ( $\pm$  standard deviations) according to the two groups.

In addition, sensitivity analyses were performed to investigate whether incidental diagnoses of specific diseases included in metric of multi-morbidity may be associated with longitudinal changes in cognitive performance, suggesting that our original results may be driven by those conditions instead of global multi-morbidity. Therefore, we tested for each of the 13 diseases included in our list of candidate conditions whether their presence/absence at each time of the study (time-dependent predictive variable) may be associated with decline in cognitive function overtime (outcome variable), adjusting for the same covariates. Additionally, we also fitted 13 different variants of the original model, obtained by removing

each time one of 13 conditions, to test whether the results were still consistent with the original ones.

To exclude the possibility that participants who were followed longer were followed longer were younger or healthier and the rate of change in number of diseases could be a biased estimated, we compute additional Spearman correlation analyses.

To verify whether the association observed was explained by the future development of MCI or dementia, additional sensitivity analyses were performed excluding from our sample population all individuals with prevalent or incident diagnosis of MCI and dementia.

Finally, a fully-adjusted model including depression, smoke status and alcohol use as covariates was run to exclude the influence of these additional potential confounders.

All analyses were performed using the SAS statistical package, version 9.3 (SAS institute Inc., Cary, NC) and R 3.1.2.

## RESULTS

### Baseline results

Baseline population included 756 BLSA participants (391 men and 365 women) aged 65-95 years (mean age  $\pm$  SD =  $73.8 \pm 7.4$  years). Of these, 531 (70.2%) were white. Average years of education were  $16.6 \pm 2.5$ . The mean number of diseases was  $2.4 \pm 1.6$ , ranging from 0 to 8. Additionally, characteristics of the baseline population (including age, sex and number of diseases) are also presented according to different cognitive tests in Supplemental Materials (TableS3). The most prevalent diseases were hypertension (67.2%), lower extremities joint diseases (51.8%) and chronic kidney disease (34.1%) (TableS2).

Baseline age-adjusted means of all neuropsychological test scores are presented in Table1, according to baseline number of diseases (0-1 vs 2 diseases). After adjustment for baseline age, participants with at least 2 diseases had significantly lower performance on the Digit Symbol Test and Trail Making Test B compared to those with none or one disease. However, the association was no longer significant when the analysis was also adjusted for sex, race and education.

### Longitudinal results

In our sample population, the number of chronic diseases significantly increased over the follow up time ( $\beta=0.19$ ,  $P<.001$ ). Informative statistics on annual rates of change in number of chronic diseases are reported in the Supplemental Material (TableS4). Estimated beta coefficients (standard errors) and corresponding P values for the average annual rate of change of cognitive measures ("time") are presented in Table 2. Estimated beta coefficients (standard errors) and corresponding P values for the comparison in rates of change in cognitive measures between the group with faster accumulation of multi-morbidity and the rest of the population ("group with faster accumulation of multi-morbidity \*time") are also presented in the same table. After adjusting for baseline age, sex, race, education and baseline number of diseases, participants who experienced faster accumulation of chronic



diseases over the follow up had significantly greater longitudinal rate of decline in Category and Letter fluency performance compared to those with a lower rate of change in number of diseases over time ( $P=.015$  and  $P=.013$ , respectively, figure 1A and 1B). Trail Making Test Part A and Part B showed similar associations that did not reach statistical significance ( $P=.084$  and  $P=.075$ , respectively). Faster accumulation of diseases was not significantly associated with rates of change in other neuropsychological measures. In addition, the baseline number of chronic diseases, used as a covariate in the present analysis, was not significantly predictive of accelerated longitudinal decline in performance for any of the neuropsychological tests assessed.

