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Relationship between frailty and executive function by age and sex in the Canadian Longitudinal Study on Aging

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Abstract Frailty reflects age-related damage to multiple physiological systems. Executive dysfunction is often a presenting symptom of diseases characterized by cognitive impairment. A decline in cardiovascular health is associated with worse executive function. We tested the hypothesis that higher frailty would be associated with executive dysfunction and that cardiovascular health would mediate this relationship. Middle- and older-aged adults at baseline ($n = 29,591$ [51% female]) and 3-year follow-up ($n = 25,488$ [49% females]) from the Canadian Longitudinal Study on Aging (comprehensive cohort) were included. Frailty was determined at baseline from a 61-item index, a cumulative cardiovascular health score was calculated from 30 variables at baseline, and participants completed a word-color Stroop task as an assessment of executive function. Multiple linear regressions and mediation analyses of cardiovascular health were conducted between frailty, Stroop interference-condition reaction time, and cardiovascular health in groups stratified by both age and sex (middle-aged males [MM], middle-aged females [MF], older-aged males [OM], older-aged females [OF]). Frailty (MM, 0.15 ± 0.05; MF, 0.16 ± 0.06; OM, 0.21 ± 0.06; OF, 0.23 ± 0.06)

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-024-01256-3.

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was negatively associated with cardiovascular health (MM, 0.12 ± 0.08; MF, 0.11 ± 0.07; OM, 0.20 ± 0.10; OF, 0.18 ± 0.09; $\beta > 0.037$, $p < 0.001$), as well as the Stroop reaction time at 3-year follow-up (MM, 23.7 ± 7.9; MF, 23.1 ± 7.3; OM, 32.9 ± 13.1; OF, 30.9 ± 12.0; $\beta > 2.57$, $p < 0.001$) across all groups when adjusted for covariates. Cardiovascular health was a partial ($\sim 10\%$) mediator between frailty and reaction time, aside from MFs. In conclusion, higher frailty levels are associated with executive dysfunction, which was partially mediated by cardiovascular health. Strategies to improve frailty and better cardiovascular health may be useful for combatting the age-related decline in executive function.

Introduction

One of the largest challenges for the global aging population is the increased prevalence of frailty, characterized as the presence of age-related damage to multiple physiological systems [1]. The frailty index defines frailty not as a specific syndrome but rather as a state of age-related accumulation of deficits that occur across the lifespan [2]. While most prevalent among older adults (65 + years), higher frailty levels may also be present and is increasingly characterized among middle-aged adults [3]. This is important as an increased frailty index score is associated with poor clinical outcomes, including an increased risk of all-cause mortality [4], hospitalization rates [5], and poor cardiovascular health [6, 7]. Additionally, frailer older adults are more likely to be cognitively impaired, as demonstrated by various longitudinal studies of aging [8] quantifying frailty via a frailty phenotype [8] or a frailty index [2]. Whether the impact of frailty on cognitive health is specific to older adults, impacted by sex, and mediated by other health-related factors is poorly understood.

Impairments in executive function, the higher-level cognitive processes involved with attention, decision-making, and working memory, are a common early symptom of neurodegenerative disease [9]. Using the color-word Stroop task [10], a longitudinal study by Buchman et al. [11] assessed 832 older adults at a baseline and 3-year follow-up and demonstrated that

an increased frailty phenotype score was associated with a higher rate of decline in executive function [11]. Whether this frailty-cognition relationship exists in middle-aged adults or is sex-specific is unclear, but understanding these relationships may be necessary to guide future interventions aimed at attenuating the frailty-related decline in executive function. An increased frailty score (via frailty phenotype) was associated with higher rates of heart failure and coronary artery disease, compared to non-frail individuals [12]. In addition, frailty (via frailty index) has been associated with poor cardiovascular health, such as increased carotid intima-media thickness in both middle-aged and older adults [7], indicating that both cardiovascular health and executive functions may be key contributors to overall frailty levels. Given the known impact of biological age on frailty scores, assessing the impact of biological age on these relationships is important to fully understand how these relationships may change across the lifespan.

There is a well-established interaction between heart and brain health. Impaired blood pressure regulation is linked with decreased executive function [13]. Furthermore, the prevalence of cognitive dysfunction among patients with cardiac disease is high [14]. While the relationship between higher frailty and decreased executive function has been previously documented [15], and that cardiovascular health impacts both outcomes independently [16, 17], the potential for cardiovascular health to mediate the relationship between frailty and executive function has not been established. Understanding the effect of cardiovascular health on the frailty-executive function relationship may aid in the development of preventative and treatment techniques for frailty-related outcomes.

The impact of biological sex on frailty, cardiovascular health, and cognition is well documented [18–20]. Males have a higher risk of mortality and increased presence of co-morbidities related to age-related cardiovascular diseases [21, 22]. Additionally, females have a higher frailty index score, as assessed via self-reported frailty indices, but the frailty-associated mortality risk is greater among males [18]. Despite this, females tend to exhibit faster reaction times than males on the interference Stroop task condition, indicating potential sex differences in executive function [23]. Therefore, the consideration of biological sex is imperative when investigating the

possible effect of cardiovascular health on explaining the frailty–executive function relationship.

