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Gender Selectively Mediates the Association Between Sex and Memory in Cognitively Normal Older Adults

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Abstract

Background and Objectives: Sex and gender are important topics of increasing interest in aging and dementia research. Few studies have jointly examined sex (as a biological attribute) and gender (as a sociocultural and behavioral characteristic) within a single study. We explored a novel data mining approach to include both sex and gender as potentially related influences in memory aging research.

Research Design and Methods: Participants were 746 cognitively normal older adults from the Victoria Longitudinal Study. First, we adapted the *Gender Outcomes INternational Group: To Further Well-being Development (GOING-FWD)* framework—which is informed by gender dimensions of the Women's Health Research Network—to identify, extract, and operationalize gender-related variables in the database. Second, we applied principal component analysis (PCA) to a pool of potential gender variables for creating empirically derived gender-related components. Third, we verified the expected pattern of sex differences in memory performance and evaluated each gender-related component as a potential mediator of the observed sex–memory association.

Results: Systematic data mining produced a roster of potential gender-related variables, 56 of which corresponded to gender dimensions represented in the GOING-FWD framework. The PCA revealed 6 gender-related components (n indicators = 37): Manual Non-Routine Household Tasks, Subjective Memory Beliefs, Leisure Free Time, Social and Routine Household Management, Health Perceptions and Practices, and Brain Games. We observed sex differences in latent memory performance whereby females outperformed males. Sex differences in memory performance were mediated by Manual Non-Routine Household Tasks, Social and Routine Household Management, and Brain Games. Follow-up analyses showed that education also mediated the sex–memory association.

Discussion and Implications: We show that (i) data mining can identify and operationalize gender-related variables in archival aging and dementia databases, (ii) these variables can be examined for associations with sex, and (iii) sex differences in memory performance are mediated by selected facets of gender.

Keywords: Data mining, Episodic memory, GOING-FWD framework, Victoria Longitudinal Study, Women's Health Research Network

Translation Significance: Sex and gender, as conceptually separable but potentially related influences in aging and dementia, are topics of growing interest. Sex is a biological attribute and gender refers to sociocultural and behavioral characteristics. We address the challenge that many studies have collected minimal direct measures of sex or gender by applying an innovative and replicable procedure for identifying indirect indicators in an archival database. We observed that select components of gender (plus education) mediated sex differences in memory performance. A viable procedure for operationalizing sex and gender in archives will provide opportunities for future studies of diversity and equity in aging.

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Background and Objectives

Sex and Gender

Sex and gender represent independently important, potentially interacting, and mutually evolving topics of increased interest in aging, health, and dementia research (1–8). For research applications, sex and gender may be represented by 2 multifaceted domains of characteristics and associated variables, both of which may influence the emergence and expression of observable phenotypic differences across the human lifespan (9–11). Binary sex is typically defined as a broad and influential set of biological and physiological attributes that humans and nonhumans (animals) possess (including chromosomes, genes, hormones, and reproductive/sexual anatomy) that combine to characterize and differentiate males, females, and intersex persons (1,8,9,12,13). Gender is defined as a set of psychological, social, cultural, and historical factors that influence the explicit rules and implicit practices of identity, family, workplace, social-economic status, institutions, behaviors, expressions, and roles that vary across men, women, and gender-diverse persons (1,4,9,10,12,13).

Issues of sex and gender influences in studies of cognitive aging and dementia are increasingly recognized as essential components of design, data collection, analysis, and interpretation (4,5,12–16). Despite the current prominence and availability of large-scale aging and neurodegeneration datasets, relatively few are equipped with predesigned measures of diverse gender facets or protocols for evaluating sex *and* gender within the context of a single study (12,17). Notably, in many available databases, the terms sex and gender are used imprecisely and even interchangeably. Reviewers note that (i) such terms frequently refer to a binary representation of gender identity, even if the goal is to determine biological sex and (ii) gender, as currently understood, is rarely measured directly or even indirectly operationalized (1,6,16). Consequently, in earlier work, the terms sex and gender can be conflated, a practice that may produce terminological and interpretive inconsistencies in the literature (1,4). An emerging perspective is that sex and gender can be conceptually and operationally distinguished and examined separately or as related factors in research applications and intervention protocols (4,18–20).

Accordingly, we specified 2 research goals (RG) for the present study. First, we systematically identified, extracted, and operationalized gender-related variables from a large-scale archival database of human aging with typical limitations in explicit measurement of gender but compensatory strengths of broad and deep coverage of multiple gender-related domains and variables. Successful identification of indirect gender indicators in one aging cohort may lead to both a precedent and a protocol for developing and testing gender-related variables in other archival databases not initially designed for this purpose. As described below, this goal was guided by the *Gender Outcomes INternational Group: To Further Well-being Development (GOING-FWD)* framework (21) which is informed by the 4 gender dimensions of the Women's Health Research Network (as defined below) (9). For our second research goal, we tested and confirmed (binary) sex differences in episodic (verbal) memory performance and evaluated multiple facets of gender (as operationalized in our first RG) as potential mediators of the observed sex–memory association. We are unaware of prior studies that have extracted and subsequently tested multiple empirically derived gender-related components as potential mediators of the association between sex and memory performance. This line of investigation may have significant applications to advancing understanding of the ways in which sex and gender may independently or jointly contribute to differential cognitive level and change trajectories, including exacerbated memory deficits or decline or subsequent transitions to impairment and dementia.

A Framework for Identifying Gender-Related Variables in Memory Aging Research

An emerging consensus is that multiple aspects of gender-related risk and protection should be considered in aging and dementia research. These include lifestyle (eg, physical activity, cognitive engagement), psychosocial and self-beliefs (eg, self-efficacy, identity, confidence), social integration (eg, social activity, social support and networks, a range of domestic conditions), and cultural characteristics (eg, customs, norms, family structure) (3,4). Examples of direct indicators typically included are gender-related scales, questionnaires, or indices (22–27) representing observable or reportable behaviors, attitudes, displays, or identities (eg, Bem Sex-Role Inventory (28)). Notably, large-scale longitudinal or life-course studies may have archival data that indirectly and cumulatively provide indicators of gender-related phenomena of relevance to memory aging and dementia research (1,4,12,21,27). Accordingly, gender-informed inspections of an archival database—such as those predicated on the GOING-FWD framework (21)—can be used to identify and extract gender-related variables.