### Sensitivity analyses

Firstly, in order to get a sense of the magnitude and clinical significance of the findings from the models, the actual annual changes in Fluency tests scores were also calculated and shown in Figure 2A and 2B. We found that the actual changes according to group with faster accumulation of multi-morbidity versus the rest of the population were consistent to the ones estimated by statistical analyses (i.e.,  $-0.31$  vs  $-0.18$  [statistical analyses] and  $-0.32$  vs  $-0.17$  [actual changes] for Categorical Fluency;  $-0.18$  vs  $-0.02$  [statistical analyses] and  $-0.19$  vs  $-0.01$  [actual changes] for Letter Fluency), confirming that the statistical models appropriately fitted the crude data.

Sensitivity analyses were also performed to exclude the possibility that the results were driven by specific diseases. In particular, we tested for each of the 13 diseases included in our list of candidate conditions whether their incidental diagnosis may be specifically associated with accelerated decline in Category and Letter fluency performance overtime, independent of covariates. None of the individual diseases was significantly associated with worse decline over time in fluency performance. In addition, we also fitted 13 different models, obtained by removing each time one of 13 conditions included in the original list of candidate diseases, whose results, summarized and presented in Table 3 as median ( $\pm$  interquartile range, IQR) of  $\beta$  coefficients and P values for “group with faster accumulation of multi-morbidity\*time” interaction across the 13 models, were consistent with the original ones.

Moreover, to exclude that participants with higher multi-morbidity tend to have a shorter follow up time because of death or losses during the follow up, additional correlation analyses were also run and we found that the duration of the follow up (years) was not correlated to either baseline age of participants or level of multi-morbidity (Table S5), making it unlikely that differential censoring in participants with different severity of multi-morbidity may have biased the results of our analysis.

Furthermore, additional sensitivity analyses were performed excluding from our sample population all individuals with prevalent or incident diagnosis of MCI and dementia, confirming that individuals with faster accumulation of diseases over the follow up showed a longitudinal steeper rate of decline overtime in Categorical and Letter Fluency tests scores compared to the rest of the population.



Finally, a fully-adjusted model including depression, smoke status and alcohol use as additional covariates was run. The significant association between faster accumulation of multi-morbidities and greater rate of decline in Fluency tests performance remained even after adjusting for these potential confounders ( $\beta=-0.14$ ,  $P=.011$  for Categorical Fluency and  $\beta=-0.17$ ,  $P=.009$  for Letter Fluency, respectively).

## DISCUSSION

The present analysis investigated the association between accelerated deterioration of physical health, operationalized as faster accumulation of multi-morbidity over time, and longitudinal changes in cognitive function over the same time frame in older BLSA participants, free of MCI or dementia over the study period. We found that faster accumulation of multi-morbidity was significantly associated with a faster rate of decline in Category and Letter Fluency Tests, with similar trends for Trail Making Test A and B. In contrast, no effect on visual and verbal memory decline was found.

In particular, we found that, independent of the baseline level of morbidity, participants who accumulated at least one more disease over 5 years of follow up presented a significantly accelerated decline in Fluency tests performance compared to the average rate of decline of the rest of the population (i.e. almost double rate of decline for Categorical Fluency and 9-times faster rate of decline for Letter Fluency).

Our study contributes to previous literature providing new insight to understand the contribution of declining physical health to age-associated cognitive decline in non-demented older persons. Except for a previous study exploring the effect of incident medical conditions on cognitive function in a normal adult population, with the important limitation of restriction of the investigation solely to verbal memory and processing speed, the interrelated connections between physical health deterioration and cognitive deterioration in non-demented older adults were still largely un-explored<sup>13</sup>. In particular, to the best of our knowledge, the longitudinal relationship between rate of increase in number of chronic diseases and rate of decline in cognitive function in older adults without dementia or cognitive impairment had never been tested.

Exploring decline in cognitive function throughout a comprehensive range of neuropsychological test, our study pointed out that accelerated physical health deterioration, operationalized as faster accumulation of multi-morbidity over time, accelerates the normal effect of aging on decline in verbal fluency in non-demented older adults. In contrast, accelerated physical health deterioration seems to have no effect on memory decline. The decline in processing speed, suggested by Trail Making Test A and B, but surprisingly not confirmed by Digit Symbol, may also be associated with accelerated physical health deterioration.

