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Cross-sectional and prospective associations between homocysteine and a frailty index: A post-hoc analysis of the multidomain Alzheimer's prevention trial (MAPT)

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ABSTRACT

Background: Homocysteine (Hcy) has been associated with several health problems, including reduced physical capacity. No study appears to have looked at the role of Hcy values longitudinally on physical capacity deterioration in older adults. The objective is to examine cross-sectional and prospective associations between Hcy values and frailty in the elderly and investigate Hcy potential association with the onset of frailty.

Methods: 769 community-dwelling older adults from the MAPT study were recruited for this study. Total Hcy was measured at baseline. Frailty was evaluated at 5 different collection timepoints: baseline, 6-month, 1-, 2-, and 3-year using a frailty index (FI) composed of 19 items. Linear regressions adjusted for all the confounders (age, gender, educational level, MAPT group allocation and Omega-3) were performed to examine the cross-sectional associations of homocysteine values with the FI. A cox model was used to test the association of Hcy with the onset of frailty. **Results:**

Mean Hcy values ($15.9 \pm 5.6 \mu\text{mol/L}$) were obtained from 769 community-dwelling adults (75.7 ± 4.6 years old). After adjustments, a significant ($\beta = 0.002$, (0.0002–0.003)) and positive association between baseline Hcy values and FI was found ($\beta = 0.002$). Additionally, higher values of Hcy were associated with a worsening of FI after 3 years ($\beta = 0.002$, $p = 0.003$). A significant association between baseline Hcy values and the likelihood of developing frailty was discovered by incident event analysis (HR: 1.04 (1.01–1.06), $p = 0.004$).

Conclusion: High levels of Hcy are associated with the fragility process in community-dwelling older adults.

1. Introduction

In healthy individuals, Hcy is quickly converted to methionine or cysteine by vitamin B, therefore the expected fasting values are not very high (Veeranki and Tyagi, 2013). To date, there is no general agreement on Hcy cut-off points (Azzini et al., 2020). In general, the reference total Hcy in plasma ranges between 5 and $10 \mu\text{mol/L}$ (Škovierová et al., 2016) and rarely exceeds $15 \mu\text{mol/L}$ in normal conditions (Azzini et al., 2020; Kim et al., 2018). Again, there are no cut-off values, however a plasma Hcy value close to or $>15 \mu\text{mol/L}$ might be classified as HHcy.

Chronically high values of plasma Hcy (HHcy) has been associated

with numerous health issues such as cognitive impairment (Marengoni et al., 2004), neurological disorders (Gu et al., 2012; Valentino et al., 2010; Zoccollella et al., 2008), bone resorption (Álvarez-Sánchez et al., 2018), and higher risk of mortality (Wong et al., 2013). High levels of Hcy, called hyperhomocysteinemia (HHcy), has also been recently linked to poorer physical performances (Kado et al., 2002; Kuo et al., 2007; van Schoor et al., 2012; Vidoni et al., 2017, 2018) and frailty (Álvarez-Sánchez et al., 2020; Wong et al., 2013).

Individuals with elevated plasma Hcy are at an increased risk of physical capacity decline over a three-year period in healthy and highly functional elderly (top third of their age group in physical and cognitive

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performance) (Kado et al., 2002). The relationship between Hcy and physical capacity, including balance, gait, lower body strength, coordination and manual dexterity, could thus be even more pronounced in less active and older elderly. Concurrently individuals with higher Hcy values tend to walk slower and have a higher prevalence of self-reported disability than individuals with lower Hcy values (Kuo et al., 2007). Activities of daily living are reported as more difficult in people with higher Hcy values when evaluated by a disability item questionnaire, even when adjusted with quadriceps strength and/or usual walking speed. Additionally, women with high Hcy values have significantly lower physical performance values (walking test, chair stands test and tandem stand) in cross-sectional analyses (van Schoor et al., 2012).