The GOING-FWD framework (21) outlines standardized methodological considerations for identifying gender-related variables in archival databases and incorporating them into focused gender-related research. Specifically, this framework uses the 4 gender dimensions proposed by the Women's Health Research Network (9) to operationalize and conceptualize gender-related variables: *Gender Identity*, *Gender Roles*, *Gender Relations*, and *Institutionalized Gender*. *Gender Identity* is conceptually defined in this prior work as the personal identification of oneself on a continuum of man, woman, or other (9). The framework explicitly acknowledges that this list is not exhaustive nor are identities static, and gender identity may or may not correspond to sex assigned at birth. *Gender Roles* refers to the behavior learned by a person as appropriate to their gender, determined by the prevailing cultural norms (eg, caregiving responsibilities, status of household's primary responsibilities, or employment). *Gender Relations* is defined as the interactions and relationships between individuals based on gender (eg, marital status, social support, sexual orientation). *Institutionalized Gender* refers to a domain within a population (eg, community or other social level) that could present gender discrepancies, such as policies, laws, and distribution of power (eg, policies that influence career progression, family leave, property ownership). In this study, we operationalized these conceptual definitions (9,21) and implemented them in a multifaceted archival database of human aging. The general aim was to identify candidate gender-related variables representing each of the 4 dimensions in the Victoria Longitudinal Study (VLS).

Sex Associations in Episodic Memory Aging

Accumulating evidence indicates that sex is differentially associated with mild cognitive impairment, dementia, and

Alzheimer's disease (AD) (5,15). Much of the available research conducted with asymptomatic (or cognitively normal) older adults has focused on sex differences in episodic memory performance or decline. This may be due in part to the fact that episodic memory (i) has established measurement techniques, (ii) is represented in virtually all cohort studies, and (iii) may be an indicator of differential risk for exacerbated cognitive decline, impairment, or dementia (14,29,30). Studies testing sex as a potential predictor or correlate of memory performance have produced a consistent pattern of results whereby females outperformed males (7,14,31). Recent findings indicated that sex (i) was an important risk factor for exacerbated memory decline (14,30,32), (ii) interacted with vascular and AD-related genetic predictions of memory trajectories (33–35), (iii) moderated memory resilience (36) or reserve (37), and (iv) moderated the impact of subjective memory impairment on later objective memory decline (38,39) or dementia (40).

Gender-Related Influences on the Sex–Memory Association

A small but promising set of recent studies have evaluated gender-related variables as potential contributors to sex differences in memory performance and decline (14,41,42). Examples of such indicators include a range of modifiable lifestyle risk and protective factors, including education, gender-normed roles or responsibilities, and physical activity. Notably, much of the previous work incorporating both sex and gender on this topic has focused on the potential moderating role of single indicators—particularly education. For example, reported female memory performance advantages were accentuated when women and men were afforded equal educational opportunities (7) and, more recently, sex differences in memory performance varied as a function of educational background (42). That is, the female memory performance advantage was larger for later-born cohorts, which was attributed to the increased educational opportunities available to women in more recent history. Thus, in aging adults, sex differences in memory performance may vary by gender-related factors such as education (or related proxies) and such inequality may extend into dementia prevalence (43,44).

Several reviews have extended this perspective to a broader scope of gender-related variables, such as those associated with gender-normed responsibilities or roles (eg, caregiving, housework, occupational status) (5,13,15). Gender differences may influence the everyday lifestyles of women and men to a degree that differentiates (decreases or increases) their proximity to risk or protective factors that may influence memory aging trajectories (30). Notably, such differential exposures to risk-reducing and elevating factors can be dynamic and mixed within and across persons (14). For example, it has been reported that women are more likely than men to engage in cognitively stimulating activities such as arts and crafts, reading, and social activities (15). Participation in such activities predicts better memory performance and reduced risk for accelerated cognitive decline, impairment, and dementia (45). Previous research also indicates that women are traditionally less likely to participate in the paid labor force as compared to men (46). In contrast to the preceding pattern (ie, increased exposure to protective pathways for women), this may lead to (i) increased exposure to AD-related risk factors (eg, caregiving, social isolation), (ii) decreased exposure to AD-related protection factors (eg, occupational engagement or complexity) (44), and thereby (iii) increased risk for adverse cognitive aging and clinical outcomes (14).

Similarly, worldwide trends in physical activity indicated that, across most countries, women tend to be less physically active than men (47). This discrepancy has been attributed in part to gender differences in normed responsibilities or roles (3). Specifically, it has been reported that women may experience (i) more limited opportunities for physical activity due to parenthood or caregiving demands (48, (ii) a lack of encouragement for physical activity (15, (iii) reduced self-confidence in physical capabilities (49), and (iv) negative attitudes towards physical activity owing to concerns surrounding cultural acceptability, gender-based stereotypes, and body image (50). Literature evaluating sex differences in exercise patterns and risk for memory performance and/or decline has produced equivocal results (for review, see (51)). For example, Anstey and colleagues (14) reported that (i) men were twice as likely to participate in vigorous activity and (ii) vigorous activity was associated with higher memory performance for men and unassociated with memory performance for women. By comparison, a systematic review and meta-analysis of sex differences in the cognitive benefits of exercise-based interventions found that, in general, women benefited more than men from such interventions (52).

Research Goals

We build on previous work by envisioning a broad scope of gender-related influences and evaluating a theoretically informed set of gender-related variables. Specifically, we investigated whether (and which) empirically identified facets of gender could function as mediators of the sex–memory association in aging persons. The conceptual model presented in Figure 1 provides a visual depiction of the investigated mediational flow. We operationalized this model in terms of 2 specific RG.