Both executive function and semantic processing ability contribute to performance in verbal fluency, which represents the ability to initiate, generate and articulate a word in response to a specific cue and is considered to reflect problem solving abilities<sup>29-31</sup>. Previous studies showed that verbal fluency declines in normal aging, with some evidence showing a greater

effect of age on category than letter fluency<sup>32-33</sup>. Variations of performance in executive function and processing speed have been associated with pathologic brain changes, in particular increase of periventricular white matter hyper intensities<sup>34-38</sup>. Moreover, speed-of-processing has been proposed as a potential mediator of the relation between aging and decline in fluid intelligence, defined as abstract reasoning or the capacity to face challenges and solve problems in new situations, independent of acquired knowledge<sup>39-41</sup>. Age-effects on fluid intelligence are robust even in the absence of cognitive impairment and, according to our findings, may be accelerated by physical health deterioration.

However, new research is required to fully understand the underlying mechanisms and validate these exploratory findings. If future investigations in larger and diverse population confirm the contribution of accelerated deterioration of physical health to longitudinal decline in cognitive performance, it may be possible to develop preventive strategies. In addition, from a clinical perspective, it may become important to monitor changes in specific cognitive domains in older adults with multi-morbidity, even in absence of diagnoses of mild cognitive impairment or dementia. Finally, the relevance of our findings also concerns ethical implications of decision-making in older patients with multiple comorbidities.

The strengths of our study include the large community dwelling study sample, the longitudinal design and the availability of multiple cognitive tests. However, several limitations need to be addressed. First, because of the demands of attending a clinic visit and enduring performance testing, the BLSA population may have lower prevalence of some illnesses and disability compared to other populations of the same age. Therefore, findings should be confirmed and validated by further studies, in more diverse populations. Second, we acknowledge that no standard methodological approach to measure multi-morbidity exists. Counts of diseases are the most common approach, but they may not be the most valid and reliable, especially when they rely exclusively on self-report. As a consequence, in the present analysis diagnoses of diseases were based on algorithms which integrated different sources of data (i.e. not only self-reported diseases and medication but also, when possible, laboratory and instrumental tests). Of note, we did not include information on disease severity in considering multi-morbidity. However, we used strict thresholds for defining diseases to minimize the chance of over-diagnosis and to increase specificity. Also, severity classification systems that homogeneously quantify the impact of diseases on health are not currently available. Third, the average length of the follow up time was quite limited, mainly due to the relatively recent introduction of some assessments included in the large pool of information used for the diagnosis of multi-morbidity.

Moreover, another important limitation was the variable duration of the follow up for the participants included in our analysis. If participants with higher multi-morbidity had a shorter follow up time because of death or losses during the follow up, there would be the potential for an important bias in our analysis which might influence the interpretation of our results. In particular, if participants who were followed longer were younger or healthier, you could expect that they had both lower multi-morbidity, and less likely to have or develop cognitive problems. To address this important issue we conducted additional correlation analyses and we found that the duration of the follow up (years) was not correlated to either baseline age of participants or level of multi-morbidity, making it unlikely that differential

censoring in participants with different severity of multi-morbidity may have biased the results of our analysis. Of relevance, mortality could have been a competing factor in the analyses of cognitive decline in association with rising multi-morbidity, only if participants with higher multi-morbidity were more likely to die and therefore to be lost during the follow-up. Because no significant correlation could be found between lengths of follow up and level of morbidity, we can conclude that mortality rate did not affect our results”.

In addition, because multi-morbidity increase and decline in cognitive performance occur in the same time frame, a temporal relationship cannot be established. As a consequence, further studies in larger populations and over a longer follow-up are required to validate our results and to better understand the temporal direction of the described association. Furthermore, due to the characteristics of our study population (community-dwelling older adults), we purposely did not focused on the association between multi-morbidity and delirium, although we acknowledge that it should be specifically examined in further investigations, using data from hospitalized older adults or nursing home residents.