The Canadian Longitudinal Study on Aging (CLSA) is a cohort study that investigates the predictors and consequences of aging among Canadian adults [24]. Due to its large sample size, the CLSA is ideal for studying age-related relationships among middle-aged males (MM), middle-aged females (MF), older males (OM), and older females (OF). Therefore, using the CLSA, the purpose of our study was to test the hypotheses that (1) a higher baseline frailty index is associated with slower interference Stroop task reaction times, (2) this relationship is mediated by worse cardiovascular health, and (3) these relationships may differ between age and sex groups.

Methods

Canadian Longitudinal Study on Aging (CLSA)

The CLSA provides comprehensive data from various aspects of health, ranging from questionnaires to biological samples for a random sample of ~50,000 Canadians (45–85 years) across seven provinces within 40 km of a data collection site [24]. The tracking cohort of the CLSA provides demographic, social, clinical, and psychological information relevant to health for all participants, while the comprehensive cohort provides further in-depth data (e.g., biological specimen collection/physical examination) for ~30,000 participants collected at one of the 11 purpose-built data collection sites [24]. Participants were excluded if they were not French or English-speaking, lived in Nunavut, the Northwest Territories, or the Yukon, were part of the Canadian Armed Forces, resided in assisted living, had severe pre-existing cognitive impairments, or resided on a federal First Nations reserve [24]. Participants with stroke, neurological disorders, history of psychiatric disorders, and those with hearing or vision loss were all included in the sample. All participants provided written consent prior to participating in the study. Participants were observed at regular 3-year intervals for 20 years, of which baseline (2012–2015) and 3-year follow-up data are presently available (2018–2021) [24]. Data used in the present study included data from both time points. Participants not

included in the comprehensive cohort (i.e., only those in the tracking cohort) did not have comprehensive frailty data and were excluded from analysis. From the initial 30,097 participants included in the comprehensive cohort, 29,845 had baseline frailty scores and were included in the analysis. Our protocol was approved by the CLSA Data and Sample Access Committee. As a matter of policy, the Nova Scotia Health Authority Research Ethics Board does not review research involving secondary analyses of datasets that contain de-identified individual-level data.

Frailty index

The frailty index used in the present study was developed from the deficit accumulation model using the CLSA baseline dataset [3] based on standard procedures [25]. This index was developed from a total of 118 items, as outlined by Blodgett et al. [26] who validated this index versus mortality records. Given the objective of the study, any cardiovascular or cognition variables were removed from the frailty index. Therefore, the frailty index used in the present study included 61 items, which are outlined in Supplemental Table 1 and well-exceeds the necessary 30-items required to reliably determine frailty [25]. Each frailty index item was coded as (0) = no deficit present or (1) = deficit present. Interval or ordinal variables were coded as a proportion of the deficit (e.g., for the variable self-rated health; excellent = 0, very good = 0.25, good = 0.5, fair = 0.75, poor = 1). The frailty index was then calculated as the deficit score divided by the number of deficits measured, with a value of 0 indicating the absence of frailty and a value of 1.00 indicating complete frailty.

Executive function

Executive functioning was assessed in the CLSA using the Stroop task [10]. The CLSA uses the Victorian version of the Stroop Color-Word Test. This version consists of a 5-min task, using three conditions, comprised of 24 items each [27]. Each item was presented on a card and arranged in a 4×6 matrix for each condition [10]. The three conditions included (1) the *Dot* condition, naming the ink color of the dots printed on the card (assessment of processing speed); (2) the *Word* condition, naming the ink color of non-color words (assessment of selective attention); and

(3) the *Interference* condition, naming the ink color of the color words (assessment of cognitive inhibition) during an incongruent condition [10]. Scoring included the time to complete each task (per condition) and was included in analysis separately. Reaction times are calculated as the total time it takes to complete each condition. The standard operating procedures for all CLSA-derived measurements are available online (https://www.clsa-elcv.ca/researchers/physical-assessments). This format of the Stroop task has good test–retest reliability but may demonstrate sex differences, as females exhibit faster reaction times [23, 28]. All executive functioning outcomes were assessed at baseline and follow-up, but given the longitudinal interest of the present study, follow-up reaction times were included in the main analysis. The relationships between frailty and baseline executive function outcomes are presented in the Supplemental material.

Cardiovascular health score

Given that there were numerous individual metrics included in the CLSA that reflect cardiovascular health, we calculated a cumulative cardiovascular score (CVS) from all relevant variables using the deficit accumulation approach using the baseline dataset [29]. From a total of 45 cardiovascular variables screened for inclusion, 30 were included in the CVS, as outlined in Supplemental Table 2. All 15 excluded variables did not have sufficient data ($> 12\%$ missing; primarily blood-based measures and poor-quality carotid images). Each item was scored as the presence of a condition (i.e., 1) or no condition (i.e., 0). The CVS was then calculated as the cardiovascular deficits divided by the total number of items. A CVS closer to 0 indicates better cardiovascular health, while a score closer to 1.00 indicates more cardiovascular damage and decreased cardiovascular health.

