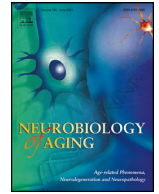




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Voice biomarkers as indicators of cognitive changes in middle and later adulthood

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ABSTRACT

Voice prosody measures have been linked with Alzheimer's disease (AD), but it is unclear whether they are associated with normal cognitive aging. We assessed relationships between voice measures and 10-year cognitive changes in the MIDUS national sample of middle-aged and older adults ages 42–92, with a mean age of 64.09 (standard deviation = 11.23) at the second wave. Seven cognitive tests were assessed in 2003–2004 (Wave 2) and 2013–2014 (Wave 3). Voice measures were collected at Wave 3 (N = 2585) from audio recordings of the cognitive interviews. Analyses controlled for age, education, depressive symptoms, and health. As predicted, higher jitter was associated with greater declines in episodic memory, verbal fluency, and attention switching. Lower pulse was related to greater decline in episodic memory, and fewer voice breaks were related to greater declines in episodic memory and verbal fluency, although the direction of these effects was contrary to hypotheses. Findings suggest that voice biomarkers may offer a promising approach for early detection of risk factors for cognitive impairment or AD.

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1. Introduction

Alzheimer's disease (AD), the most common type of dementia, which affects approximately one in 3 seniors (age 65+), is projected to affect nearly 13 million Americans by the year 2050 (Alzheimer's Association, 2019; Petersen, 2004). With the emergence of voice biomarkers for dementia, it is of interest to explore their influences on cognitive aging before clinical impairment. Although cognitive dysfunction is apparent in AD, methods are needed to identify the covert neuropathological changes that begin years ahead of obvious clinical symptoms, which could help provide earlier treatment and possible intervention. Pre-clinical cognitive declines are subtle enough to be overlooked until the emergence of more apparent symptoms several years later, by which point there are significant cognitive impairments in life (Alzheimer's Association, 2019; Eley et al., 2015; Lopez-de-Ipina et al., 2017; Mundt et al., 2005; Sperling et al., 2011; Twamley et al., 2006). Moreover, recent findings on the most promising treatments suggest that early diagnosis provides the greatest hope for slowing progression, or ultimately reversing symptoms (König et al., 2015; Meilán et al., 2020). One promising

biomarker involves voice features (Martinez-Sanchez et al., 2012; Meilán et al., 2020, 2014, 2012).

1.1. Voice biomarkers

Recent studies suggest that voice measures, most commonly from the category of prosody, are associated with AD (Konig et al., 2019, 2018; Mirheidari et al., 2019; Testa et al., 2001). Cognitive difficulties in domains such as memory and executive function are associated with lower prosody measures of pitch (vibration rate of vocal folds producing higher or lower sound), pulse (burst of air when vocal cords open/close distinguishing voice quality), the number of voice breaks (vibration of vocal cords producing articulated sound), jitter (pitch instability), shimmer (volume instability), and higher measures of amplitude (vocal cord vibration producing highness or lowness of volume) (Martinez-Sanchez et al., 2012; Meilán et al., 2020, 2014, 2012).

Voice measures are sensitive enough to acutely discriminate between participants with healthy cognition, MCI, and mild dementia (Beltrami et al., 2018; Kato et al., 2018; Themistocleous et al., 2020; Thomas et al., 2020; Toth et al., 2017; Xue and Deliyiski, 2001). Recent research has found that machine-learning classification models of temporal, spectral, and prosodic voice feature sets can distinguish between normal cognition and cognitive impairment or Alzheimer's disease (Haider et al., 2020; Nagumo et al., 2020). However, it is of interest whether individual prosody features of

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voice can be used to identify possible early signs of risk for cognitive impairment. Past work suggests that speech may be an early predictor of cognitive decline years before AD clinical diagnosis (Le et al., 2018; Van Velzen et al., 2014). Voice analysis may be less expensive, less invasive, and more readily obtained to monitor cognitive health compared to traditional diagnostic data such as brain imaging, cerebrospinal fluid, blood plasma, blood serum, urinary cortisol, and salivary cortisol (Johnson et al., 2012; Karlamangla et al., 2005; Lu et al., 2015; Österberg et al., 2012; Paterson et al., 2018; Quadri et al., 2004; van Himbergen et al., 2012; Wolf et al., 2002). Therefore, voice measures may be promising to integrate with other biomarkers to monitor cognitive health, potentially improving detection of presymptomatic dementia biomarkers and facilitating early intervention and treatment.

Longitudinal work at the Framingham Heart Study examining midlife and older age found that dementia risk is related to acoustic voice features, such as higher jitter, which was associated with a greater risk of developing dementia during their 7-year follow-up period (Lin et al., 2020). However, their work mainly looked at temporal voice features. In comparison, they did not assess other acoustic features of prosody that were previously found to be significantly related to AD (such as the prosody measures of pitch, pulse, voice breaks, and amplitude that we included in our current study) (Martinez-Sanchez et al., 2012; Meilán et al., 2014; Nasreen et al., 2021; Nishikawa et al., 2022; Testa et al., 2001). These additional measures may also be promising as markers. It would be helpful to assess individual differences in cognitive changes before impairment, which may identify early warning signs for eventual cognitive impairment.