For RG1, we (i) applied an adaptation of the GOING-FWD framework (21) to the identification, extraction, and operationalization of gender-related variables in the VLS archives and (ii) tested the candidate gender-related variables in a data-driven principal component analysis (PCA). We expected that (i) this systematic data mining approach would reveal a broad roster of candidate gender-related variables that collectively spanned the 4 dimensions represented in the GOING-FWD framework and (ii) the subsequent PCA would reduce the dimensionality of these data into key observed gender-related variables that could be assimilated into a meaningful set of gender-related components. In this way, we expected the theoretical continuum of gender to be rendered empirically in terms of related categories. For RG2, we (i) evaluated sex differences in episodic memory performance (7,14,31) and (ii) examined each gender-related component as a potential mediator of the expected sex–memory association. We anticipated that (i) females would perform better than males in episodic memory and (ii) the female memory performance advantage would be mediated by selected facets of gender.

Research Design and Methods

Participants

Cross-sectional data were included from a cohort of cognitively normal, community-dwelling older adults from the VLS. The VLS data collection procedures were in full compliance

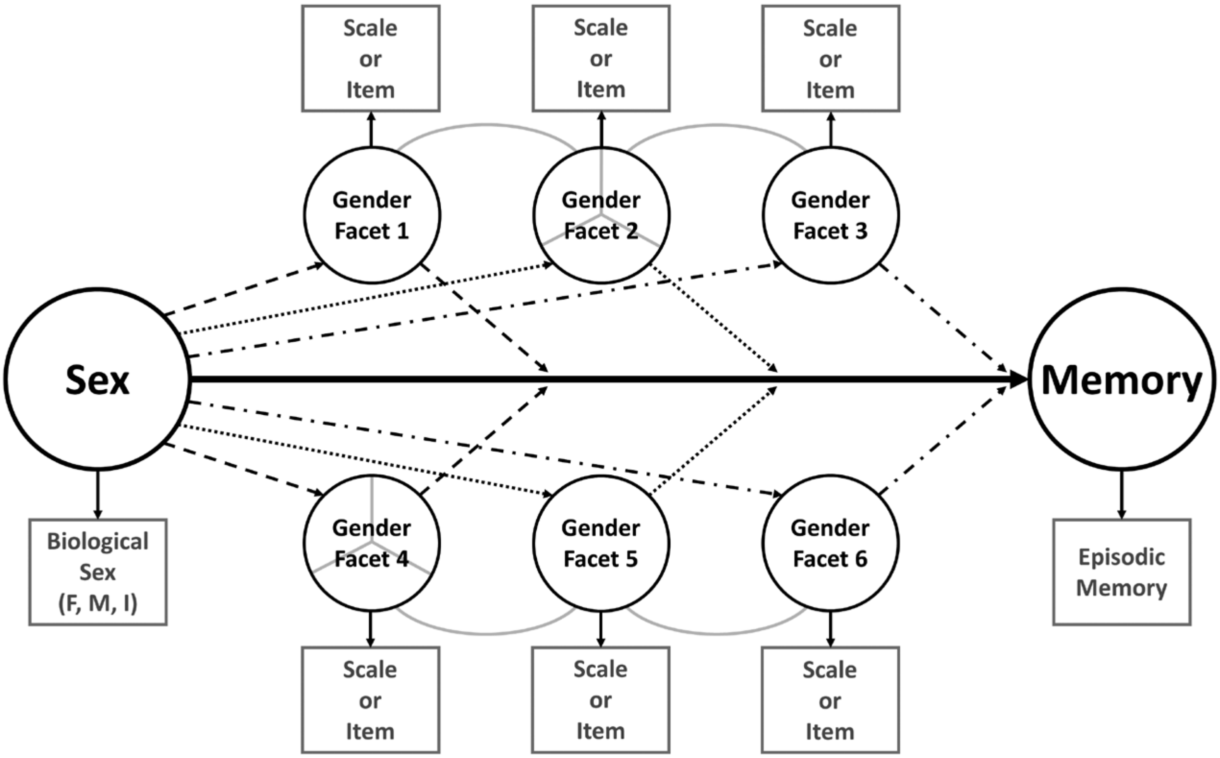

Figure 1. Conceptual model for evaluating sex and gender as dissociable but complementary contributors to memory aging. F = Female; M = Male; I = Intersex. Principal features: The often-observed association between sex and memory performance in aging adults is featured in the center of the figure. The present research represents gender as multifaceted and postulates that some facets may mediate the sex–memory association. This investigated mediational flow is represented by (**A**) 6 hypothetical Gender Facets, (**B**) the geographical location of these facets as intermediate to Sex and Memory, and (**C**) each dashed/dotted arrow flowing from Sex through one Gender Facet and then towards Memory. The boxes associated with the main constructs (Sex, Gender Facet, Memory) show possible measurement operations for each. Supplemental Features: Future research may investigate 2 potential gender-related intricacies that could intensify or suppress mediation effects: (**A**) potential interactions (or associations) amongst the Gender Facets (shown in the figure as gray curved lines linking the Gender Facets) and (**B**) the presence of subcomponents of one or more Gender Facet (shown in the figure for Gender Facet 2 and 4). Annotations: The model does not include potential gender-related background considerations, as these are addressed in theoretical treatments. Two aspects of the figure are intended to be illustrative. First, the depiction of 6 hypothetical Gender Facets in this figure is a convenience as numbers of available facets will vary across databases. Second, the facets in the figure are unnamed as variations in available content will also occur.

with prevailing research ethics guidelines and approved by the Human Research Ethics Board, Health and Biomedical. Participants provided written and informed consent. The source cohort consisted of 912 older adults who were tested during the period of 2000–2004. Participants were excluded from the current research if they were missing data (i) across all episodic memory measures (n = 30) or (ii) on one or more of the extracted gender-related variables (n = 96). Participants with a self-reported history of the following clinical conditions or considerations were also excluded: dementia diagnosis (n = 0), moderate or severe stroke (n = 8), moderate or severe Parkinson's disease (n = 4), severe epilepsy (n = 1), severe head injury (n = 14), use of antipsychotic or psychotropic medication (n = 4), and rated severity of drug or alcohol dependence (n = 8). Participants with clinically low Mini-Mental State Exam scores were also excluded (≤24; n = 1).