In individuals with high values of Hcy, the lower ability of muscle cells to regenerate and adapt to meet the body's needs could result in skeletal muscle weakness and atrophy, leading to impaired physical capacity (Kado et al., 2002). Thus, it is reasonable to believe that Hcy plays an important role in the frailty process by affecting, among other things, important elements associated with physical capacity.

Nevertheless, the exact role of Hcy in the frailty process of elderly is not clear. Very few studies have looked at the relationship between HHcy and physical capacity in older people at risk of frailty, with or without intervention. Furthermore, it appears that no study has examined the impact of HHcy over time on the risk of frailty in older persons who are at risk for this condition. The present objective is to examine cross-sectional and prospective associations, over 3 years, between Hcy values and frailty in the elderly. In addition, we seek to determine if baseline Hcy values are associated with the onset of frailty in this population. The hypothesis tested in this study is that Hcy concentration is associated with worsening physical capacity in the elderly in a cross-sectional and prospective manner.

2. Method

This study is a secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT) (registration: NCT00672685). The MAPT study is a large multicentre, 3-year phase III RCT which had a four-arm design that comprised: 1) multidomain intervention (physical activity (PA), nutritional counseling and cognitive training), 2) omega-3 fatty acid (n-3 PUFA), 3) multidomain intervention combined with n-3 PUFA supplementation and 4) no intervention with a placebo. The study protocol (Vellas et al., 2014) and the main results were published elsewhere (Andrieu et al., 2017). The participants (n = 1680) signed informed consent, and the study protocol was approved by the French Ethics Committee located in Toulouse (CPP SOOM II).

2.1. Frailty index

Frailty was evaluated at 5 different timepoints: at baseline, 6-month, and 1-, 2-, and 3-year. A FI composed of 19 items (see Table S1 for details on the elaboration of the FI) was built following standard procedures (Searle et al., 2008). The FI has been largely used in the literature and has proven its validity in predicting adverse health events (Clegg et al., 2013; Mitnitski et al., 2002; Rockwood et al., 2011). For this study, the FI was based on all tests based on physical capacity (ie, subjective and objective measures that were not directly related to cognitive function). Therefore, the FI was calculated as the sum of 19 deficits divided by the total number of deficits, giving a continuous variable ranging from 0 (no deficits) to 1 (all deficits present). For example, an individual who has five deficits would have a FI of 0.26 (ie. 5/19). The cut-off for defining frailty was ≥ 0.25 , as previously suggested (Ma et al., 2018; Rockwood and Mitnitski, 2007; Song et al., 2011; Sutorius et al., 2016). This FI cut-off was used in this population in a previous publication (Maltais et al., 2019).

2.2. Participants

The participants of the MAPT study were community-dwelling men and women, aged ≥ 70 years old, without dementia and meeting at least one of the following criteria: spontaneous memory complaints or limitation in executing ≥ 1 Instrumental Activity of Daily Living or slow gait speed (≤ 0.8 m/s). In this sense, the participants in the present study were considered to be at risk for frailty. Of the 1680 participants, a total of 769 participants had baseline data on Hcy and were selected for this study.

2.3. Nutrient biomarkers: plasma Hcy and red blood cell n-3 PUFA

Total plasma Hcy was measured at the study baseline using a commercially available enzymatic cycling assay (Cobas 8000, Roche) (Dou et al., 2005) as described elsewhere (Bowman et al., 2019). Briefly, the concentration of total plasma Hcy was measured in plasma samples against a standard curve. Hcy was reduced and combined with S-adenosylmethionine to form methionine and S-adenosyl Hcy (SAH). SAH is hydrolyzed into adenosine and Hcy by SAH hydrolase. Hcy is then cycled back into the Hcy conversion reaction, which amplifies the detection signal. Hcy concentration is proportional to the amount of hydrolyzed adenosine: nicotinamide adenine dinucleotide converted to NAD⁺, which is read at an absorbance of 340 nm. This yields units expressed as $\mu\text{mol/L}$. N-3 PUFA was measured by lipid extraction and is detailed elsewhere (Maltais et al., 2022).