The Framingham Heart Study significantly identified voice measures, including prosody measures of jitter and shimmer, which identified healthy participants who were more likely to develop dementia over 7 years (Lin et al., 2020). Thus, there is evidence that jitter and shimmer are potential biomarkers for early detection of significant cognitive impairment. Overall, it seems that voice measures, which have been linked with AD diagnosis, may be related to individual differences in cognitive changes before impairment. The current study builds on the 7-year-long analysis of Lin et al. (2020) by analyzing 10-year longitudinal data based on cognitive tests administered twice over the 10-year period with voice prosody measures of jitter and shimmer that were analyzed from cognitive interviews. However, we added other measures of voice prosody previously linked to MCI and AD, such as pitch, pulse, voice breaks, and amplitude (Martinez-Sanchez et al., 2012; Meilán et al., 2014; Nasreen et al., 2021; Nishikawa et al., 2022; Testa et al., 2001). Compared to past studies, our study also adjusted for neurological conditions, depressive symptoms, and chronic conditions in addition to age, sex, and education (Xue et al., 2021; Zhang et al., 2021). We looked at voice features predicting cognitive change over 10 years, a more extended range in timespan than the study by Lin et al. (2020). Our dataset also had a lower average age ($M = 54.99 \pm 11$) compared to Lin et al. (2020) ($M = 63 \pm 15$) and included a more extensive age range (33–83 at occasion 1). Thus, our research focused on more voice prosody measures in a more extensive range of cognitively healthy adults, specifically adding participants in middle age.

Additionally, to assess temporal voice features, Lin et al. (2020) analyzed voice using OpenSMILE, a program developed for speech-based emotion recognition (Eyben et al., 2010). In contrast, we used Praat, a program designed for analyzing, synthesizing, and manipulating speech (Boersma and van Heuven, 2001), a method frequently used to assess prosody measures (Martínez-Nicolás et al., 2021; Martínez-Sánchez et al., 2012; Meilán et al., 2014). Past work also noted limitations in the quality of voice recordings, which created the need for expensive and time-

consuming manual transcription (Xue et al., 2021). Our measures were from high-quality voice recordings that did not require transcription. Our results suggest possibilities for developing efficient and non-invasive methods that could be used for long-term monitoring throughout cognitive aging.

Cognitive aging is accompanied by less perceivable physiological changes caused by decline in information integration in the memory and executive function cerebral cortex regions responsible for voice production and speech syntax (Funahashi, 2001; Guenther, 2006; Hirano et al., 2004; Lieberman, 2007). Therefore, changes detected in the voice tied to brain aging could help identify early signs of cognitive impairment and dementia. Further research is needed to investigate whether voice prosody measures could serve as biomarkers of individual differences in cognitive change. This method could differentiate normal and abnormal cognitive changes, which could be used to detect preclinical stages of MCI and resulting AD (Bondi et al., 1999).

1.2. Physiological biomarkers

Other biomarkers besides voice are related to AD, such as neuroinflammation, allostatic load, vascular disease, APOE4 genetic predisposition, amyloid protein and tau (phosphorylated and total), measured by cerebrospinal fluid and blood, plasma proteins and lipids in blood, and neurofilament light chain in blood (Craig-Schapiro et al., 2011; Fransquet and Ryan, 2019; Heneka et al., 2006; Heutink, 2000; Holmes and Butchart, 2011; Humpel, 2011; Jones et al., 2014; Ling et al., 2017; Matos and De Souza-Talarico, 2019; Shahim et al., 2018; Shoji, 2011; Zou et al., 2020). These factors could potentially inform early interventions, which may decrease the risk of developing AD. However, these measures are collected through invasive methods, such as blood draws and spinal taps, which may also be expensive and cannot necessarily be measured repeatedly over time. In contrast, monitoring voice features remotely and more regularly may help to detect subtle changes that could indicate heightened risk. It is also possible that combining voice measures with the more traditional AD biomarkers may provide a more comprehensive assessment of cognitive status.

Further, past research suggests that neuropathobiological changes associated with AD risk, such as reduced mitochondrial functioning, reduced signaling in the insulin/IGF pathway, and reduced hypothalamic regulation of stress hormones, may appear years, even decades, before clinical manifestation of AD (Arenaza-Urquijo et al., 2015; Bishop et al., 2010; Blalock et al., 2004; Freiherr et al., 2013; Haigis and Guarente, 2006; Honer et al., 2012; Lesuis et al., 2018; Liang et al., 2008; Miller et al., 2008; Stacey et al., 2017; Wilcox et al., 2011). Thus, if researchers can develop a non-invasive and accessible method to identify early indicators of dementia risk, early treatment may be more readily provided, ultimately delaying or possibly preventing the progression to AD. Some of these changes include reduced mitochondrial functioning, reduced signaling in the insulin/IGF pathway, and reduced hypothalamic regulation of stress hormones (Arenaza-Urquijo et al., 2015; Bishop et al., 2010; Blalock et al., 2004; Haigis and Guarente, 2006; Honer et al., 2012; Lesuis et al., 2018; Liang et al., 2008; Miller et al., 2008; Stacey et al., 2017; Wilcox et al., 2011). Age-related changes to the autonomic nervous system and coordination of extraneural tissues have also been associated with declined function of the brain (Beer et al., 2017; Bishop et al., 2010; Goodall et al., 2018; McLean and Le Couteur, 2004; Parashar et al., 2016; Pfeifer et al., 1983; Shimazu et al., 2005; Strickland et al., 2019). Some of these biomarkers can predict cognitive change over a few years, whereas others are useful in assessing risk over decades (Albert et al., 2011).