Statistical analysis

All statistical analyses were conducted using SPSS Statistics (Version 28, IBM Corp., Armonk, NY, USA). Results were considered statistically significant if $p < 0.05$. Interaction effects were assessed between age and sex groups for frailty and reaction time across all three Stroop conditions to determine stratification and were significant across all Stroop conditions (i.e., dot, word, interference; all $p < 0.001$) and time points (i.e., baseline, follow-up; all $p < 0.001$). Based on these interaction effects, groups were stratified by sex and age resulting in four groups: MM (45–64 years), MF (45–64 years), OM (65–85 years), and OF (65–85 years). Marital status, education level, dwelling status, smoking status, and language were included as covariates.

The Baseline and Follow-up Stroop task data were used for the cross-sectional and longitudinal analyses, respectively. The primary objective was to investigate the frailty-executive function and cardiovascular health mediator relationship longitudinally, but cross-sectional analyses at baseline are presented for completeness. Cross-sectional analyses observations can be found in Supplementary Content 1–4.

One-way ANOVAs with Bonferroni post hoc testing was conducted for baseline frailty, CVS, systolic blood pressure, diastolic blood pressure, and heart rate between age and sex groups (MM, MF, OM, OF).

A repeated-measures ANCOVA with Bonferroni post hoc testing was conducted on Stroop reaction time, with the inclusion of covariates: marital status, dwelling status, and language for each age and sex group across each Stroop condition (i.e., dot, word, interference) at each time point (i.e., baseline, follow-up).

Separate linear regressions were conducted on baseline frailty versus cognition, with the inclusion of covariates: marital status, dwelling status, and language for each age and sex group across each Stroop condition (i.e., dot, word, interference) at each time point (i.e., baseline, follow-up). To determine the linearity of the frailty and executive function relationship, alternative models were investigated including (1) linear and quadratic frailty terms or (2) linear, quadratic, and cubic frailty terms. Corresponding regressions were also conducted for the relationship between CVS and executive function across all conditions and time points, as well as between frailty and baseline CVS. All statistical assumptions for linear regressions were met.

Mediation analyses

Mediation models were used to test whether there was a relationship between the independent variable, frailty, and the dependent variable, executive function, cross-sectionally, and longitudinally that could be further explained by the presence of a mediator, CVS. Frailty score and CVS were extracted from baseline, while separate mediation models were conducted using Stroop reaction times at baseline and 3-year follow-up for each Stroop condition. Mediation occurs if the strength of the relationship between the predictor (i.e., frailty) and outcome (i.e., executive function) variable (direct effect) is decreased in the presence of the mediator (indirect effect). The strength of each relationship included in the model was determined via the unstandardized β-values from the regression models. Mediation was determined through the 10,000 bootstrapped 95% confidence intervals of the β values [30]. All mediation analyses were adjusted for covariates. Bootstrapped 95% confidence intervals without 0 indicated a mediation effect. All statistical assumptions required to conduct mediation analyses were met.

Results

Participant stratification and participant characteristics

Participant characteristics are outlined in Table 1. MM had a higher systolic blood pressure compared to MF ($p < 0.001$), but OM and OF had higher systolic blood pressures than their younger counterparts (all, $p < 0.001$). MF had a higher resting heart rate compared to all groups ($p < 0.001$), while OM had a lower resting heart rate compared to MM and OF (Table 1; $p < 0.001$).

Sex and age interaction effects were observed across all Stroop conditions (all, $p < 0.001$). The number of participants with available data for each outcome varied slightly following stratification, and the detailed participant breakdown included for each outcome by age/sex group is outlined in Supplemental Table 3. All relationships between frailty and Stroop reaction times were linear, except for OF at follow-up in the dot condition (to the quadratic term).

Table 1 Participant characteristics at baseline

Variable	Middle-aged males (45–64 years)	Middle-aged females (45–64 years)	Older-aged males (65–86 years)	Older-aged females (65–86 years)
Participants (N)	8374	8937	6248	6223
Age (years)	55.7 ± 5.5	55.5 ± 5.4	73.1 ± 5.6	73.0 ± 5.7
Height (m)	1.8 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.1*†
Weight (kg)	88.9 ± 16.9	73.9 ± 17.0	84.5 ± 14.4	71.1 ± 14.8*†
Hypertension (#Y) (%)	2575 (31%)	2246 (25%)	3098 (50%)	3075 (49%)
Diabetes (#Y) (%)	737 (9%)	581 (7%)	946 (15%)	646 (10%)
Stroke (#Y) (%)	90 (1%)	79 (1%)	209 (3%)	133 (2%)
Heart rate (beats/min)	71.7 ± 12.2	73.8 ± 10.8	68.6 ± 11.9	72.0 ± 11.1*†
Systolic blood pressure (mmHg)	120.6 ± 14.8	115.3 ± 15.5	125.0 ± 17.0	126.1 ± 16.7*†
Diastolic blood pressure (mmHg)	78.3 ± 9.5	72.7 ± 9.3	73.0 ± 9.9	70.4 ± 9.5*†
Marital status (#Y) (%)	6590 (78%)	6107 (68%)	1449 (23%)	3224 (51%)
Home-owner (#Y) (%)	1143 (13%)	1383 (15%)	1412 (22%)	2029 (33%)
Language (%English, %French)	81%, 19%	81%, 19%	83%, 17%	81%, 19%
Smoking history (#Y) (%)	1026 (12%)	934 (10%)	402 (6%)	296 (5%)
Education level (#Post-Secondary) (%)	5619 (67%)	6047 (68%)	3641 (58%)	3259 (52%)