Measures

Sex

Biological sex was measured by asking participants to self-report whether they were male or female. At the time of data collection, this was the standard approach for large-scale aging databases and has been associated with numerous studies (4,14,34,35,38).

Gender

To identify, extract, and operationalize gender-related variables, we collected 282 items (potential gender-related variables) from 5 multifaceted inventories and questionnaires in the VLS archives (see Supplementary Table 1 for a sampling of constituent items and corresponding response scales): (i) Metamemory in Adulthood (MIA) (53); (ii) Memory Compensation Questionnaire (MCQ) (54,55); (iii) VLS Personal Data Sheet (PDS) (56); (iv) VLS Activity Lifestyle Questionnaire (VLS-ALQ) (57,58); and (v) Center for Epidemiological Studies—Depression Scale (CES-D) (59). The MIA, MCQ, and VLS-ALQ were developed and validated by VLS researchers and have contributed to numerous published research studies. Brief descriptions of each are provided below.

The MIA instrument (53) is comprised of 108 items that evaluate memory knowledge, subjective memory beliefs, and how respondents use and support their memory. For example, participants are asked to rate their agreement on a 5-point Likert-type scale (*agree strongly* to *disagree strongly*) with relevant subjective memory belief items such as "I am good at remembering conversations I have had" and "I can remember things as well as always." Participants are also asked to indicate the frequency with which they engage in memory practices (*never* to *always*) such as "keeping a list or otherwise noting important dates, such as birthdays and anniversaries" and "asking others to remind you of something." Items from the MIA can be evaluated as separate indicators or assembled into psychometric subscales that represent leading facets of metamemory.

The MCQ (54,55) has 45 items that are distributed into 7 subscales. Five subscales represent memory compensation strategies, while the remaining 2 represent more general compensation-related processes. Participants respond to items (*always* to *never*) such as "do you put effort in when you want to memorize a funny story" and "when you want to remember an appointment do you sometimes ask somebody else (eg, spouse or friend) to remind you."

The VLS PDS (56) is a broad inventory that contains 45 items evaluating demographic, health, and personal characteristics. Examples include education (years of formal schooling), health beliefs (eg, "compared to other people my age, I believe my overall health to be": *very good* to *very poor*), health practices (eg, "about how many times have you seen a doctor in the past year"), and lifestyle risk factors (eg, years of smoking or using tobacco products).

The VLS-ALQ (57,58) has 70 items that measure the frequency of engagement in (i) activities of daily living (eg, "prepare a meal"), (ii) social interactions (e.g., "visiting relatives, friends, or neighbors"), and (iii) leisure-based activity (eg, "traveling to a foreign country"). Participants respond to each item on a 9-point Likert-type scale (*never* to *daily*).

The CES-D (59) is comprised of 20 items that measure the frequency of depressive symptoms within the past week (eg, "I felt that everything I did was an effort" and "I felt that people disliked me"). Responses to each item can range between 0 (*rarely or none of the time*) and 3 (*all of the time*). An overall score on the CES-D is subsequently calculated by summing responses across the 20 items.

We implemented a procedure for identifying a subset of variables related to sex and gender from these 5 inventories and questionnaires. First, we completed the interactive Canadian Institutes of Health Research training module, *Sex and Gender in the Analysis of Secondary Data from Human Participants* (60). This course provided a standardized approach for detecting, evaluating, and integrating sex- and gender-related variables from archival databases. Second, the GOING-FWD framework (21) was applied in 2 steps. First, coauthors AYH and GPM independently evaluated each available item ($N = 282$) for convergence with the 4 gender dimensions; namely, Gender Identity, Gender Roles, Gender Relations, and Institutionalized Gender (9). Second, by consensus, the coauthors finalized a list of candidate gender-related variables that were eligible for inclusion in the subsequent PCA.

Episodic memory

As described in Supplementary Material, we represented episodic memory performance as a single-factor latent variable using 4 established (30,38) manifest indicators from the following 2 verbal memory tasks: (i) VLS Word Recall (2 lists) (56) and (ii) Rey Auditory Verbal Learning Test (2 list tasks) (61). Latent variables have several advantages over single- or composite-variable approaches, including the ability to (i) correct for sources of measurement error that affect the reliability of measurement and (ii) establish the content, criterion, and construct validity of the latent variable under investigation (62).

Statistical Analyses

For RG1, we applied PCA to the final list of candidate gender-related variables (SPSS v24; IBM Corp, Armonk, NY). PCA is a data-driven approach to reducing large, multidimensional data sets into a smaller number of interpretable components (or clusters of variables with shared characteristics). Each of the extracted components represents uncorrelated linear combinations of the original variables (63). Consistent with prevailing conventions, the gender-related variables were standardized using a *z*-score transformation (64). We tested and confirmed the suitability of our data set for PCA using (i) Kaiser–Meyer–Olkin Test, for which values ≥0.6 indicate the sampling is adequate and (ii) Bartlett's Test of Sphericity, for which p values <.05 indicate there is sufficient redundancy between variables in the dataset. Decisions related to the number of components to retain were made by visual inspection of the corresponding scree plot of eigenvalues (63). Specifically, we retained components before an inflection point in the distribution where the downward trend of eigenvalues began to curve toward horizontal (ie, the "elbow" of the curve), as these contribute most to the model and adequately summarize variable redundancies. Variables with low loadings across all components ($<|0.30|$) or high cross-loadings ($>|0.30|$) were sequentially eliminated (65). Following varimax rotation, we assigned qualitative labels to the final solution based on observed commonalities between the variables with high loadings on the corresponding component. Participants' component scores were determined via regression and employed in all subsequent analyses.