Neuropathological changes in the brain may begin 10 or more years before overt clinical symptoms appear (Green et al., 2000; Tuladhar et al., 2016). Thus, it is helpful to identify the underlying mechanisms that link voice biomarkers with cognitive changes so that a risk of AD can be identified before significant neuropathology and functional impairments appear. Such risk factors, along with cognitive changes, may provide warning signs for cognitive impairment up to 13 years before a clinical diagnosis (Linn et al., 1995; Sperling et al., 2011; Stewart et al., 2009). Although researchers have explored these biomarkers to improve AD identification, there is currently no widely accepted method to detect the preclinical stages (Alzheimer's Association, 2019; National Academies of Sciences and Medicine, 2017). Providing reliable methods to detect early warning signs of cognitive impairment is particularly important given the vast individual differences in the nature and timing of cognitive declines with aging (Dixon and Lachman, 2019). For example, healthy adults with lower baselines of cognitive functioning have a higher risk of developing neurocognitive disorders such as AD within just a few years (Chen et al., 2001; Elias et al., 2000; Fox et al., 1998). By identifying possible risk factors of abnormal cognitive aging, early detection and intervention may be possible, leading to more effective treatment (National Academies of Sciences and Medicine, 2017).

1.3. Cognitive aging

The most conventional method of identifying cognitive impairment and AD, neuropsychological testing, allows for improved clinical diagnostic accuracy by assessing various cognitive factors (Albert et al., 2011; Ang et al., 2019; Ding et al., 2020). Resulting criteria have aided in identifying those performing below normative expectations who may be at risk or already experiencing progressive cognitive impairment. For example, participants with mild cognitive impairment (MCI) can be identified by 1 to 1.5 standard deviations below the mean score for their age and education on verbal recall tests (Albert et al., 2011; Jak et al., 2016). This result suggests that relatively low cognitive test scores could be indicative of MCI. Further, the risk of a 10-year decline from MCI to AD can be identified by impaired performance in memory and executive function (Albert et al., 2011). Thus, identifying those with impaired cognitive performances or decline may facilitate early intervention, potentially lowering their risk of conversion to dementia. Specifically, past work suggests that the range of cognitive score decline can differentiate the type of risk. For example, mean yearly cognitive declines indicative of change to MCI have been found for Episodic Memory measured by Word List Learning (0.14 ± 0.44) and Executive Function measured by Category Fluency (0.18 ± 0.28); and mean yearly cognitive declines indicative of change to dementia have been found for Episodic Memory (0.25 ± 0.32) and Executive Function (0.18 ± 0.28) (Carmichael et al., 2012). Therefore, examining decline in cognitive scores in previous research has provided information about cognitive impairment, such as MCI or dementia. Examining individual differences in cognitive changes in relation to voice measures among a relatively healthy sample could identify those at risk of later-life cognitive impairment and potential biomarkers for dementia.

1.4. Current study

Research investigating preclinical cognitive changes in midlife and later life with previously identified voice biomarkers of AD may provide insights into early indicators of dementia. We tested the hypothesis that voice biomarkers of AD would be associated with individual differences in cognitive changes in midlife and later life, specifically among community-residing and well-functioning

middle-aged and older adults who are part of a long-term longitudinal study. We examined voice prosody and cognitive changes in the MIDUS national sample of middle-aged and older adults with a wide range in educational attainment, using a battery of cognitive tests at 2 time points over 10 years. The goal was to investigate whether voice prosody measures previously associated with AD are also related to individual differences in the extent of cognitive changes over 10 years. Based on previous findings with voice prosody and AD, we hypothesized that higher pitch, higher pulse, more voice breaks, higher jitter, higher shimmer, and lower amplitude would be associated with greater decline in cognitive tests while controlling for demographic and health factors.

2. Methods

2.1. Participants

The current study included participants from the second wave (M2) and third wave (M3) of the Midlife in the United States Study (MIDUS) (Radler and Ryff, 2010) who completed cognitive assessments at both time points. MIDUS is a national longitudinal study that was initiated in 1995–1996 through random digit dialing households in 48 states that had a telephone (with further data collection approximately 9 and 19 years later) to assess how social, psychological, and behavioral factors affect mental and physical health in English-speaking, noninstitutionalized adults ranging from young adult to older life (Brim et al., 2004). The original participants in M1 ($N = 7100$) ranged from age 24–75 years ($M = 46.40 \pm 13.00$), were 51.7% women, had a mean education of 13.21 years, and had a mean self-rated health on a 5-point scale (1 = poor, 5 = excellent) of $3.53(\pm 1.02)$ (Brim et al., 2004). The second wave of data collection (M2) occurred an average of 9 years later in 2003–4. Cognitive testing was added at the second and third waves. The third wave (M3) occurred an average of 9.12 years later in 2013–4 ($N = 3294$). In prior publications, additional information about the samples and selective attrition is available (Hughes et al., 2018; Radler and Ryff, 2010).