2.4. Confounders

We selected age, gender, educational level, and N3-PUFA index as confounding variables. Since high N-3 PUFA concentration is associated with improved muscle function (Isanejad et al., 2022), it was added as a confounder. Additionally, since MAPT interventions had no significant effects on the FI used in this study (de Souto Barreto et al., 2018), we decided not to restrict our analyses to the placebo group and use the whole population with available data; MAPT group allocation was thus entered as a confounding factor.

2.5. Statistical analysis

Descriptive statistics are presented as means (SD) for continuous variables and absolute numbers and percentages for categorical variables. Linear regressions adjusted for all the confounders were performed to examine the cross-sectional associations of the Hcy values with the FI. For the over-time analysis, mixed-effect regressions (with a random effect at the participant's level) adjusted for confounders were performed to test the associations of baseline Hcy values on the 3-year evolution of FI.

A cox model was used to test the association of Hcy with the risk of having frailty ($\text{FI} \geq 0.25$) was adjusted by age and MAPT groups; proportional hazards were systematically checked (*estat phtest* command; p -value > 0.05 was considered as non-violation of the proportional hazards assumption). Participants were censored at follow-up if they did not have the event (i.e. frailty). Time-to-event was calculated as a discrete variable according to MAPT waves of data collection (ie, 6-month, 1-, 2-, or 3-year).

We performed a sensitivity analysis on the prospective associations of Hcy levels with frailty severity only in the placebo group with the same confounders as the primary analyses. All statistical analyses were performed with Stata v14 (College Station, TX, USA). Significance was set at a p -value ≤ 0.05 . There was no correction for multiple testing due to the exploratory nature of this study.

3. Results

Baseline characteristics are presented in Table 1. Participants were

Table 1
Baseline characteristics of participants with baseline Hcy values.

Variable	Value
Age, years	75.7 ± 4.6
Sex, women (%)	519 (67.5 %)
Education (%)	
No diploma	31 (4.1)
Primary school diploma	147 (19.6)
Secondary education	258 (34.4)
High school diploma	108 (14.4)
Higher diploma	207 (27.6)
Group allocation (%)	
Multidomain + Omega-3	188 (24.5)
Omega-3	197 (25.6)
Multidomain	191 (24.8)
Control	193 (25.1)
Frailty Index (0 to 1, higher is worse)	0.17 ± 0.10
n3-PUFA index (%)	5.8 ± 1.5
Homocysteine (µmol/L)	15.9 ± 5.6

aged 75.7 ± 4.6 years and had a mean FI score of 0.17 ± 0.10, translating into an average of 3.0 ± 1.9 deficits out of 19. Baseline Hcy was 15.9 ± 5.6 µmol/L.

Results from the linear regression showed a significant and positive association between baseline Hcy values and baseline FI (adjusted model: β = 0.002 (0.0003–0.003), p = 0.018), adjusted for intervention group, age, n3-PUFA index, gender, and education (Table 2).

As for the associations between baseline Hcy values and FI overtime, higher baseline Hcy was associated with a worsening of FI after three years, adjusted for age, intervention groups, n3-PUFA index, gender and education (β = 0.002 (0.001–0.003), p = 0.003). After performing a sensitivity analysis with the control group only, no association was found between baseline Hcy and FI (β = -0.0004 (-0.003–0.003), p = 0.776, Table 2).

Regarding the incident event analysis, frailty occurred 155/391 participants (39.6). Discrete-time cox model, adjusted for age and MAPT groups, found a significant association between baseline Hcy values and the risk of frailty onset (HR: 1.04 (1.01–1.06), p < 0.004, Table 3).

4. Discussion

In this study, we examine cross-sectional and prospective associations, over 3 years, between Hcy values and frailty in the elderly as a secondary analysis of the MAPT study. We also investigated if high baseline Hcy levels was associated with the incidence of frailty.

From a cross-sectional perspective, a higher Hcy value was associated with a higher frailty score, suggesting that HHcy may play a role in frailty in the elderly. Additionally, higher values of Hcy were associated with a worsening of FI after 3 years.

