Homocysteine, Frailty, and All-Cause Mortality in Older Men: The Health in Men Study

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Background. Frailty and hyperhomocysteinemia are common in the older population. The researchers' objectives were to determine whether elevated homocysteine (tHcy) is associated with frailty and mortality.

Methods. The researchers conducted a prospective cohort study. tHcy was measured by immunoassay in 4,248 community-dwelling men aged 70–88 years. Frailty was assessed with the Fatigue, Resistance, Ambulation, Illness and Loss of weight (FRAIL) scale. Mortality was determined from the death registry.

Results. At baseline, 1,117 men (26.3%) had high tHcy (≥15 µmol/L) and 685 (16.2%) were frail (ie, having three or more deficits in the FRAIL scale). There were 749 deaths during a follow-up duration of 5.1 ± 1.3 years. In cross-sectional analysis, high tHcy was associated with increased prevalent frailty (odds ratio 1.49, 95% CI 1.22–1.81) after adjusting for confounding factors. After a period of 5.3 ± 0.8 years, the longitudinal relationship between high tHcy and frailty was weakened in multivariate analysis (hazards ratio 1.25, 95% CI 0.95–1.65). When assessing the relationship between tHcy and incident frailty, the odds of being frail at follow-up for men with high tHcy and having zero deficit at baseline (ie, FRAIL scale = 0) were 1.59 (95% CI 0.88–2.89) in adjusted analysis. High tHcy also predicted all-cause mortality (hazards ratio 1.25, 95% CI 1.06–1.48) after adjusting for frailty and other covariates.

Conclusions. Hyperhomocysteinemia is associated with the prevalence of frailty. It is also predictive of all-cause mortality, independent of frailty. The results suggest that the association between tHcy and mortality is largely not mediated through the occurrence of frailty.

Key Words: Homocysteine—Frailty—All-cause mortality.

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Frailty is becoming increasingly common as the world’s population ages. It is defined as “a state of excess vulnerability to stressors due to age-related decline in physiologic reserve across multisystems, resulting in reduced ability to maintain or regain homeostasis after a destabilizing event (1).” Differing conceptual approaches have been applied to describe this phenomenon, including incorporation of physical characteristics and function (2), and utilizing a combination of clinical deficits and comorbidity domain (3). The FRAIL scale was subsequently developed, which incorporates the above two approaches (4,5). Frailty has been reported to independently predict risks of adverse health outcomes including falls, disability, institutionalization, health-related quality of life, and mortality (6–9). Various factors are thought to mediate the development of frailty, such as advanced age and medical comorbidities (10). The physiological correlates of frailty have also been explored, with no conclusive evidence of association between biomarkers and frailty to date (11). Homocysteine (tHcy), a B-vitamin metabolite, is one possible candidate that may underlie the development of the frailty syndrome. This is a sulfur amino acid whose metabolism stands at the intersection of two pathways: remethylation, which requires folic acid and B12 coenzymes, and transsulfuration, which requires pyridoxal-5′-phosphate, the B6 coenzyme. Total plasma tHcy has been shown to be inversely related to the intake and plasma levels of folate and B-vitamins (12), and as such, may be used as a surrogate biochemical marker to reflect their metabolic function (13). At the cellular level,
sufficient stores of B-vitamins are essential for “one-carbon” transfer metabolisms, and their deficiencies may result in mitochondrial dysfunction with deleterious changes in cellular function (14). These could conceivably cause muscle weakness and atrophy, leading to sarcopenia with progressive physical decline (15). At the molecular level, B-vitamin deficiency may be mediated via hyperhomocysteinemia through mechanisms of oxidative stress (16), or by homocysteinylation (17), which involves covalent binding of tHcy to proteins. These modified proteins or neoantigens can trigger the inflammatory cascade, resulting in vascular endothelium damage and subsequently vascular events, further leading to functional decline and frailty. tHcy-induced endothelial dysfunction can occur through different mechanisms, via atherosclerotic plaque formation and increased risk of thromboembolic events (18). All these biologic pathways could lead to a multisystem decline due to destabilization of the neuromuscular and metabolic balance. In addition, severe hyperhomocysteinemia can cause endoplasmic reticulum stress leading to cellular growth arrest and apoptosis (19), and ultimately accelerated aging (20). This can result in a higher risk of mortality, thus making this biochemical marker an important target for investigating this adverse health outcome in older people. As frailty also predicts survival (21), its influence should not be ignored while elucidating the biologic association of tHcy with mortality.