Available data for participants. Participants were included in our analysis sample if they had demographic and cognitive assessments from M2 and M3, as well as at least 2 of the 3 voice recordings selected from M3 cognitive interviews ($N = 2585$). At M3, the participants ranged from age 42–92 years ($M = 64.09$, standard deviation = ± 11.23), were 55.20% women, and had an average education (out of 20 years) of 14.57 years (standard deviation = ± 2.67). Information is summarized in Table 1. Additionally, 90.2% of participants in our analysis sample were white, 3.2% African American, 0.9% Native American, 0.3% Asian, and 5.4% identified as “other.”

To investigate selective attrition, differences between the analysis sample and participants not included in analyses due to dropping out from the study at Wave 3 or not having usable voice data were assessed by independent samples *t*-tests. As commonly found in longitudinal studies (including MIDUS), retention in our analysis sample was higher among those who were white, married, and had higher education (Agrigoroaei and Lachman, 2011; Karlamangla et al., 2014; Radler and Ryff, 2010). Additionally, retained participants showed higher performance on all cognitive tests compared to dropouts (Hughes et al., 2018) (see Table 2 for means).

Compared to excluded participants ($N = 2378$), those in the analysis sample ($N = 2585$) at M2 were younger, had a higher proportion of women, had more years of education, had fewer neurological conditions, were less likely to have depressive symptoms,

Table 1
Subjects, demographics, voice variables, and cognitive variables included in our analysis sample.

	N	Minimum	Maximum	Mean	Std. deviation
Age	2585	42.00	92.00	64.09	11.23
Sex (55.20% women)	2585	1.00	2.00	1.55	0.50
Education (years)	2577	6.00	20.00	14.57	2.67
Neurological conditions	2579	0.00	3.00	0.12	0.36
Depressive symptoms	2585	0.00	1.00	0.10	0.29
Chronic conditions	2531	0.00	22.00	2.22	2.07
Word List Immediate pitch	2549	12.00	609.00	167.34	42.84
Word List Immediate pulse	2558	0.00	30735.00	739.44	804.75
Word List Immediate voice breaks	2558	0.00	374.00	20.74	16.76
Word List Immediate jitter	2548	0.00	20.00	1.77	0.89
Word List Immediate shimmer	2547	2.00	38.00	11.74	2.66
Word List Immediate amplitude	2548	0.00	1.00	0.19	0.10
Word List Delayed pitch	2424	80.00	607.00	164.61	42.94
Word List Delayed pulse	2440	0.00	22022.00	626.51	708.37
Word List Delayed voice breaks	2440	0.00	536.00	17.82	18.49
Word List Delayed jitter	2424	0.00	18.00	1.92	1.10
Word List Delayed shimmer	2425	2.00	32.00	12.00	3.10
Word List Delayed amplitude	2423	0.00	10.00	0.20	.22
Category Fluency pitch	2574	0.00	610.00	159.55	40.01
Category Fluency pulse	2578	0.00	24,495.00	1458.28	1006.60
Category Fluency voice breaks	2578	0.00	255.00	41.91	22.25
Category Fluency jitter	2572	0.00	12.00	1.76	0.87
Category Fluency shimmer	2574	2.00	45.00	11.69	2.66
Category Fluency amplitude	2573	0.00	69.00	0.21	1.35
Pitch composite	2581	87.48	608.60	164.06	39.49
Pulse composite	2585	3.67	25,750.67	947.84	753.97
Voice breaks composite	2585	0.00	318.00	27.02	15.56
Jitter composite	2580	0.60	15.27	1.82	0.84
Shimmer composite	2580	2.44	30.55	11.81	2.53
Amplitude composite	2580	0.05	34.43	0.21	0.68
M2 Word List Immediate	2412	0.00	15.00	7.00	2.19
M2 Word List Delayed	2332	0.00	14.00	4.69	2.51
M2 Category Fluency	2416	1.00	42.00	19.70	6.00
M2 Backward Digit Span	2415	0.00	8.00	5.10	1.45
M2 Number Series	2414	0.00	5.00	2.51	1.51
M2 30 Second and Counting Task	2415	-2.00	90.00	38.76	11.19
M2 Stop and Go Switch Task	2346	-3.77	-0.61	-1.07	0.23
M3 Word List Immediate	2582	0.00	15.00	6.70	2.38
M3 Word List Delayed	2460	0.00	14.00	4.37	2.68
M3 Category Fluency	2582	0.00	40.00	18.80	6.05
M3 Backward Digit Span	2583	0.00	8.00	4.97	1.47
M3 Number Series	2517	0.00	5.00	2.33	1.56
M3 30 Second and Counting Task	2557	-10.00	90.00	36.40	11.50
M3 Stop and Go Switch Task	2492	-7.67	-0.42	-1.27	0.39

Table 2
Demographics and cognitive variables for subjects analyzed and excluded.