Finally, because this study was largely exploratory, adjustments were not carried out for multiple comparisons.

In conclusion, accelerated deterioration of physical health is associated with accelerated decline over time in verbal fluency in older adults, without mild cognitive impairment or dementia. Although further investigations are required to fully explain the underlying mechanisms and validate our results, our findings suggest that accelerated deterioration of physical health may be one of the multiple pathways that can lead to age-related cognitive deterioration and point to future development of possible strategies to prevent and decrease the decline in cognitive performance in older adults with multi-morbidity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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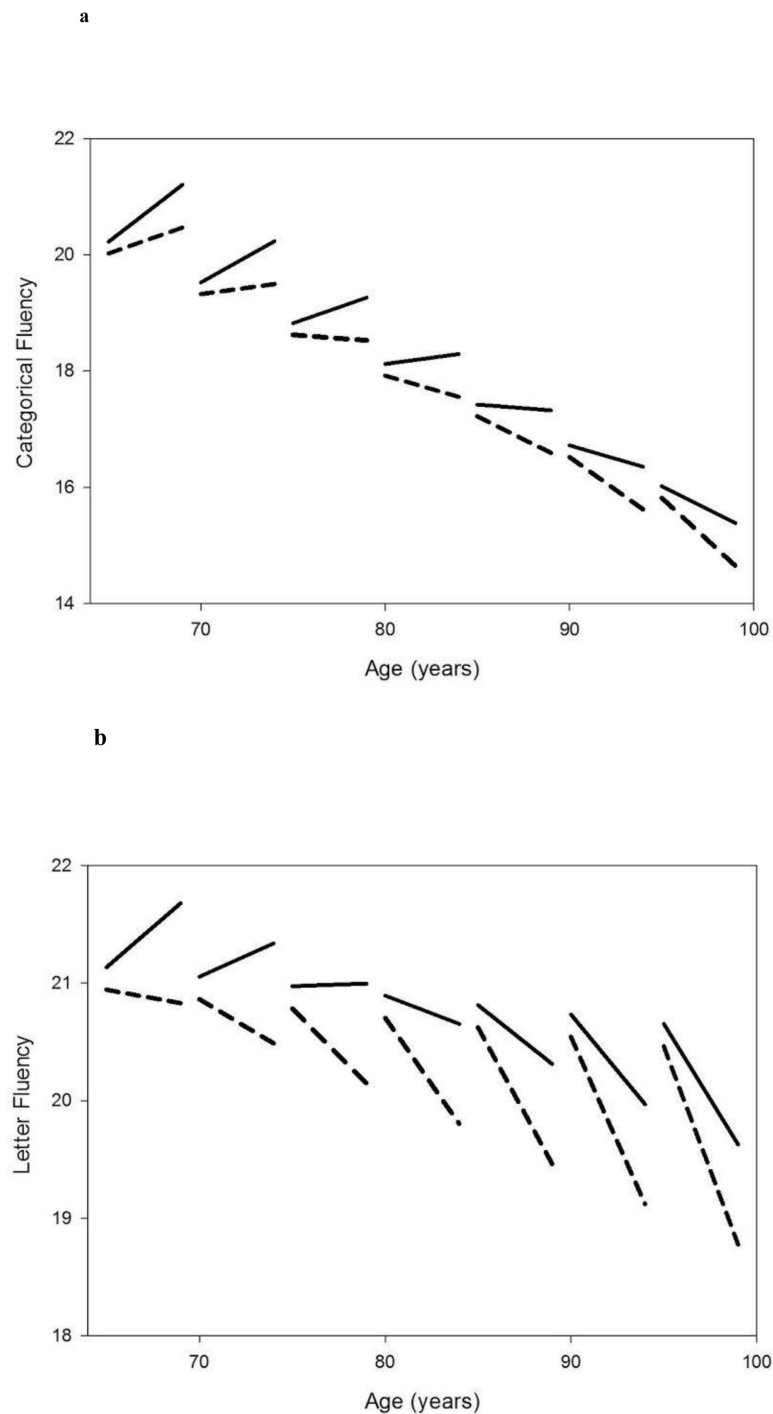
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**Figures 1A and 1B.**