Data presented as means ± standard deviations or proportions (%) as indicated. Results compared age and sex groups via one-way ANOVA. * $p < 0.05$ difference between the age-matched group, † $p < 0.05$ difference between sex-matched group

Frailty and cardiovascular health score by age and sex

Frailty levels were higher in older adults regardless of sex ($p < 0.001$), as well as higher in females than males, regardless of age ($p < 0.001$). Frailty scores were different among all groups ($p < 0.001$), as presented in Fig. 1.

Males had a higher CVS compared to age-matched females ($p < 0.001$), and older adults had higher scores compared to younger adults, regardless of sex ($p < 0.001$; Fig. 2). A positive relationship between CVS and frailty was observed for all groups (Fig. 3), but this was the strongest among OM ($\beta = 0.053$; 95% CI, 0.048–0.058).

Frailty and Stroop performance by age and sex

At baseline and follow-up, MF had the fastest reaction times ($p < 0.001$), while OM had the slowest reaction times ($p < 0.001$) across each Stroop condition (Fig. 4). From baseline to 3-year follow-up, reaction times were slower among older adults across all conditions, with the largest increase in time observed among OM during the Interference condition ($p < 0.001$). No differences in reaction time were noted among MM. Reaction times increased from baseline to follow-up during the dot condition among MF ($p < 0.001$) but remained unchanged under the word and interference conditions (all, $p > 0.77$).

Fig. 1 Bar graphs outlining the average frailty index of middle-aged males (0.15 ± 0.05), middle-aged females (0.16 ± 0.06), older-aged males (0.21 ± 0.06), and older aged females (0.23 ± 0.06). Error bars denote standard deviation. One-way ANOVA with Bonferroni-adjusted post hoc testing revealed significant differences between each age and sex group (all $p < 0.001$)
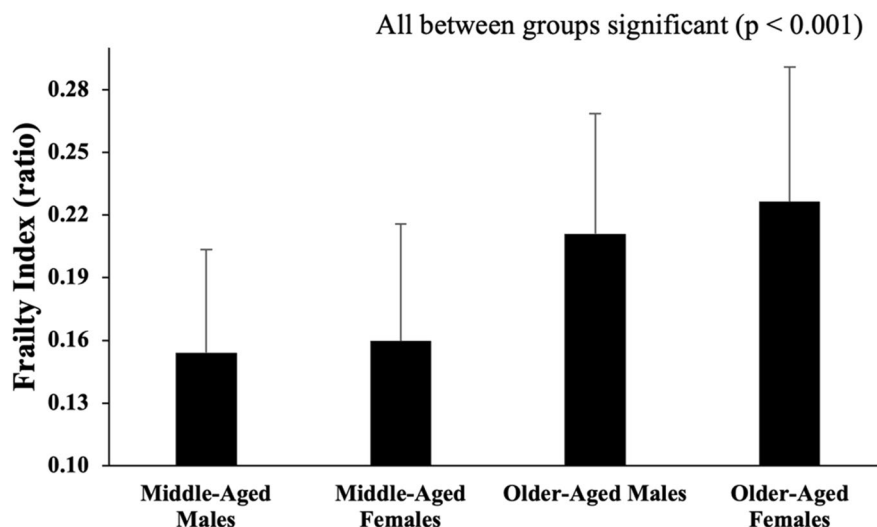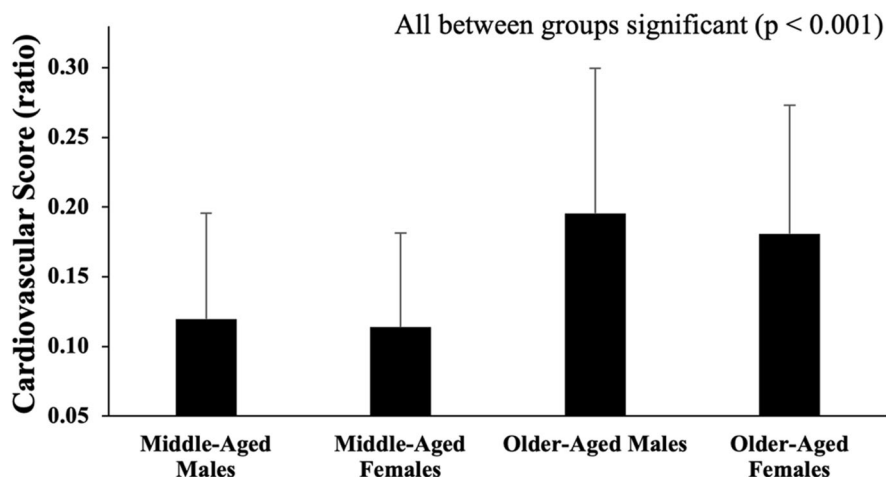