	Analysis sample					Excluded						
	N	Min	Max	Mean	SD	N	Min	Max	Mean	SD		
M2 Age ^a	2585	33.00	83.00	54.99	11.23	2377	28.00	84.00	55.91	13.64		
M2 Sex ^a	2585	(55.20% women)					2378	(51.30% women)				
M2 Education (years) ^a	2582	6.00	20.00	14.58	2.65	2374	6.00	20.00	13.76	2.60		
M2 Neurological conditions ^a	2556	0.00	3.00	0.11	0.34	2348	0.00	3.00	0.12	0.37		
M2 Depressive symptoms ^a	2585	(9.70% depressed)					2378	(11.40% depressed)				
M2 Chronic conditions ^b	2572	0.00	20.00	1.64	1.79	2373	0.00	20.00	1.64	2.07		
M2 Word List Immediate ^a	2412	0.00	15.00	7.00	2.19	1777	0.00	15.00	6.35	2.37		
M2 Word List Delayed ^a	2332	0.00	14.00	4.69	2.51	1664	0.00	14.00	4.05	2.72		
M2 Category Fluency	2416	1.00	42.00	19.70	6.00	1776	0.00	40.00	17.53	6.16		
M2 Backward Digit Span ^a	2415	0.00	8.00	5.10	1.45	1778	0.00	8.00	4.88	1.56		
M2 Number Series ^a	2414	0.00	5.00	2.51	1.51	1752	0.00	5.00	1.94	1.46		
M2 30 Second and Counting Task	2415	-2.00	90.00	38.76	11.19	1760	2.00	100.00	35.21	11.44		
M2 Stop and Go Switch Task ^a	2346	-3.77	-0.61	-1.07	0.23	1672	-7.36	-0.22	-1.13	0.33		
Valid N (listwise)	2235						1561					

^a T-test between the 2 groups is significant at the 0.01 level (equal variance assumed).

^b T-test between the 2 groups is significant at the 0.05 level (equal variance assumed).

had fewer chronic conditions, and performed better on all cognitive assessments at Wave 2.

2.2. Cognitive measures

All cognitive measures from M2 and M3 were collected with the Brief Test of Adult Cognition by Telephone (BTACT), a reliable and valid brief cognitive battery designed for telephone administration that assesses key cognitive domains related to cognitive aging (Lachman and Tun, 2008; Lachman et al., 2014; Tun and Lachman, 2006). Participants were administered the BTACT at their preferred time of day. They were instructed to be in a place without distractions, close their eyes to help with concentration, and not write anything during the 7 cognitive tests.

The BTACT included measures of episodic memory (Word List Immediate [WLI] and Delayed [WLD]; immediate and delayed free recall of 15 words), inductive reasoning (Number Series [NS]; completing a pattern in a series of 5 numbers), category verbal fluency (Category Fluency [CAT]; the number of words produced from the category of animals in 60 seconds), working memory span (Backward Digit Span [DS]; the highest span achieved in repeating strings of digits in reverse order), processing speed (30 Second and Counting Task [BC]; the number of digits produced by counting backward from 100 in 30 seconds), and attention switching and inhibitory control reaction time (Stop and Go Switch Task [SGST]; (Lachman and Tun, 2008). For SGST, reaction times were calculated with the mean of switch and nonswitch trials median latencies on a task requiring alternating between the “normal” condition (i.e., respond “Go” to the stimulus “Green” and “Stop” to the stimulus “Red”) and the “reverse” condition (i.e., respond “Stop” to the stimulus “Green” and “Go” to the stimulus “Red”). See Hughes et al. (2018) for more information about the BTACT and scoring procedures.

2.3. Voice measures

Voice measures include the 6 prosody variables that have been most frequently associated with dementia in prior research: pitch was measured by the mean number of vocal cord vibrations per second; pulse was measured by the frequency of glottal pulses of air; number of voice breaks was measured by total time length of breaks divided by total time length of voice; jitter was measured by frequency instability; shimmer was measured by amplitude instability; and amplitude was measured by the average noise-to-signal ratio (Al-Hameed et al., 2019; Boersma and Weeink, 2019; Fraser et al., 2016; König et al., 2015; Martinez-Sanchez et al., 2012; Meilán et al., 2014; Ruz et al., 2014).

The voice data were extracted from the 3 tests from the cognitive interview which had the most extended segments of uninterrupted participant voice (WLI, WLD, and CAT), with a total of 7763 recordings. Two research assistants (RAs) were randomly assigned to each voice recording to identify the time frame of the participant’s voice within the recording, to analyze that time frame for voice measures using Praat voice analysis software (Boersma and Weeink, 2019), and finally to document the voice measures in an assigned secure excel file. Reliability between the 2 RAs was calculated across all ratings by calculating the percentage of audio files with consistent values (97.14%). Afterward, the first author resolved any discrepancies by reanalyzing the voice segments. Voice recordings determined to be of poor quality or for which participants did not complete the cognitive measures were excluded from analyses ($n = 4.24\%$). For each voice measure, we computed an aggregate composite score from the Praat values averaged across the 3 cognitive tests and computed internal consistency reliability using coefficient alpha: pitch ($\alpha = 0.928$), pulse ($\alpha = 0.871$), voice breaks

($\alpha = 0.732$), jitter ($\alpha = 0.852$), shimmer ($\alpha = 0.878$), and amplitude ($\alpha = 0.535$).