Linear mixed model estimated trajectories of decline in cognitive performance in Category Fluency Test (fig 1A) and Letter Fluency Test (fig 1B) in participants with faster accumulation of diseases overtime (25%, red lines) versus the rest of the population (75%, dark lines), according to different baseline age groups.

Note: Possible range of values (best-worse) for Categorical and Letter Fluency are 35-0 and 31.7-0, respectively.

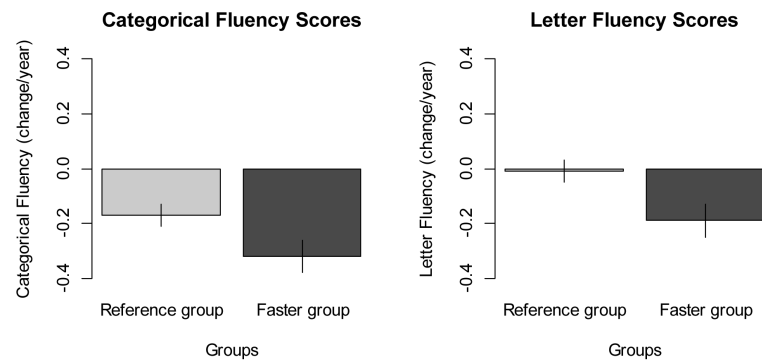
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**Figure 2A and 2B.**

Actual annual changes in Categorical and Letter Fluency tests score according to group with faster accumulation of multi-morbidity (“faster group”, i.e. 0.25 diseases/year or 1 diseases in 4 years) versus the rest of the population (“reference group”), adjusted by baseline age and sex and weighted on length of follow up.

Note: Possible range of values (best-worse) for Categorical and Letter Fluency are 35-0 and 31.7-0, respectively.

**Table1**

Age adjusted means ( $\pm$ Standard Deviations) for all neuropsychological measures according to number of diseases (0-1 vs 2 diseases) in the baseline population.

<b>Domain</b>	<b>Baseline population</b>					<b>Age adjusted P value</b>
	<b>Neuropsychological Measure</b>	<b>N</b>	<b>Possible range of values (best –worse)</b>	<b>0-1 disease (mean, SD)</b>	<b>2 diseases (mean, SD)</b>	
<b>Global cognition</b>	MMSE	702	30-0	28.7 (0.1)	28.6 (0.1)	.192
<b>Verbal fluency</b>	Category Fluency	652	35 <sup>*</sup> -0	15.6 (0.2)	15.5 (0.1)	.784
	Letter Fluency	652	31.7 <sup>*</sup> -0	14.1 (0.3)	14.3 (0.2)	.534
<b>Figural Memory</b>	Benton Visual Retention Test (BVRT)	749	0-30 <sup>#</sup>	7.2 (0.3)	6.9 (0.2)	.397
<b>Verbal Memory</b>	California Verbal Language (CVLT) Learning & Immediate Free Recall	684	80-0	50.8 (0.9)	51.5 (0.6)	.498
	CVLT Short Delay Free Recall	683	16-0	9.9 (0.2)	10.2 (0.2)	.284
	CVLT Long Delay Free Recall	679	16-0	10.3 (0.3)	10.7 (0.2)	.179
<b>Attention and Working Memory</b>	Digitspan Forward	750	14-0	7.7 (0.2)	7.71 (0.1)	.929
	Digitspan Backward	750	14-0	6.8 (2.6)	6.6 (2.7)	.507
	Digit Symbol	697	93-0	45.3 (0.7)	42.9 (0.4)	.005
<b>Executive functions</b>	Trail Making Test A	653	5-300	32.8 (0.9)	34.8 (0.6)	.069
	Trail Making Test B	647	5-300	80.4 (3.2)	90.8 (2.0)	.006
<b>Spatial Ability</b>	Card Rotations Test	715	224-(–224)	82.9 (2.5)	82.8 (1.7)	.959