In this study, the researchers sought to determine if elevated tHcy is associated with frailty and mortality in later life. The researchers addressed these aims by investigating the cross-sectional and longitudinal relationship between tHcy and frailty (measured by the FRAIL scale) using a large cohort of community-dwelling men aged 70–88 years, as well as the longitudinal relationship between elevated tHcy and all-cause mortality, taking into account the possible mediating effect of frailty.

Methods

Study Design and Participants

The researchers conducted a prospective cohort study, using participants from the Health in Men Study (HIMS), which has been described in detail elsewhere (22). In brief, 12,203 community-dwelling men aged 65–87 years sampled from the electoral roll of Australia completed a health assessment between 1996 and 1999 (HIMS wave 1). In 2001–2004, 10,940 men were invited to participate in the second phase of this study (HIMS wave 2) and blood samples were collected from 4,249 of them. In 2008–2009 (HIMS wave 3), 7,445 surviving men were mailed a third questionnaire, of which 3,274 responded. The Human Research Ethics Committee of the University of Western Australia approved the protocol for HIMS, which was conducted in accordance with the Helsinki Declaration for Human Rights.

Outcome of Interest

Frailty was assessed during waves 2 and 3 with a FRAIL scale (4,5). This consists of five domains: fatigue, resistance, ambulation, illness, and loss of weight. A score of 1 for each domain indicates its presence, and a score of 0 indicates its absence. Responses to the SF-36 Health Survey (23) during waves 2 and 3 were used to assess symptoms of fatigue (worn out or feeling tired most of the time), resistance (inability to climb a flight of stairs), and ambulation (ability to walk 100 m). A score of 1 was recorded for illness if the participant reported having more than five of the following during waves 2 and 3, respectively: arthritis, diabetes, angina or myocardial infarction, hypertension, stroke, asthma, chronic bronchitis, emphysema, osteoporosis, colorectal cancer, skin cancer, depression or an anxiety disorder, Alzheimer’s disease or other dementia, or leg ulcers. Participants scored 1 for weight loss if their weight decreased by more than 5% between waves 1 and 2, and between waves 2 and 3. The researchers considered participants to be frail if they scored a total of three or more in these domains (ie, FRAIL scale ≥ 3). This approach has been validated by analyzing the predictive utility of the scale for all-cause mortality and disability (6,24).

Records of all hospital admissions and mortality were obtained from the Western Australian Data Linkage System (25), which links together records from the mental health data, cancer registry, death registry, and hospital morbidity data.

Explanatory Variables

The following sociodemographic variables were collected from participants: age (difference in years between date of assessment and date of birth), education (completed high school or better by wave 1), living circumstance (living alone or in residential aged care facility during waves 2 and 3), and smoking status (classified as never, former, or current smoker during waves 2 and 3). The researchers identified cardiovascular disease, hypertension, diabetes, and dyslipidemia as potential confounders in the relationship between tHcy and mortality, and hence further elaborated the prevalence of these comorbid diseases from self-reported, clinical, and biochemical data available from waves 1 to 3. Cardiovascular disease was present when the participant reported having a history of angina, myocardial infarction, heart failure, coronary artery bypass grafting, coronary angioplasty, carotid endarterectomy, aortic bypass surgery, peripheral arterial surgery or stroke, or use of medications at the time of assessment for these conditions. Men were considered to have hypertension if they reported having the condition or use of antihypertensive medications or had measured blood pressure of greater than or equal to 140/90 mmHg. Men who were diagnosed with diabetes, reported use of glucose-lowering medication, or had a fasting or nonfasting glucose of greater than or equal to 7 mmol/L or greater than or equal to 11 mmol/L, respectively, were
considered to have diabetes. Men who self-reported the condition or use of lipid-lowering medication, or had fasting low-density lipoprotein of 3.4 mmol/L or higher, high-density lipoprotein less than 0.9 mmol/L, triglycerides of 1.8 mmol/L or higher, or total cholesterol of 5.5 mmol/L or higher were considered to have dyslipidemia.