Fig. 2 Mean cardiovascular score by age and sex group. Error bars denote standard deviation. Middle-aged males (0.1198 ± 0.08); middle-aged females (0.1138 ± 0.07); older-aged males (0.1956 ± 0.10); older-aged females (0.1808 ± 0.09). One-way ANOVA with Bonferroni-adjusted post hoc testing revealed significant differences between each age and sex group (all $p < 0.001$)

Fig. 3 β-coefficients and confidence intervals (95%) between frailty index and cardiovascular score at baseline. All models were adjusted for age, marital status, dwelling status, smoking history, education level, and language
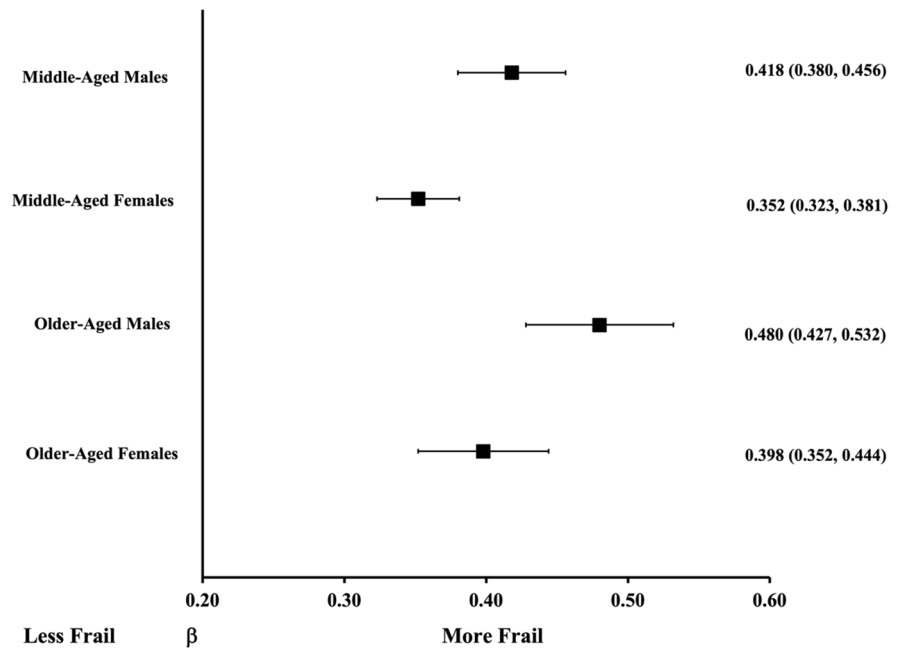
The association between frailty index and Stroop task reaction time is presented for each group in Fig. 5. The interference condition had the largest increase in reaction time per increase in frailty score. This change was largest among older adults (OF, 2.81 s; OM, 2.57 s, per 0.01 change in frailty score).

Frailty and Stroop dot and word relationship mediated by cardiovascular health score

Baseline frailty was independently associated with both CVS and all Stroop conditions across all age and sex groups (all, $p < 0.001$). CVS score was associated with all Stroop conditions across all age and sex groups (all, $p < 0.001$). CVS was determined to be a partial mediator (range: 4–16%) during the dot and word conditions across all groups except for MF during the dot condition (Supplemental Figs. 5-6).

Frailty and Stroop interference relationship mediated by cardiovascular health score

CVS was a partial mediator between frailty and the interference condition (Fig. 6). CVS was a 12% mediator in MM and a 5% mediator in MF. The frailty interference reaction time was partially mediated by CVS in OM by 11% and 12% in OF. In general, CVS

was not as strong a mediator between frailty and cognition among MF compared to other groups.

Discussion

The present study aimed to investigate whether higher frailty levels were positively associated with decreased executive function among middle- and older-aged CLSA participants, and if this relationship was mediated by worsened cardiovascular health. A higher frailty level was associated with worse reaction times during the Stroop task, across all groups. CVS partially mediated the relationship between frailty and Stroop interference condition (the most demanding of executive function conditions) regardless of sex and age group. These outcomes provide support for healthcare providers in the development and implementation of programs focusing on reducing frailty and improving cardiovascular health to possibly prevent the decline in executive function.