<sup>\*</sup> best value in our study population;

<sup>#</sup> worse value in our study population (for tests that do not have a standardized range of possible values)

SD=standard deviation; MMSE=Mini Mental State Examination; BVRT=Benton Visual Retention Test; CVLT= California Verbal Language Test.

**Table2**

Results from multiple linear mixed models, testing the relationship between longitudinal decline in cognitive performance and faster accumulation of chronic diseases, conceptualized as group with faster accumulation of multi-morbidity (upper quartile of the sample population, 25%) versus the rest of the sample (75%).

Longitudinal analyses					
Effect of faster accumulation of multi-morbidities on longitudinal decline in cognitive performance ("Group with faster accumulation of multi-morbidity*time" vs rest of the population), after adjustment for covariates <sup>†</sup>					
		Time		Group with faster accumulation of multi-morbidity *time (Vs rest of the population)	
Domain	Neuropsychological Measure	$\beta$ (SE)	P value	$\beta$ (SE)	P value
Global cognition	MMSE	-0.07 (0.02)	.015	-0.04 (0.04)	.249
Verbal fluency	Category Fluency	-0.18 (0.03)	<.001	-0.13 (0.05)	.015
	Letter Fluency	-0.02 (0.04)	.658	-0.16 (0.06)	.013
Figural Memory	Benton Visual Retention Test (BVRT)	0.37 (0.05)	<.001	0.03 (0.08)	.752
Verbal Memory	California Verbal Language (CVLT) Learning & Immediate Free Recall	-0.24 (0.13)	.079	-0.25 (0.22)	.269
	CVLT Short Delay Free Recall	-0.07 (0.04)	.079	-0.06 (0.07)	.393
	CVLT Long Delay Free Recall	-0.02 (0.04)	.524	-0.05 (0.07)	.448
Attention and Working Memory	Digitspan Forward	-0.11 (0.03)	<.001	0.06 (0.05)	.232
	Digitspan Backward	-0.09 (0.03)	.002	0.07 (0.05)	.179
	Digit Symbol	-1.26 (0.08)	<.001	0.05 (0.13)	.672
Executive functions	Trail Making Test A	0.28 (0.24)	.236	0.71 (0.41)	.084
	Trail Making Test B	1.48 (0.49)	.003	1.46 (0.82)	.075
Spatial Ability	Card Rotations Test	-1.05 (0.25)	<.001	0.53 (0.42)	.208

<sup>†</sup> covariates included baseline age, sex, race, education, baseline number of diseases, time, baseline age\*time, sex\*time, race\*time, education\*time, baseline number of diseases\*time.

$\beta$ =beta coefficient; SE=standard error

**Table3**

Results from Sensitivity Analyses for Letter and Category Fluency Tests, presented as mean and median ( $\pm$  interquartile range, IQR) of  $\beta$  coefficient and P value for “group with faster accumulation of multi-morbidity \*time” interaction across 13 different models obtained by removing each time one of 13 conditions included in the original list of candidate diseases.

Neurophysiological Measure	Sensitivity Analyses	
	“Group with faster accumulation of multi-morbidity *time” interaction	
	$\beta$ median (IQR)	P value median (IQR)
Category Fluency	−0.14 (0.13-0.14)	.012 (.009-.017)
Letter Fluency	−0.19 (0.16-0.19)	.004 (.003-.021)

$\beta$  = beta coefficient

IQR= inter-quartile range