Clinical information from the Western Australian Data Linkage System were collected from 1990 to the time of blood sampling and the weighted Charlson comorbidity index calculated (26). The latter takes into account 17 common medical conditions that predict 1-year mortality: myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcers, liver disease, diabetes (including diabetes with end organ damage), hemiplegia, renal disease, leukemia, lymphoma, other tumors, metastatic tumors, and AIDS.

Biochemical Analyses and Other Measures

Blood samples were collected during wave 2 between 08:00 and 10:30. Plasma was separated from the blood samples within 1 hour of collection and stored at −80°C until assayed. tHcy was measured by fluorescence polarization immunoassay on an IMx analyzer (27) and dichotomized into “high tHcy” (≥15 µmol/L) and “normal tHcy” (<15 µmol/L) as determined by the laboratory’s reference range. The interassay coefficient of variation was 4%.

Serum creatinine, glucose, cholesterol, low-density lipoprotein, and triglycerides were measured with a Roche Hitachi 917 analyzer (Roche Diagnostics). High-sensitivity C-reactive protein was measured with assay on a BNII analyzer (Dade Behring, Birmingham, United Kingdom). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (28).

Height, weight, and blood pressure were measured by trained research assistants during wave 2. Height and weight were self-reported during wave 3. Body mass index was calculated from height and weight in kg/m².

Statistical Analysis

Data were analyzed using Stata release 11.1 (StataCorp, College Station, TX). Descriptive statistics were calculated for the demographic, lifestyle, and clinical variables in waves 2 and 3 according to the FRAIL scale. The association between tHcy and frailty was investigated in three different ways: according to whether tHcy was greater than or equal to 15 µmol/L, per 5-µmol/L increment in tHcy, and by doubling of tHcy concentration (by dividing the natural logarithm of tHcy by the natural logarithm of 2). To determine the cross-sectional and longitudinal relationship between tHcy and frailty, logistic regression analyses were used. Adjustments were made for age, education, living circumstance, smoking, and renal function (using estimated glomerular filtration rate as proxy in this study). A sensitivity analysis was performed to determine whether exclusion of men who had a history of cardiovascular disease would affect the cross-sectional association. Logistic regression analyses were repeated for incident cases of frailty during wave 3 for those men with zero deficit at baseline (ie, FRAIL scale = 0 during wave 2). The association between high tHcy and individual components of the FRAIL scale during wave 3 was tested using multivariate logistic regression analyses.

Cox proportional hazards models and Cuzik’s test for trend were used to explore the association between tHcy and all-cause mortality. Adjustments were made for age, education, living circumstance, smoking, cardiovascular disease, diabetes, hypertension, dyslipidemia, Charlson comorbidity index, renal function, and baseline frailty status. The results were reported as odds ratio (OR) or hazards ratio (HR) with 95% confidence interval (95% CI). p Values less than 0.05 were considered statistically significant.

RESULTS

A flow chart detailing disposition of the study participants is shown in Figure 1. Men who had died prior to wave 2 follow-up or did not attend due to various reasons were older in age (p < .001), more likely to be current or former smokers (p < .001), and self-report a history of cardiovascular disease (p = .025), hypertension (p < .001), and diabetes (p < .001) during wave 1, in comparison to those men who subsequently responded in wave 2. Similarly, men who had died prior to wave 3 follow-up or had not attended to the questionnaire were older in age (p < .001) and more likely to be current or former smokers (p < .001) in wave 2, compared with those men who had completed the questionnaire in wave 3. However, there was no statistically significant difference in their Charlson comorbidity indices (p = .155).