While two adults may have the same chronological age, biological age (represented by frailty) provides more insight into an ability to cope with adverse health events [31, 32]. Herein, frailty levels were higher among older adults, particularly OF. This remains consistent with previous work studying sex differences in frailty, as females are known to present

Fig. 4 Reaction time (s) across each Stroop condition, dot (**A**), word (**B**), and interference (**C**), for each age/sex group. Data are presented as means with error bars denoting standard deviation. Repeated measures ANOVA with Bonferroni-adjusted post hoc testing indicates significant differences between all groups at each condition and time point ($p < 0.001$). Significant between-group changes across time points were noted for all groups under the Word and Interference conditions ($p < 0.001$). *($p < 0.05$) within-group differences
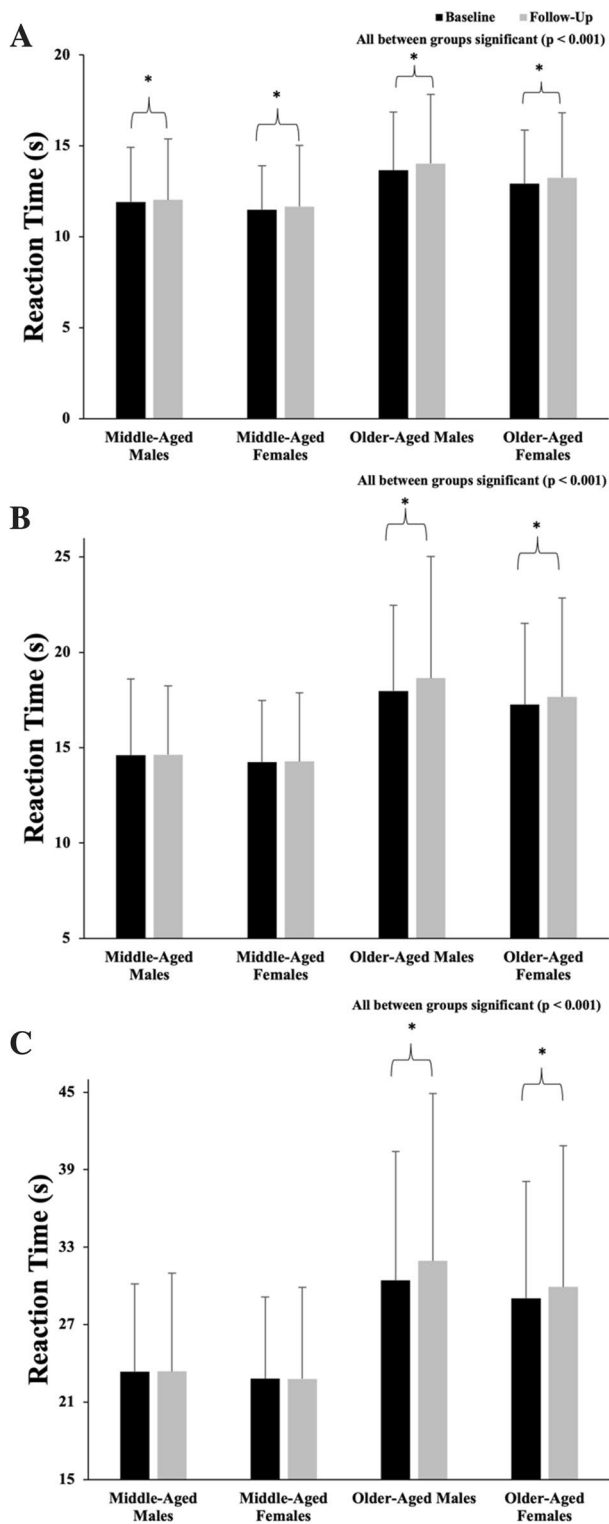
Fig. 5 β-coefficients and confidence intervals (95%) between frailty score and Stroop test reaction time during each task by age and sex group. [a]An adjusted value divided by 10 for reporting. [b]An adjusted value divided by 100 for reporting. Older-aged females (dot) demonstrated a non-linear cubic relationship and are presented in linear, quadratic, and cubic terms. All models were adjusted for age, marital status, dwelling status, smoking history, education level, and language
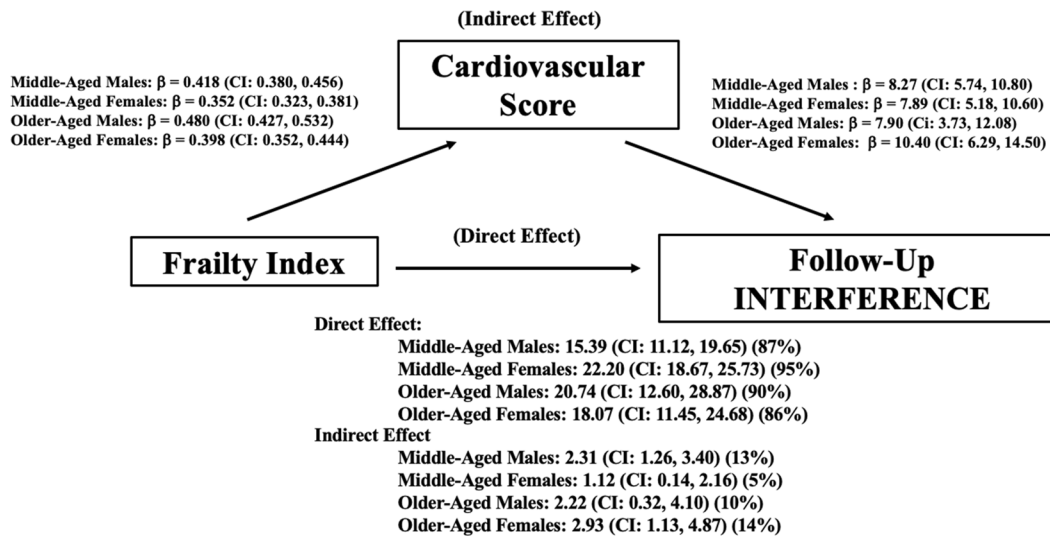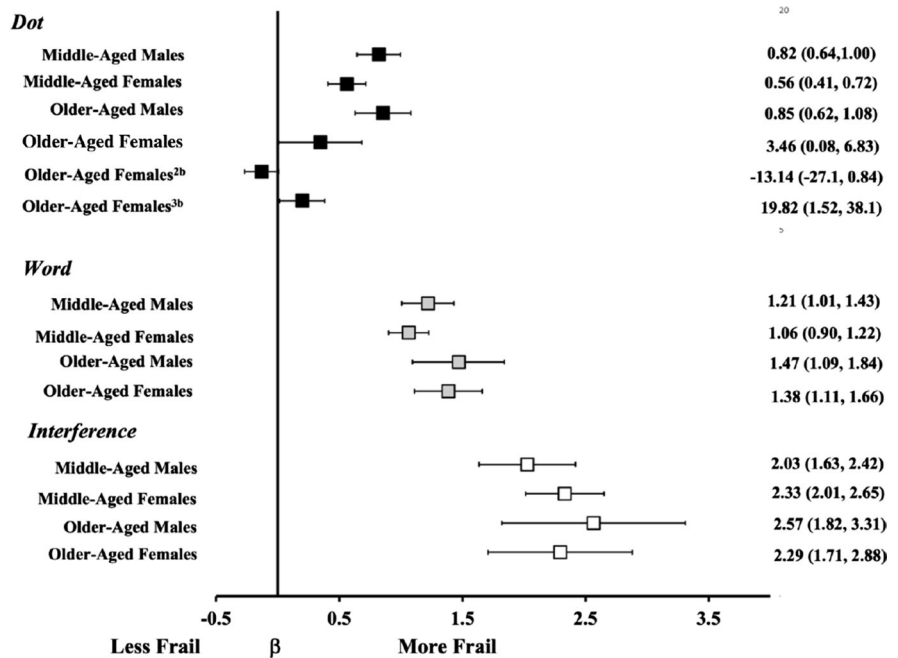
Dot