4.1. The effect of Hcy on physical capacity and frailty

Marengoni et al. (2004) demonstrated that not only was HHcy a very prevalent condition in hospitalized elderly people, but it was also associated with disability, measured by the Basic Activities of Daily Living scale. However, the mechanisms that may explain how higher

Table 2
Cross-sectional and prospective associations between baseline homocysteine values and frailty index.

	Adjusted model ^a				Unadjusted model			
	n	β-coefficient	95 % CI	p-value	n	β-coefficient	95 % CI	p-value
Cross sectional association between Hcy and FI	670	0.002	0.0003–0.003	0.018	720	0.002	0.001–0.004	<0.001
Prospective association between Hcy and FI	708	0.002	0.001–0.003	0.003	760	0.003	0.002–0.004	<0.001
Sensitivity analyses for the prospective association (restricting to control group)	176	-0.0004	-0.003–0.003	0.776	189	0.001	-0.001	0.003

^a Adjusted for age, MAPT intervention groups, sex, education and baseline n3-PUFA index.

Table 3
Adjusted and unadjusted discrete-time cox regression displaying the associations of baseline homocysteine with the incidence of frailty.

	Adjusted model ^a		Unadjusted model	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
Homocysteine (n = 546, 155 cases)	1.04 (1.01–1.06)	0.004	1.04 (1.02–1.07)	<0.001

^a Adjusted for MAPT groups and age.

Hcy values may impact physical capacity remain to be elucidated. Although the population studied is different, the current study's findings support this, demonstrating that high levels of Hcy are linked to decreased physical capacity both cross-sectionally and longitudinally. Our findings, however, do not suggest that HHcy is a common condition in community-dwelling older adults at risk of frailty.

The contribution of HHcy values on the increased risk of frailty is not fully elucidated. Protein damages and oxidative stress caused by a high concentration of Hcy are among the hypotheses involved (Perna et al., 2003). In individuals with HHcy, the lower ability of muscle cells to regenerate and adapt to meet the body's needs could result in skeletal muscle weakness and atrophy, leading to impaired physical capacity (Kado et al., 2002). In fact, inflammatory markers and various proteins during tissue repair may have a major role in influencing Hcy values (Dudman, 1999; Gori et al., 2007).

Some authors suggest that frailty is associated with HHcy by an independent relationship, not by a causal one (Ma et al., 2020). These authors suggest that a high level of Hcy would be a biomarker for a higher risk of frailty in at-risk elderly populations since polymorphisms in the Hcy metabolic gene are not associated with frailty.

4.2. Grip strength

With older age, strength tends to decrease (Hurley, 1995) and resting Hcy values tend to increase (Marengoni et al., 2004). However, it is not clear whether Hcy plays a role in the loss of strength with age. A cross-sectional study examined the relationship between Hcy values and grip strength (Ao et al., 2019), reporting lower grip strength values in the tertile with higher Hcy values. However, in the multiple regression analysis, Hcy was not a significant contributor, suggesting that higher Hcy values act as a biomarker rather than a cause in individuals with low grip strength. Similarly, Swart et al. (2013) observed a relationship between higher Hcy values and lower grip strength values in older men but not in elderly women. The frailty index used in our study contained, non-exclusively, strength-related items and our results are consistent with the findings of Swart et al. (2013) and Ao et al. (2019).

In elderly, gait speed seems to be affected by Hcy levels (Ng et al., 2012; Vidoni et al., 2017). Hcy is more favorable to alter gait speed by an alteration in muscle, nerve or vascular function (Vidoni et al., 2017). Also, Vitamin B12 and folate levels over the clinical threshold does not seem to protect against gait speed decline in elderly (Vidoni et al., 2017). Hence, the efforts to reduce geriatric frailty should not be concentrated on keeping homocysteine levels below or vitamin levels

over the clinical threshold but rather on enhancing the individual's physical capabilities.