The sociodemographic, clinical, and biochemical characteristics of the study population during waves 2 and 3 according to FRAIL scale are shown in Table 1. tHcy levels were available for 4,248 men, aged between 70 and 88 years, during wave 2. One thousand one hundred and seventeen men (26.3%) had high tHcy (≥15 µmol/L) and the mean (±SD) tHcy concentration for the wave 2 cohort was 13.4±5.6 µmol/L. Four thousand two hundred and twenty-seven men had complete data for frailty and were thus the focus of this cross-sectional analysis. Six hundred and eighty-five (16.2%) of these men were frail (ie, having three or more deficits). After a follow-up period of 5.3 ± 0.8 years (wave 3), 237 men (34.6%) who were frail at baseline died, compared with 498 men (14.0%) who were nonfrail (ie, having less than three deficits; p < .001). Of those participants who responded to wave 3, 1,824 had complete data for frailty, comorbidities, and tHcy levels at baseline. They were similar in age, smoking, and comorbidity status compared with the rest of the wave 3 cohort who were not included in this longitudinal analysis. Four hundred and sixty-one men (25.3%) during wave 3 were frail, out of which 131 (28.4%) had high tHcy.
In univariate cross-sectional logistic regression analyses (Table 2), high tHcy was associated with increased odds of being frail (OR 2.11, 95% CI 1.78–2.51). The association persisted after adjusting for age, education, living circumstance, smoking, and estimated glomerular filtration rate (OR 1.49, 95% CI 1.22–1.81). When men with a history of cardiovascular disease were excluded from the models, the association persisted in univariate (OR 2.03, 95% CI 1.56–2.63) and multivariate (OR 1.43, 95% CI 1.06–1.93) analyses. When modeled as continuous variables, elevated tHcy continued to be associated with prevalent frailty.

In longitudinal logistic regression analyses (Table 2), high tHcy was associated with increased odds of being frail after a period of 5.3 ± 0.8 years (OR 1.66, 95% CI 1.30–2.12). The association was weakened after adjusting for age, education, living circumstance, smoking, and estimated glomerular filtration rate (OR 1.25, 95% CI 0.95–1.65). When assessing the longitudinal relationship between tHcy and incident frailty, only 809 men with FRAIL scale = 0 during wave 2 were included in the analyses. The odds of being frail at follow-up for these men with high tHcy were 1.59 (95% CI 0.88–2.89). The association between high tHcy and individual components of the FRAIL scale during wave 3 was tested using multivariate logistic regression analyses. High tHcy at baseline predicted the ambulation (OR 1.32, 95% CI 1.01–1.72) component. There was no statistically
significant association with the fatigue (OR 1.21, 95% CI 0.96–1.53), resistance (OR 1.07, 95% CI 0.84–1.37), illness (OR 1.07, 95% CI 0.77–1.48), and weight loss (OR 1.10, 95% CI 0.85–1.42) components.

Among those participants who had data for tHcy levels during wave 2, 749 (17.6%) men subsequently died during a mean follow-up duration of 5.1 ± 1.3 years (range 0.1–7.2 years). Men who died were older (\(p < .001\)), had more comorbidities (\(p < .001\)) and had higher tHcy levels (15.1 ± 8.1 µmol/L vs 13.0 ± 4.8 µmol/L, \(p < .001\)) than those who were alive by the end of the study. There was a graded association between tHcy and all-cause mortality, as shown in Figure 2 (\(z = 8.9, p < .001\)). This association was tested with multivariate Cox proportional hazards models (Table 3). After adjusting for age, education, living circumstance, smoking, cardiovascular disease, diabetes, hypertension, dyslipidemia, Charlson comorbidity index, renal function, and frailty status at baseline, high tHcy continued to predict all-cause mortality (hazards ratio 1.25, 95% CI 1.06–1.48). When tHcy was included as quantitative variables, the associations remained significant.

### Discussion

The researchers’ study has demonstrated an association between elevated tHcy and prevalent frailty, independent of age and other known confounding factors. The researchers also demonstrated that elevated tHcy levels are predictive of all-cause mortality, independent of frailty status and of other covariates. Although tHcy is likely to play some role in the development of frailty in older men, frailty is unlikely to be a major mediator of the association between tHcy and all-cause mortality.