Analyses for RG2 included 3 interrelated steps. In the first step, we applied confirmatory factor analysis to the 4 manifest episodic memory indicators (Mplus 8.0; Muthén & Muthén). Using standard indices (Supplementary Material), we confirmed that a single-factor variable provided a good model fit and all indicators had strong loadings (>0.30) on the latent memory construct (Supplementary Results). Using this model, we estimated factor scores for each participant (ie, standardized values representing performance on the latent memory variable). These data were used in all subsequent analyses. In the second step, we evaluated sex differences in latent memory performance using linear regression (SPSS v24). In the third step, we used the PROCESS macro (66) (v4.1; see Figure 2 for model depiction) to sequentially examine each of the extracted gender-related components as potential mediators of the sex–memory association. The PROCESS macro is a preferred approach to conducting mediation analyses and making inferences regarding indirect effects (67). For each model, we specified 5 000 bootstrap samples and reported 95% confidence intervals (CIs). The statistical significance of each indirect effect was inferred from the corresponding 95% CI.

Results

Descriptive statistics for the final cohort of 746 participants are presented in Table 1 (M age = 71.9, range = 53.2–95.3 years; 66.8% female). All participants were English-speaking and the majority ($n = 738$; 99%) self-identified as non-Hispanic White.

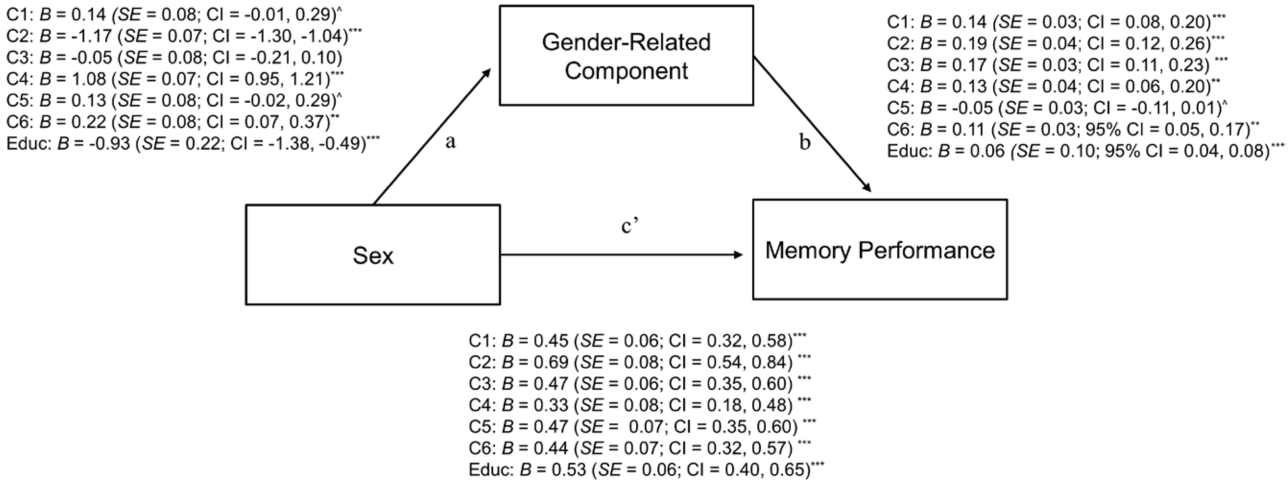

Figure 2. Visual depiction of the mediation model (PROCESS model 4) and the corresponding pathway coefficients. *B* = unstandardized coefficient; *SE* = standard error; C1 = Subjective Memory Beliefs; C2 = Manual Non-Routine Household Tasks; C3 = Leisure Free Time; C4 = Social and Routine Household Management; C5 = Health Perceptions and Practices; C6 = Brain Games; Educ = Education. a = conditional direct effect of sex on the corresponding gender-related component; b = conditional direct effect of the gender-related component on memory performance; c′ = conditional direct effect of sex on latent episodic memory performance. The direct effect of sex (0 = male, 1 = female) on latent episodic memory performance (i.e., with no mediators in the model) indicated a female memory performance advantage ($B = 0.47$, $SE = 0.07$, $p < .001$; 95% CI = 0.34, 0.60). Separate mediation models were tested for each gender-related component and education. Statistical significance was inferred from the corresponding 95% confidence interval (CI). *** $p < .001$; **$p < .01$; ^$p < .10$.

Table 1. Demographic Characteristics and Descriptive Statistics

Variable	Total Cohort (*N* = 746)	Males (*n* = 248)	Females (*n* = 498)
Demographic characteristics			
Female sex (%)	498 (66.8)	–	–
Age (years)	71.92 (8.99)	73.47 (8.35)	71.16 (9.21)***
Range	53.24–95.25	54.13–95.25	53.24–91.31
MMSE	28.55 (1.35)	28.35 (1.37)	28.65 (1.33)**
Range	24–30	24–30	24–30
Currently married, *n* (%)*	438 (59)	216 (87)	222 (45)***
Non-Hispanic White	737 (98.8)	245 (99.2)	492 (98.8)
Education (years)	15.16 (2.94)	15.78 (3.14)	14.85 (2.79)***
Range	5.0–23.5	8.0–23.0	5.0–23.5
Gender-related component†			
Subjective memory beliefs	0 (1.00)	–0.09 (1.04)	0.05 (0.98)^
Manual non-routine tasks	0 (1.00)	0.78 (1.06)	–0.39 (0.70)***
Leisure free time	0 (1.00)	0.04 (1.02)	–0.02 (0.99)
Social and routine household management	0 (1.00)	–0.72 (1.09)	0.36 (0.72)***
Heath perceptions and practices	0 (1.00)	–0.09 (0.93)	0.04 (1.03)^
Brain games	0 (1.00)	–0.15 (0.98)	0.07 (1.00)**
Latent memory performance‡	0 (0.87)	–0.31 (0.76)	0.16 (0.88)***

Notes: Results presented as mean (standard deviation) unless specified as otherwise. *p* Values are based independent samples *t*-test or chi-square test, as appropriate. MMSE = Mini-Mental State Exam.
* These values reflect the proportion of participants currently married. Across the total cohort, 36 (5%) were single, 156 (21%) were widowed, 107 (14%) were divorced, and 9 (1%) were separated. For males: 4 (2%) were single, 10 (4%) were widowed, 14 (5%) were divorced, and 4 (2%) were separated. For females: 32 (6%) were single, 146 (29%) were widowed, 93 (19%) were divorced, and 5 (1%) were separated.
†Results represent mean (standard deviation) of component scores.
‡Latent memory performance was estimated using factor scores derived from the best fitting confirmatory factor analysis model.
***$p < .001$. **$p < .01$. ^$p < .10$.