The association between Hcy and muscle fatigue is currently unclear. However, some authors have proposed the hypothesis that HHcy may limit the liver supply of creatine and eventually limit muscular endurance and increase muscle damage (Veeranki and Tyagi, 2013). Also, excess Hcy could compromise nitric oxide signaling and limit hemodynamics in muscle blood vessels. Thus, excess Hcy could hypothetically lead to fatigue and limit physical endurance. Further studies are needed to fully understand how HHcy may increase fatigue in older adults at risk of frailty. The FI in the current investigation considers factors linked to measured and self-reported fatigue.

In light of all these elements, Hcy, and more specifically HHcy, has the ability to affect a number of the frailty components that were taken into account in calculating FI. Although the exact impact of Hcy on each of these is unclear, HHcy seems to be linked to a higher risk of frailty in older people.

Hcy lowering with exercise intervention and increased B vitamins intake.

Few interventions such as the MAPT study, combining physical activity and supplementation in parallel, have been carried out with the objective of reducing Hcy in the elderly. Ng et al. (2015) demonstrated that a PA intervention, a supplementation intervention, and a combined intervention were all effective in reducing the degree of frailty, assessed by the Frailty score, among community-living older adults. Nutritional supplementation reduces frailty independently of physical exercise and a combined intervention (supplementation and PA intervention) is effective in reducing frailty, and particularly improves muscle strength and energy level of participants.

4.3. Limitations

This study has some limitations. The participants in the MAPT study are older adults who report memory loss or functional limitations. Thus, they are likely to be health conscious people. Those most at risk for frailty who are not aware of their health status are unlikely to participate in this type of study. Additionally, some items in the FI are self-reported components and may be suggestive of potential bias by the participant. Finally, the MAPT study did not aim to identify the determinants of Hcy concentration, but the inclusion of IL-6 as a covariate in our model could have been interesting. In fact, IL-6 interacts with vitamin B metabolism by the activity of pyridoxal phosphatase and has an indirect effect on Hcy concentrations (Gori et al., 2007; McCarty, 2000).

Study strengths include the long and rigorous follow-up time for measures of Hcy and deficit items. Additionally, our study sample comes from a population that is not subject to folic acid fortification requirements, which may mitigate the association between frailty and Hcy values that has been found. Jacques et al. (1999) reported that the prevalence of HHcy (>13 $\mu\text{mol/L}$) decreased significantly since the implementation of the regulation requiring all enriched grain products to be fortified with folic acid by the Food and Drug Administration (FDA). At the same time, the health issues linked to HHcy are also seen in North American populations, corroborating the notion that HHcy is not the main factor causing frailty and Hcy values may actually serve more as a biomarker of frailty (Booth and Wang, 2000).

5. Conclusion

In conclusion, this study found a cross-sectional and prospective association, over 3 years, between Hcy and a frailty score in older adults at risk of frailty. Additionally, the incident event analysis identified a significant association between the Hcy levels at baseline and the likelihood of developing frailty. Researchers have attempted to explain the biotoxicity process of HHcy (Škovierová et al., 2016) without providing a clear pathogenesis explanation. Therefore, it remains to be determined whether HHcy has a direct impact on the pathogenesis of frailty, or

whether it is a biomarker reflecting an underlying problem.

In any case, interventions designed to lower Hcy values should simultaneously attempt to ameliorate the individuals' state of frailty. Physical activity is a key element in the management of a person with frailty, as is nutritional intervention. Interventions that include counseling, physical activity, and supplements have a higher likelihood of reducing frailty and possible Hcy toxicity.

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Declaration of competing interest

None.

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Principal investigator: Bruno Vellas (Toulouse); *Coordination:* Sophie Gillette-Guyonnet; *Project leader:* Isabelle Carrié; CRA: Lauréane Brigitte; *Investigators:* Catherine Faisant, Françoise Lala, Julien Delrieu; *Psychologists:* Emeline Combrouze, Carole Badufle, Audrey Zueras; *Methodology, statistical analysis and data management:* Sandrine Andrieu, Christelle Cantet, Virginie Gardette, Christophe Morin; *Multidomain group:* Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation) (Toulouse). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.exger.2022.112066>.

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