Middle-Aged Males	0.82 (0.64, 1.00)
Middle-Aged Females	0.56 (0.41, 0.72)
Older-Aged Males	0.85 (0.62, 1.08)
Older-Aged Females	3.46 (0.08, 6.83)
Older-Aged Females[2b]	-13.14 (-27.1, 0.84)
Older-Aged Females[3b]	19.82 (1.52, 38.1)

Word

Middle-Aged Males	1.21 (1.01, 1.43)
Middle-Aged Females	1.06 (0.90, 1.22)
Older-Aged Males	1.47 (1.09, 1.84)
Older-Aged Females	1.38 (1.11, 1.66)

Interference

Middle-Aged Males	2.03 (1.63, 2.42)
Middle-Aged Females	2.33 (2.01, 2.65)
Older-Aged Males	2.57 (1.82, 3.31)
Older-Aged Females	2.29 (1.71, 2.88)

-0.5   0.5   1.5   2.5   3.5

Less Frail   β   More Frail

(Indirect Effect)

Cardiovascular Score

Middle-Aged Males: β = 0.418 (CI: 0.380, 0.456)
Middle-Aged Females: β = 0.352 (CI: 0.323, 0.381)
Older-Aged Males: β = 0.480 (CI: 0.427, 0.532)
Older-Aged Females: β = 0.398 (CI: 0.352, 0.444)

Middle-Aged Males : β = 8.27 (CI: 5.74, 10.80)
Middle-Aged Females: β = 7.89 (CI: 5.18, 10.60)
Older-Aged Males: β = 7.90 (Ci: 3.73, 12.08)
Older-Aged Females: β = 10.40 (CI: 6.29, 14.50)

Frailty Index

(Direct Effect)

Follow-Up INTERFERENCE

Direct Effect:
Middle-Aged Males: 15.39 (CI: 11.12, 19.65) (87%)
Middle-Aged Females: 22.20 (CI: 18.67, 25.73) (95%)
Older-Aged Males: 20.74 (CI: 12.60, 28.87) (90%)
Older-Aged Females: 18.07 (CI: 11.45, 24.68) (86%)
Indirect Effect
Middle-Aged Males: 2.31 (CI: 1.26, 3.40) (13%)
Middle-Aged Females: 1.12 (CI: 0.14, 2.16) (5%)
Older-Aged Males: 2.22 (CI: 0.32, 4.10) (10%)
Older-Aged Females: 2.93 (CI: 1.13, 4.87) (14%)