This study, to the researchers’ knowledge, is the first to investigate the relationship between tHcy and frailty in a large cohort of community-dwelling older men. Previous...
studies have explored the relationship between B-vitamins and metabolites with frailty, which resulted in mixed findings. Investigators of the Italian InCHIANTI study (29) found that low folate intake was independently associated with frailty (OR 1.84; 95% CI 1.14–2.98). Biochemical marker levels were, however, not analyzed or correlated. Using cross-sectional data from the combined Women’s Health and Ageing Study (I and II), Michelon and colleagues (30) found a higher prevalence of vitamin B12 deficiency among the frail community-dwelling older women compared with the nonfrail, but no apparent association between frailty and serum levels of B-vitamins. Semba and colleagues (31) analyzed the relationship prospectively using a subset of this cohort (Women’s Health and Ageing Study I) and concluded that there was no association between the B-vitamins and incident frailty after 3 years of follow-up. Analyses from the combined Women’s Health and Ageing Study cohort were further race-stratified by Matteini and colleagues (32) and investigations limited to Caucasian women. There were higher proportions of vitamin B12 deficiency and elevated methylmalonic acid among the Caucasian women compared with the African American women, and these biomarkers were subsequently found to be related to frailty in Caucasian women (OR 0.69, 95% CI 0.49–0.99 for quantitative vitamin B12 levels; and OR 1.34, 95% CI 1.00–1.80 for methylmalonic acid). Fifty-four (9.8%) of the Caucasian women presented with hyperhomocysteinemia (defined as >13.9 µmol/L in the study), and there was no association

Figure 2. Univariate Cox proportional hazards model exploring total plasma homocysteine (tHcy) levels and association with all-cause mortality. The tHcy scale of 8–22 µmol/L relates to the range between 5th and 95th percentiles of values (n = 3,823). tHcy is entered as restricted cubic spline. Reference value for hazard ratio is 15 µmol/L. Dashed lines denote 95% confidence interval.

Table 3. Univariate and Multivariate Cox Proportional Hazards Models of Associations Between Elevated Homocysteine (tHcy) and All-Cause Mortality After 5.1 ± 1.3 y

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<th>Univariate</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<tr>
<td></td>
<td>HR (95% CI)</td>
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<tr>
<td>tHcy ≥ 15 µmol/L§</td>
<td>1.75 (1.51–2.03)</td>
<td>1.50 (1.29–1.74)</td>
<td>1.30 (1.10–1.54)</td>
<td>1.25 (1.06–1.48)</td>
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<td>Per 5-µmol/L increment in tHcy</td>
<td>1.14 (1.11–1.17)</td>
<td>1.12 (1.09–1.16)</td>
<td>1.11 (1.06–1.15)</td>
<td>1.11 (1.07–1.16)</td>
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<td>Doubling of tHcy</td>
<td>1.89 (1.65–2.17)</td>
<td>1.60 (1.38–1.86)</td>
<td>1.41 (1.18–1.67)</td>
<td>1.37 (1.15–1.65)</td>
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Notes: 95% CI = 95% confidence interval; HR = hazards ratio.
Model 1: adjusted for age.
Model 2: adjusted for age, education, living circumstance, smoking, cardiovascular disease, diabetes, hypertension, dyslipidemia, Charlson comorbidity index, and renal function (eGFR).
Model 3: adjusted for age, education, living circumstance, smoking, cardiovascular disease, diabetes, hypertension, dyslipidemia, Charlson comorbidity index, renal function (eGFR), and frailty status at baseline.
§HR presented for high tHcy (≥15 µmol/L) in comparison with normal tHcy (<15 µmol/L).
between tHcy and frailty in adjusted analysis (OR 1.08; 95% CI 0.72–1.62). This is the only study to date that had explored the relationship between tHcy and frailty, and as the authors noted, should be extended to other races and gender to better elucidate the metabolic pathways of frailty. It may also have lacked statistical power to detect small to moderate effect changes.

The researchers’ finding that men with low and very high body mass indices (<18.5 and ≥30 kg/m², respectively) showed increased frailty was consistent with a previous study conducted by Hubbard and colleagues that utilized the English Longitudinal Study of Ageing cohort (33). Sarcopenia, arbitrarily defined as a loss of muscle protein mass and function, plays a predominant role in the pathogenesis and development of frailty (15). An increase in body fat mass may obscure the loss of muscle tissue, a condition termed as “sarcopenic obesity,” which is related to physical disability (34). Hence, the weight loss component of this FRAIL scale may be of less significance in the operational definition of sarcopenia and frailty. About 19.8% of participants met weight loss criterion, compared with 43.2% for the fatigue domain and 29.9% for the resistance domain, both of which were measurements of physical health and function.