2.4. Covariates

Based on their significant relationships with cognitive performance in prior literature, we included self-reported age (continuous), sex (male = 0, female = 1), education (in years) obtained from a telephone interview, as well as the number of neurological conditions, depressive symptoms, and the number of chronic conditions obtained from a self-administered questionnaire (Alzheimer’s Association, 2019, Gatz et al., 2001; Karlamangla et al., 2014; Kessler et al., 2004; Meilán et al., 2020, 2014; Mielke, 2018; National Academies of Sciences and Medicine, 2017; Podcasy and Epperson, 2016; Tsenkova and Karlamangla, 2016). The number of neurological conditions was calculated by a count of the number of “yes” answers on self-reported neurological conditions (stroke, serious head injury, Parkinson’s disease, or other neurological disorder), with a higher score indicating more neurological conditions (M2 range: 0–3; M3 range: 0–3).

Depressive symptoms were calculated as a binary variable (0 = no, 1 = yes) using phone interview questions per the Diagnostic and Statistical Manual of Mental Disorders third edition (American Psychiatric Association, 1987). The depressive symptoms variable was coded as “yes” if, within the past 12 months, the participant experienced 2 weeks of either depressed mood or anhedonia most of the day or nearly every day and also had at least 4 common depression symptoms (such as poor eating, poor sleeping, low energy, low concentration, low feelings of self-worth, and suicidal thoughts or actions) (Kessler et al., 2004; Tsenkova and Karlamangla, 2016).

The number of chronic conditions was calculated at M3 by a count of the number of “yes” answers on self-reported health conditions in the last 12 months (asthma/bronchitis/emphysema, tuberculosis, other lung problems, arthritis/rheumatism/other bone or joint disease, thyroid disease, recurring stomach trouble/indigestion/diarrhea, urinary/bladder problems, being constipated all or most of the time, gall bladder trouble, AIDS/HIV infection, Lupus/other autoimmune disorders, persistent trouble with gums/mouth, persistent trouble with teeth, high blood pressure/hypertension, alcohol/drug problems, migraine headaches, chronic sleeping problems, diabetes/high blood sugar, ulcer, hernia/rupture, cancer, or heart trouble) with a higher score indicating more chronic conditions (M3 range: 0–22). Participants were not assessed for neurocognitive disorders, although this does not exclude the possibility of some undiagnosed cognitive impairment or AD.

2.5. Data analyses

Descriptive statistics were conducted in SPSS 28.0 (IBM Corp., 2021). We used longitudinal multilevel modeling (MLM) (Bolger and Laurenceau, 2013) and the lme4 package (Bates et al., 2011) in R (R Core Team, 2021) to examine whether voice measures of pitch, pulse, voice breaks, jitter, shimmer, and amplitude were associated with individual differences in change in each cognitive test over 10 years. Time was coded linearly as 0 = M2 and 1 = M3. Age, gender, education, neurological conditions, depressive symptoms, and chronic conditions were the control variables. The M2 and M3 cognitive measures were standardized using means and standard deviations from M2 scores. The SGST Latency variable was multiplied by (-1) to keep the direction consistent with other cognitive tests (i.e., a higher score indicates better (faster) performance).

The following multilevel model was tested for each of the 7 cognitive tests:

$$\begin{aligned} \text{Cognitive_test_score}_{ti} = & \beta_{0i} + \text{time}_{ti}\text{pitch}_{ii} + \text{time}_{ti}\text{pulse}_{ii} \\ & + \text{time}_{ti}\text{voicebreaks}_{ii} + \text{time}_{ti}\text{jitter}_{ii} + \text{time}_{ti}\text{shimmer}_{ii} \\ & + \text{time}_{ti}\text{amplitude}_{ii} + \text{age}_{ii} + \text{sex}_{ii} + \text{education}_{ii} \\ & + \text{neurological_conditions}_{ii} + \text{depressive_symptoms}_{ii} \\ & + \text{chronic_conditions}_{ii} + e_t + e_i \end{aligned}$$

Equation 1 shows the simple linear growth model with the interaction effect of time, and it is based on the 2 waves of cognitive test scores for the i -th participant: time (t) represents the 2 waves ($0 = \text{M2}$ and $1 = \text{M3}$). β_{0i} is the average cognitive test score at M2 when each covariate equals zero.

3. Results

3.1. Covariates associated with voice measures

The correlations of the covariates with voice variables were consistent with prior work (Gatz et al., 2001; Martinez-Sanchez et al., 2012; Meilán et al., 2020, 2014, 2012; Mielke, 2018; Podcasy and Epperson, 2016). Age was negatively correlated with pulse and voice breaks and positively correlated with jitter and shimmer. Sex was negatively correlated with jitter, shimmer, and amplitude and positively correlated with pitch, pulse, and voice breaks. Education was negatively correlated with pitch and positively correlated with pulse, voice breaks, and shimmer. Neurological conditions were negatively correlated with pulse. Depressive symptoms were positively correlated with pitch and negatively correlated with shimmer. Chronic conditions were negatively correlated with jitter and positively correlated with pulse and voice breaks. The correlations are presented in Table 3.

Because voice was measured from the same time point as M3 cognitive tests, we compared results from our primary longitudinal analyses with correlations between voice measures and M3 cognitive performance. All of the multilevel results were replicated with the M3 correlations. However, there were some other significant relationships in the correlations for concurrent assessments of cognition and voice at M3 that did not appear in the primary analyses of cognitive change: WLI was positively correlated with pitch and negatively correlated with shimmer and amplitude; WLD was positively correlated with pulse and pitch, and negatively correlated with shimmer; CAT was positively correlated with pulse; DB was positively correlated with pulse and voice breaks; NS was positively correlated with pulse and voice breaks, and negatively correlated with pitch; BC was positively correlated with pulse and voice breaks, and negatively correlated with pitch; SGST was positively correlated with pulse and voice breaks, and negatively correlated with pitch. All correlations are presented in Table 3.