RG1: Identification, Extraction, and Operationalization of Gender-Related Variables

We identified 56 candidate gender-related variables from the roster of 282 items represented in the 5 VLS inventories and questionnaires. Forty-one of these variables corresponded to the Gender Roles dimension (eg, little control over my memory ability; housework), 10 corresponded to Gender Relations (eg, memory recruitment; visiting relatives, friends, or neighbors), and 5 corresponded to Institutionalized Gender (eg, education; travel). We did not identify any variables that corresponded to the representation of the Gender Identity dimension, as derived from the Women's Health Research Network (9) and represented in the GOING-FWD framework (21). We present these variables (i) together with corresponding response scales in Supplementary Table 1 and (ii) disaggregated by the 4 gender dimensions in Supplementary Table 2.

Results from the subsequent application of PCA to the candidate variables revealed an adequate fit of assumption metrics (Kaiser–Meyer–Olkin Test = 0.76; Bartlett's Test of Sphericity, $p < .001$). Visual inspection of the corresponding scree plot (Supplementary Figure 1) showed that 16 components had eigenvalues larger than 1 and the inflection point was located at the sixth component. Examination of component loadings suggested that the 6-component solution was the most viable and interpretable. In this solution, 19 of the 56 variables were sequentially eliminated due to low loadings across each of the extracted components. In Supplementary Table 3, we present supportive details, including (i) component loadings for the final set of 37 gender-related indicators, (ii) the percentage of variance explained by each component (total explained variance = 41.8%), and (iii) exploratory Cronbach's alpha for each of the gender-related components.

We interpreted the 6 gender-related components as representing a system of categories that reflect both commonalities of gender characteristics and empirical separation of constituent indicators. The first component was characterized by 8 indicators that largely correspond to subjective reports of day-to-day memory performance (eg, I am less efficient at remembering things now) and was thus labeled *Subjective Memory Beliefs*. The second component was characterized by 6 indicators that primarily reflect manual maintenance and instructive activities (eg, repair car, lawnmower, or other mechanical device) and was therefore labeled *Manual Non-Routine Household Tasks*. The third component, *Leisure Free Time*, was characterized by 6 indicators that largely correspond to activities that are undertaken for enjoyment or well-being (eg, travel). The fourth component was characterized by 6 indicators that primarily reflect social (eg, visiting relatives, friends, or neighbors) or instrumental activities (eg, meal preparation) and was thus labeled *Social and Routine Household Management*. The fifth component, labeled *Health Perceptions and Practices*, was characterized by 6 indicators that represent subjective perceptions of health (eg, overall health relative to peers) or health-seeking behavior (eg, number of times seeing a doctor). The sixth component was characterized by 5 indicators that represent engagement in cognitively stimulating activities (eg, word games) and was thus labeled *Brain Games*. In Table 1, we present mean component scores for both the overall study cohort and the cohort disaggregated by sex.

Notably, education (years of formal schooling) was not selected as a constituent indicator for any of the extracted gender-related components. We noted in our earlier review of the literature that several studies have indicated that education may be an important gender-related variable that moderates sex differences in memory performance and decline (7,31,42). We aimed to contribute to and extend this prior work by retaining and separately evaluating education as a potential mediator of the sex–memory association (Table 1).

RG2: Evaluating Gender-related Components (and Education) as Mediators of the Sex–Memory Association

Results from the linear regression verified the expected pattern of sex differences in latent episodic memory performance ($B = 0.47$; 95% CI = 0.34, 0.60; $p < .001$), whereby females ($M = 0.15$, standard deviation [SD] = .88) outperformed males ($M = -0.31$, $SD = 0.76$).

The following 3 gender-related components mediated the sex–memory association: Manual Non-Routine Household Tasks ($B = -0.22$; 95% CI = −0.31, −0.14), Social and Routine Household Management ($B = 0.14$; 95% CI = 0.05, 0.22), and Brain Games ($B = 0.02$; 95% CI = 0.01, 0.05). Significant findings were also observed for education ($B = -0.06$; 95% CI = −0.10, −0.03). See Figure 2 for a complete depiction of all path coefficients.

For Manual Non-Routine Household Tasks, the depicted results indicate that male sex predicted higher component scores on this gender-related component (path *a*). Notably, higher component scores were positively associated with memory performance (path *b*). As a result, when this mechanistic pathway is held constant, the female memory performance advantage is accentuated (path *c'*). A different pattern of results was observed for Social and Routine Household Management. Specifically, female sex predicted higher component scores (path *a*) and higher scores contributed to better memory performance (path *b*). When this indirect effect is held constant, the female memory performance advantage is attenuated (path *c'*). Convergent findings were observed for Brain Games. Female sex predicted higher component scores (path *a*) and higher scores were positively related to memory performance (path *b*). Statistically accounting for this pathway attenuates the female memory performance advantage (path *c'*). Regarding education, male sex was associated with more years of formal schooling (path *a*) and higher values contributed positively to memory performance (path *b*). Accordingly, when this indirect effect is statistically controlled, the memory performance advantage for females is accentuated (path *c'*).

In sum, 3 gender-related components and one typical gender-related variable (education, years of schooling) mediated sex differences in latent episodic memory performance. Notably, 3 of the gender-related components did not mediate the sex–memory association (see Figure 2): Subjective Memory Beliefs ($B = 0.02$; 95% CI = −0.002, 0.04), Leisure Free Time ($B = -0.01$; 95% CI = −0.03, 0.02), and Health Perceptions and Practices ($B = -0.01$; 95% CI = −0.02, 0.002). We verified these results through follow-up analyses that applied stricter cutoff criteria in the PCA (ie, $<|0.40|$ for component loadings, $>|0.40|$ for cross-loadings (68)). Specifically, the PCA produced the same 6 gender-related components and the mediation analyses produced an identical pattern of results.