Despite demonstrating that high tHcy levels predicted the ambulation component of the FRAIL scale, the researchers were unable to definitively exclude reverse causality where hyperhomocysteinemia may be a consequence of poor physical health. To further eliminate the possibility of tHcy being a marker for a vascular event causing frailty (35), the researchers performed a sensitivity analysis after excluding all men with a history of cardiovascular disease. The association between tHcy and frailty in the cross-sectional analysis persisted, suggesting a possible direct effect of tHcy in the pathogenesis of the frailty syndrome in aging men. The hypothesis of tHcy-induced inflammation as a mechanism of physical decline (36) was tested when high-sensitivity C-reactive protein was added to the fully adjusted model for frailty. The effect estimates were altered minimally (data not shown), implying that the relationship between tHcy and frailty in this cohort may be independent of the inflammatory pathway.

Frailty is known to be a dynamic condition, as frail older individuals can become nonfrail, and prefrail older individuals are more likely than nonfrail individuals to transit to the full frailty syndrome (2). The researchers did not establish strong associations between tHcy and frailty in this longitudinal analyses, and it is possible that they might have missed transitions of the frailty state that occurred during shorter intervals than the follow-up duration. The researchers refined this analysis by excluding men who were prefrail (ie, having one or two deficits) and frail at baseline, and derived a stronger relationship between high tHcy and incident frailty in those men with zero deficit at baseline. Statistical power was reduced with the smaller number of men, and hence the wider CI.

The researchers’ finding that elevated tHcy-predicted all-cause mortality complements and extends those of prior epidemiological studies (37–41) and suggests that lowering tHcy levels may potentially reduce mortality risk, regardless of the frailty status. On the other hand, a meta-analysis of large randomized trials has not indicated a beneficial effect of B-vitamin therapies on vascular events or mortality in people at risk of or with established cardiovascular disease (42). It has been argued that these findings may be limited by study methodology and patient selection (43, 44), hence supporting the need for further observational and clinical trials with a view to developing appropriate primary preventive strategies. To address the possibility of reverse causality due to preexisting ill health that might have led to elevated tHcy levels, the researchers repeated the analyses after excluding those men who died within 6 months from baseline. The association with all-cause mortality persisted (OR 1.24, 95% CI 1.04–1.47), suggesting that tHcy might be a risk factor rather than a biomarker of this adverse outcome.

The strengths of this study include the researchers’ large sample size of population-based community-dwelling men at baseline, with a wide range of tHcy concentrations and high prevalence of hyperhomocysteinemia to investigate these hypotheses. The focus on this well-established cohort of men aged 70 and older was highly relevant in the study of frailty and mortality, with these men being at the highest risk for these adverse health outcomes, and from whom a wealth of clinical information was available. However, limitations include the researchers’ reliance on self-reported weight data at wave 3 that could possibly lead to an under- or overestimation of its value, and hence misclassification bias of the FRAIL scale. The problems in using the SF-36 Health Survey among older adults have been discussed previously (45), and the measurement of frailty based on its components might be subjected to potential recall bias and day-to-day variation. The researchers did not have access to B-vitamin concentrations for this cohort, and thus were unable to exclude the possibility of effect modification by prevailing folate concentrations. Sixty (8.8%) men who were frail at baseline reported taking B-vitamin supplements at the time of assessment, compared with 181 (5.1%) men who were nonfrail (p < .001). The researchers repeated this cross-sectional analysis after excluding those men who took B-vitamin supplements and found that the effect estimate of high tHcy on frailty remained essentially unchanged (OR 1.55, 95% CI 1.26–1.90). The self-selection of study participants might have biased the findings toward lower tHcy and less frailty compared with the nonrespondents, hence limiting the generalizability of this study results to the total population in Australia. As the researchers have pointed out, men who did not respond or had died prior to the follow-up were older in age, more likely to be smokers or exsmokers, and had more comorbidities compared with those who had responded. This is likely to move this results toward the null hypothesis and lead to an underestimation.
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of the association between elevated tHcy and increased risk of frailty. Interpretation of the results will need to take this caveat into consideration.

In conclusion, hyperhomocysteinemia is associated with the prevalence of frailty. The researchers’ attempt to demonstrate a longitudinal relationship did not yield a significant correlation between tHcy and incident frailty. Hyperhomocysteinemia is also predictive of all-cause mortality, independent of the baseline frailty status. The researchers’ results suggest that the association between tHcy and mortality is largely not mediated through the occurrence of frailty.

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