3.2. Multilevel models of voice relating to cognitive measures

For each of the 7 cognitive tests, we applied a linear mixed-effects multilevel model (LMER) to investigate whether voice measures were associated with change in cognitive performance over time when controlling for the covariates. Results for cognitive tests that were used for the voice composites (WLI, WLD, and CAT) are shown in Tables 4–6, and results for the relationships between changes in cognitive tests from M2 to M3 and significant voice composites are shown in Figs. 1–3: as expected, higher jitter was associated with greater decline in WLI ($p = 0.033$), WLD ($p = 0.010$), and CAT ($p = 0.006$) (see Fig. 1 graphs showing greater 10-year declines in WLI, WLD, and CAT when M3 jitter is higher).

Contrary to hypotheses, lower pulse was associated with greater decline in WLI ($p = 0.038$) (see Fig. 2 graphs showing greater 10-year decline in WLI when M3 pulse is higher); fewer voice breaks were associated with greater decline in WLI ($p = 0.005$), WLD ($p < 0.001$), and CAT ($p < 0.001$) (see Fig. 3 graphs showing greater 10-year declines in WLI, WLD, and CAT when M3 amount of voice breaks is lower). Results for cognitive tests that were not used for the voice composites (DB, NS, BC, and SGST) are shown in Tables 7–10. Results for SGST, a cognitive test not used in voice composite, are summarized in Table 7; as expected, higher jitter was associated with greater decline in SGST reaction time ($p = 0.001$) (see Fig. 2 graphs showing greater 10-year decline in SGST when M3 jitter is higher).

3.3. Sensitivity analyses

Given that voice prosody could reflect how one performs on a given test, we conducted sensitivity analyses to explore this further for the 3 tests used to measure voice prosody. We added to the models the measures of total voice duration for the test and the number of intrusions or errors made on the test. These are indirect measures of how well the participant performed on a test and could potentially result in more voice breaks. In other words, those with longer voice duration presumably remember more words. However, having more intrusions also adds to duration but not to the test score. The sensitivity analysis results were consistent with the original findings: as expected, higher jitter was associated with greater decline in WLI ($p = 0.038$), WLD ($p = 0.010$), and CAT ($p = 0.006$). Also consistent with the primary analyses, lower pulse was associated with greater decline in WLI ($p = 0.040$); and fewer voice breaks were associated with greater decline in WLI ($p = 0.006$), WLD ($p < 0.001$), and CAT ($p = 0.001$). As the MIDUS sample includes some siblings, we tested whether including within-family dependence (including an additional random effects term for family) would change the results. We confirmed that for this test, the estimates of the key covariates and their significance remained the same. Thus, all reported analyses did not include the family random effects term in the model.

4. Discussion

The current study is the first, to our knowledge, to examine a selection of 6 voice prosody measures previously associated with AD as possible indicators of risk for cognitive impairment by examining their relation to cognitive changes over 10 years in a large community-residing national sample of midlife and older adults. We collected voice measures from participant voice segments, a method used in work measuring temporal and spectral voice features to assess dementia risk in participants (Lin et al., 2020; Nasreen et al., 2021). Our study extended this work by assessing the relationships between these voice prosody measures and cognitive changes in a sample with a larger age range while controlling for health and demographic factors. Our results replicate prior significant findings for jitter by Lin et al. (2020), but not for shimmer. One possible reason is that our model controlled for additional covariates, including neurological conditions such as Parkinson's disease, which is associated with higher jitter and shimmer (Hertrich and Ackermann, 1995; Ramig et al., 1988). In addition, our study suggests new relationships linking 10-year cognitive changes with prosody measures of pulse and voice breaks in middle-aged and older participants.

Our study examined individual differences in cognitive change over 10 years, assuming that more decline is worse than less or no decline and that more decline is potentially associated

Table 3
Correlations of demographic measures and cognitive measures with voice measures.