Discussion and Implications

A prevailing challenge in the goal of integrating sex and gender in research on aging and dementia is to operationalize and evaluate them as unique and separable characteristics. Although sex is typically operationalized as a binary variable and readily available in large-scale databases, relatively few study archives are equipped with predesigned measures or direct gender indicators (1,6,16). In this study, we (i) explored a novel approach to identifying, extracting, and operationalizing gender-related variables from a large-scale archival database of human aging, (ii) verified the expected female episodic memory performance advantage, and, as depicted in Figures 1 and 2, (iii) tested whether empirically derived gender-related components (plus education) mediated the sex–memory association.

RG1: Identification, Extraction, and Operationalization of Gender-Related Variables

In the absence of direct measures of key gender dimensions, several studies (22,24–26) have assembled indirect indicators of selected facets of gender relevant to aging. For example, composite indices have been constructed to represent such gender-related facets as occupation (23) or personality (27). An emerging perspective is that effective identification and incorporation of gender-related variables in focused empirical research requires representation from multiple domains (3,4). Our results reflect this perspective in that the pool of prospective variables spanned lifestyle, self-beliefs, psychosocial, and sociocultural domains. We then extended this perspective by identifying variables that were consistent with 3 of the 4 gender dimensions (9) represented in the GOING-FWD framework (21): Gender Roles, Gender Relations, and Institutionalized Gender. Although we searched the current dataset thoroughly, we did not identify any variables that corresponded to the representation of the Gender Identity dimension (9). Nevertheless, we showed that systematic and theory-guided inspection of large-scale aging databases can yield relevant indicators reflecting multiple facets of gender. Our subsequent PCA revealed 6 empirically derived gender-related components, each of which featured multiple indicators. These 6 components were interpreted as Subjective Memory Beliefs, Manual Non-Routine Household Tasks, Leisure Free Time, Social and Routine Household Management, Health Perceptions and Practices, and Brain Games.

RG2: Evaluating Gender-Related Components (Plus Education) as Mediators of the Sex–Memory Association

We confirmed the expected pattern that females would outperform males in episodic memory (14,34,35). Accumulating literature has attributed sex differences in memory aging to biologically based explanations (5,69–71), including genetic, neurological, neuroanatomical, gonadal, and hormonal characteristics. Less research has explored whether sex differences in memory aging may also operate through a range of gender-related variables (3,5). We advance this line of investigation by delineating multi-indicator gender-related components and evaluating them as potential mediators of sex differences in episodic memory performance. We discuss the 4 observed mediators and then briefly comment on the 3 gender-related components that did not mediate the sex–memory relationship.

Manual non-routine household tasks and social and routine household management

We provide integrative interpretations for the 2 gender-related components that pertain to the performance of household labor; namely, Manual Non-Routine Household Tasks and Social and Routine Household Management. As depicted in Figure 2, an unsurprising pattern of sex differences was detected for each of these components (72–74). Specifically, males were more likely to engage in Manual Non-Routine Household Tasks (eg, mechanical repairs, woodworking) and females were more likely to engage in Social and Routine Household Management (eg, food shopping, meal preparation). Prior work has reported that higher levels of engagement in domestic activity predict accelerated memory decline (75) and increased risk for mild cognitive impairment (76). In contrast, we found that Manual Non-Routine Household Tasks and Social and Routine Household Management were positively associated with memory performance. This pattern may reflect the cognitive complexity (eg, learning new skills, anticipating needs, making decisions, monitoring progress) of the tasks covered in these components (72). This, in turn, could contribute to enhanced cognitive (5) and/or brain reserve (77,78). Indeed, recent neuroimaging research showed that household physical activity (eg, household repairs, meal preparation) is positively associated with gray matter, hippocampal, and frontal lobe volumes (41). Results from our mediation analyses demonstrate that sex differences in memory performance are explained in part by Manual Non-Routine Household Tasks and Social and Routine Household Management. Emerging literature suggests that gender-based interventions targeting these domains may have positive downstream effects on physical health and emotional well-being (79). For example, participation in Men's Sheds (a community-based initiative that orchestrates hands-on activities such as woodworking or furniture repair) predicts greater preventative health-seeking behaviors, as well as an increased ability to manage or overcome physical and mental health issues (80). The present findings suggest that such interventions may also contribute to long-term memory performance maintenance. This possibility merits examination in future research.

Brain games: platform for sustained cognitive activity

Previous results regarding sex differences in the level of engagement in cognitively stimulating activities (eg, crosswords, jigsaw puzzles) have been mixed. For example, studies have reported higher rates of participation amongst females (15), males (75), and equivalency (81). As displayed in Figure 2, the present results show that females were more likely than males to engage in cognitively stimulating Brain Games. Sex differences in profiles of engagement may be attributed to females perceiving greater benefits (eg, enjoyment, escapism, social interaction, or connectedness) from such activities relative to males (82). Substantial evidence has characterized cognitively stimulating activity as a protection factor for adverse brain (78,83) and cognitive aging outcomes (14,57). Regarding the former characterization, cognitive stimulation is associated with a reduced rate of hippocampal atrophy (84) and accumulation of amyloid-beta burden (85). Regarding the latter characterization, a recent systematic review and meta-analysis reported that participation in cognitively stimulating activity predicts better memory performance and reduced risk for accelerated decline, impairment, and dementia (45). Similarly, we found that Brain Games was positively associated with memory performance. The constituent indicators represented in this component have been evaluated as potential mediators in previous memory aging and dementia research (58,86), though none specifically focused on explaining sex differences in memory performance. The present study fills this gap and indicates that observed sex–memory associations may be mediated by levels of participation in cognitively stimulating activities.

Education: years of schooling

Previous research has shown that education (years of schooling) is positively associated with memory performance in aging adults (5,7,42,87). We tested and confirmed that education mediates sex differences in memory performance.