Fig. 6 Mediation models demonstrating the effect of frailty (predictor variable) on Stroop test reaction time mediated by cardiovascular health score (mediator variable) by age and sex group at 3-year follow-up under the Stroop interference con- dition. Percentage of the total mediation effect is indicated in brackets. All models were adjusted for age, marital status, dwelling status, smoking history, education level, and language

with higher frailty index scores, derived from self-reported items, compared to age-matched males [33]. Despite frailty being associated with Stroop reaction times, males had slower reaction times, regardless of age or Stroop condition. While the reason for this consistent sex difference in a Stroop task [23] is unknown, the impact of sex differences in frailty on Stroop test reaction time may be better explained by non-cardiovascular outcomes such as self-reported health, mental health, or other co-morbidities. This

is reflected by the partial, but not full, mediation of CVS on Stroop test reaction time. While reaction time across any condition increases with chronological age, the relationship between frailty and reaction time differed across groups and conditions. The influence of frailty score on Stroop test reaction time indicates linear relationships across all groups under the word and interference conditions but was non-linear among OF under the dot condition (Fig. 5). Linear relationships among the more complex tasks (i.e., word and interference) indicate that higher frailty scores are associated with slower reaction times. However, the nonlinearity of this relationship under the most accessible task, the dot condition, indicates that the frailty index is not associated with changes in reaction time, until the higher frailty scores are reached (e.g., frailty index score > 0.10), particularly among females (Figs. 3 and 4). During the interference condition, increased frailty scores resulted in the largest decrease in reaction time, regardless of age and sex (e.g., > 25-s decrease in reaction time per 0.1 increase in frailty). These findings indicate that regardless of sex and age, executive function may be greatly affected by increases in frailty. Previous research has indicated the impact of poor executive function on higher frailty outcomes [34], but no research has investigated the impact of higher frailty scores on lower levels of executive functions. The findings from the present study provide further support for the relationship between executive function and frailty and indicate that strategies to mitigate high frailty levels may aid in the attenuation of executive dysfunction and cognitive decline.

Chronological aging is associated with damage to the cardiovascular system and a higher risk of developing cardiovascular disease [35]. While the independent associations of cardiovascular dysfunction and executive function with frailty have been established [14, 36, 37], these studies have not considered the impact of frailty. This study indicates that cardiovascular dysfunction may be associated with worse executive function among frailer adults. Males exhibited worse CVS compared to females regardless of age, while older adults demonstrated a higher CVS regardless of sex. Cardiovascular health among OM has the strongest effect on changes in frailty compared to other age and sex groups, which demonstrated a similar strength of relationship between frailty and CVS (Fig. 3). Mediation analyses determined that CVS was a partial mediator of the effect of increased frailty scores on decreased executive functioning across all age/sex groups, conditions, and time points. A partial effect of ~ 10% was observed across each mediation model, regardless of sex and age, indicating that additional factors mediate the relationship between frailty and Stroop test reaction time. As the prevalence of cognitive impairment is greater among individuals with cardiovascular disease [14], it may be possible that similar mechanisms that lead to the development of cardiovascular disease (e.g., atherosclerosis of the carotid or middle cerebral arteries) may contribute to the onset of cognitive impairments [38]. Additionally, the incorporation of various electrocardiogram outcomes into the CVS indicates that potential mechanisms involved with neurocardiac function may contribute to executive dysfunction. Heart rate variability, a neurocardiac outcome, has been considered an early biomarker of cognitive decline [39], but additional research is needed to elucidate mechanisms. Further work is needed to understand the impact of CVS as a mediator for frailty and cognitive impairment to provide proper interventions to patients.

The present study is strengthened by the inclusion of a large sample of Canadian adults and the study design, incorporating data from baseline and follow-up time points, which allowed relationships to be investigated both cross-sectionally and longitudinally. A longer follow-up period would further contribute to understanding declines in executive function and development of other cognitive impairments as it relates to frailty trajectories. The findings of the present study are specific to Stroop test-derived executive function and one domain of cognition, and do not provide a measure of memory or other domains of cognition. Finally, the present study was observational in nature. Future randomized controlled trials are needed to study the direct effects of strategies to mitigate frailty and cardiovascular outcomes (e.g., physical activity and medication) on executive function. The CLSA sample is indicative of a generally healthy population, excluding older adults above the age of 85 years at baseline, those in institutionalized long-term care, and those with cognitive impairment at baseline [24]. The outcomes from this study should not be extrapolated to these populations. These persons may exhibit even higher levels of frailty and be further susceptible to the development of cardiovascular health or cognitive issues. As well, the

sample of Canadians was predominantly White people who perceived their income as adequate. Accordingly, the results of this study should not be extrapolated to populations that were not included in the CLSA. Furthermore, this analysis did not consider the development of comorbidities included in the frailty index or cardiovascular score between baseline and Follow-up time points, such as hypertension, diabetes, or stroke.

In conclusion, higher frailty levels were associated with poorer executive function measured by the Stroop test that was partially explained by cardiovascular health among MM, MF, OM, and OF. Models that help middle-aged and older adults manage or prevent health deficits, possibly through strategies that improve cardiovascular health (e.g., lifestyle and medications), may prevent the decline in the ability to perform tasks reliant on executive function.

Declarations

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