Specifically, we found that males in our study reported more years of formal schooling than females and education contributed positively to memory performance. When this indirect effect was held constant, the memory performance advantage for females was accentuated. A complementary pattern was observed in an earlier cross-sectional study featuring a broad age range (ie, 20–64 years) (88). Together, these results suggest that decreasing disparities across sex in access to education may have beneficial effects on female memory performance (42) and perhaps subsequent risk for impairment or dementia (89). Further research on this pattern with later-born and diverse cohorts can be explored.

Nonmediating gender-related components: subjective memory beliefs, leisure free time, health perceptions and practices

We discuss the 3 gender-related components that did not mediate the sex–memory association (Figure 2). Regarding Subjective Memory Beliefs and Leisure Free Time, we found that component scores did not vary across sex; however, higher scores were associated with better memory performance. Related research has previously reported that subjective memory perceptions (38,90–92) and leisure activity (75,78,93) are related to objective memory performance and decline, impairment, and dementia. This study is the first to our awareness to investigate and subsequently report that these facets of gender do not mediate the sex–memory association. Accordingly, we identify this as an important avenue for follow-up research. For example, future work could evaluate whether mediation effects are more likely to be detected for specific types of leisure activity (eg, travel, home-based entertainment). Regarding Health Perceptions and Practices, we found that component scores did not differ across sex nor were they associated with memory performance. Prior research has shown sex differences in episodic memory performance (94) and dementia risk (71) are mediated by objective indicators of physical health. We contribute to and extend this line of investigation by demonstrating that an empirically derived gender-related component representing subjective health perceptions and health-seeking behavior does not mediate the sex–memory association.

Strengths and Limitations

This study has several notable strengths. First, the large and well-characterized cohort of cognitively normal older adults included (i) substantial numbers of both male and female participants spanning an age range of 53–95 years and (ii) multifaceted measures that were successfully mined for gender-related variables. Second, we operationalized a theory-guided approach for identifying and characterizing candidate gender-related variables. The subsequent application of data-driven PCA enabled us to calculate multi-indicator gender-related components. Such components are empirically verified as relatively homogeneous constructs and require fewer statistical comparisons than would the constituent indicators. Third, in the foundational sex–memory association analyses, we used multiple episodic memory measures to calculate a latent variable for a broader and more effective representation of the episodic memory construct (30,62). Fourth, mediation analyses were performed using the PROCESS macro, which is among the preferred approaches for investigating indirect effects (67).

We note the following study limitations. First, we operationalized sex using the available intake form from the VLS database. As was the practice in this and other longitudinal studies (4,14,35,38), the item invited participants to self-report whether they were male or female. We acknowledge that this binary variable does not explicitly measure the biological and physiological attributes that jointly differentiate males, females, and intersex persons. As a result, the obtained responses could conflate binary representations of sex and gender. For example, this study could not consider potential subgroups of participants who are intersex (ie, reproductive anatomy that does not conform to a binary designation), who possess both male and female chromosomes (ie, XXY, XXX), or who experience crossover developmental pathways (ie, congenital adrenal hyperplasia). Expanding the assessment of sex indicators is a priority area for future studies and database development (69).

Second, our comprehensive data mining approach was quite successful, but we did not identify any variables in the VLS archives that corresponded to the representation of the Gender Identity dimension (9,21). Thus, we could not explore the potential impact of such variables on the sex–memory association. We note that some related research has also not included indicators representing all 4 gender dimensions (23,25,26). Moreover, the GOING-FWD framework explicitly states that such instances should not preclude gender-based analyses. Instead, researchers are encouraged to proceed with the available data (1,9,95), even if only one gender dimension is represented. We encourage follow-up studies to evaluate whether self-determined gender identity may also mediate sex differences in memory performance.

Third, 2 design-related limitations can be noted. The present cross-sectional design does not permit a full analysis of potential change-related characteristics. For example, both gender mediation of memory change and the fact that aspects of gender may also change over time. Regarding the latter, gender is a dynamic construct that is shaped by historical, cultural, generational, and sociopolitical or economic shifts (96–98). Future studies could explore whether gender-related components change over time and how this, in turn, may affect memory aging trajectories.

Fourth, we note that the Canadian-based VLS dataset is predominantly non-Hispanic White, generally well-educated, and benefiting from a national public health policy. The present results are not known to generalize to other ethnicities, cultures, and communities.

Conclusion

The current study applied an adaption of the GOING-FWD framework (21) to archival data from a large-scale study of human aging. Systematic data mining led to the identification, extraction, and operationalization of a broad scope of indirect gender-related variables, a subset of which were assimilated into empirically derived components. Mediation analyses produced results that converged with our conceptual model (Figure 1), in that the observed sex–memory association was explained in part by 3 of the novel gender-related components; namely, Manual Non-Routine Household Tasks, Social and Routine Household Management, and Brain Games, as well as education. The remaining 3 gender-related components did not mediate this relationship; namely, Subjective

Memory Beliefs, Leisure Free Time, and Health Perceptions and Practices.

Overall, this approach and these results provide both a precedent and protocol for developing and testing nuanced gender-related indicators in archival aging and neurodegeneration datasets that were not initially designed for this purpose. Our findings suggest that sex differences in episodic memory performance are mediated by select facets of gender, including everyday pursuits associated with (i) manual maintenance and instructive tasks (eg, household repairs, item assembly, woodworking), (ii) social and instrumental household management (eg, visiting relatives or friends, shopping, meal preparation), (iii) cognitively stimulating activities (eg, crosswords, jigsaw puzzles, word games), as well as (iv) years of formal schooling. Future large-scale epidemiological research could explore the extent to which (i) educating older adults on the cognitive benefits associated with such activities and (ii) interventions targeting these gender-related domains (99) may contribute to sustained memory performance in aging adults.

Supplementary Material

Supplementary data are available at *Innovation in Aging* online.

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Conflict of Interest

None.

Data Availability

The data, analytical methods, and study materials are available upon reasonable request. Requests to access these data should be directed to corresponding author. This study was not preregistered with an analysis plan in an independent, institutional registry.

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