		Pitch composite	Pulse composite	Voice breaks composite	Jitter composite	Shimmer composite	Amplitude composite
Age	Pearson Correlation	0.012	-0.082 ^a	-0.046 ^a	0.159 ^a	0.080 ^a	-0.004
	Sig. (2-tailed)	0.542	<0.001	0.020	<0.001	<0.001	0.836
	N	2581	2585	2585	2580	2580	2580
Sex	Pearson Correlation	0.590	0.309 ^a	0.099 ^a	-0.240 ^a	-0.496 ^a	-0.068 ^a
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N	2581	2585	2585	2580	2580	2580
Education	Pearson Correlation	-0.055 ^a	0.053 ^a	0.108 ^a	0.026	0.062 ^a	0.000
	Sig. (2-tailed)	0.005	0.007	<0.001	0.194	0.002	0.996
	N	2573	2577	2577	2572	2572	2572
Neurological conditions	Pearson Correlation	-0.011	-0.040 ^a	-0.025	0.050 ^b	0.059 ^a	-0.001
	Sig. (2-tailed)	0.581	0.042	0.205	0.011	0.003	0.972
	N	2575	2579	2579	2574	2574	2574
Depressive symptoms	Pearson Correlation	0.042 ^b	0.036	0.007	-0.022	-0.050 ^b	-0.011
	Sig. (2-tailed)	0.033	0.068	0.734	0.270	0.011	0.567
	N	2581	2585	2585	2580	2580	2580
Chronic conditions	Pearson Correlation	0.086 ^a	-0.018	-0.021	0.060 ^a	0.010	0.015
	Sig. (2-tailed)	<0.001	0.355	0.288	0.003	0.623	0.451
	N	2528	2531	2531	2527	2527	2527
M2 Word List Immediate	Pearson Correlation	0.147 ^a	0.179 ^a	0.125 ^a	-0.112 ^a	-0.158 ^a	-0.105 ^a
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N	2410	2410	2410	2409	2409	2409
M2 Word List Delayed	Pearson Correlation	0.136 ^a	0.174 ^a	0.101 ^a	-0.117 ^a	-0.176 ^a	-0.105 ^a
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N	2330	2330	2330	2329	2329	2329
M2 Category Fluency	Pearson Correlation	-0.038	0.110 ^a	0.170 ^a	-0.034	0.006	-0.018
	Sig. (2-tailed)	0.062	<0.001	<0.001	0.099	0.780	0.366
	N	2414	2414	2414	2413	2413	2413
M2 Backward Digit Span	Pearson Correlation	0.028	0.088 ^a	0.081 ^a	0.000	0.015	-0.009
	Sig. (2-tailed)	0.163	<0.001	<0.001	0.990	0.469	0.665
	N	2413	2413	2413	2412	2412	2412
M2 Number Series	Pearson Correlation	-0.065 ^a	0.051 ^b	0.096 ^a	-0.011	0.032	-0.001
	Sig. (2-tailed)	0.001	0.012	<0.001	0.590	0.113	0.959
	N	2412	2412	2412	2411	2411	2411
M2 30 Second and Counting Task	Pearson Correlation	-0.071 ^a	0.053 ^a	0.089 ^a	0.009	0.053 ^a	0.006
	Sig. (2-tailed)	<0.001	0.009	<0.001	0.644	0.009	0.759
	N	2413	2413	2413	2412	2412	2412
M2 Stop and Go Switch Task	Pearson Correlation	-0.078 ^a	0.011	0.039	-0.016	0.023	-0.032
	Sig. (2-tailed)	<0.001	0.578	0.059	0.437	0.271	0.118
	N	2344	2344	2344	2343	2343	2343
M3 Word List Immediate	Pearson Correlation	0.126 ^a	0.247 ^a	0.202 ^a	-0.168 ^a	-0.200 ^a	-0.056 ^a
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	0.004
	N	2581	2581	2581	2580	2580	2580
M3 Word List Delayed	Pearson Correlation	0.148 ^a	0.248 ^a	0.187 ^a	-0.169 ^a	-0.225 ^a	-0.035
	Sig. (2-tailed)	<0.001	<0.001	<0.001	<0.001	<0.001	0.087
	N	2460	2460	2460	2460	2459	2459
M3 Category Fluency	Pearson Correlation	-0.016	0.185 ^a	0.247 ^a	-0.073 ^a	-0.025	-0.026
	Sig. (2-tailed)	0.419	<0.001	<0.001	<0.001	0.208	0.181
	N	2581	2581	2581	2580	2580	2580
M3 Backward Digit Span	Pearson Correlation	0.004	0.089 ^a	0.117 ^a	-0.025	-0.015	-0.006
	Sig. (2-tailed)	0.852	<0.001	<0.001	0.204	0.446	0.776
	N	2582	2582	2582	2581	2581	2581
M3 Number Series	Pearson Correlation	-0.078 ^a	0.041 ^b	0.090 ^a	-0.026	0.038	-0.019
	Sig. (2-tailed)	<0.001	0.038	<0.001	0.190	0.056	0.352
	N	2517	2517	2517	2516	2516	2516
M3 30 Second and Counting Task	Pearson Correlation	-0.069 ^a	0.056 ^a	0.104 ^a	-0.017	0.029	-0.018
	Sig. (2-tailed)	<0.001	0.005	<0.001	0.400	0.145	0.354
	N	2556	2556	2556	2555	2555	2555
M3 Stop and Go Switch Task	Pearson Correlation	-0.062 ^a	0.057 ^a	0.053 ^a	-0.070 ^a	-0.005	-0.030
	Sig. (2-tailed)	0.002	0.004	0.008	<0.001	0.818	0.140
	N	2492	2492	2492	2491	2491	2491

^a Correlation is significant at the 0.01 level (2-tailed).

^b Correlation is significant at the 0.05 level (2-tailed).

with a greater risk of later impairment. The goal was to examine whether voice prosody measures show meaningful relationships with individual differences in change over the 10 years. Although having 2 occasions is not ideal for examining patterns of age-related changes, the results are consistent with previous aging research investigating different domains of cognitive function-

(Hultsch et al., 1990; Karlamangla et al., 2009; Salthouse, 1996). First, the expected relationships with age were found, with older people showing greater declines over the 10 years compared to younger people. Second, the extent of change across measures is consistent with previous work; for example, Digit Symbol Backwards does not show significant declines until later in life, whereas

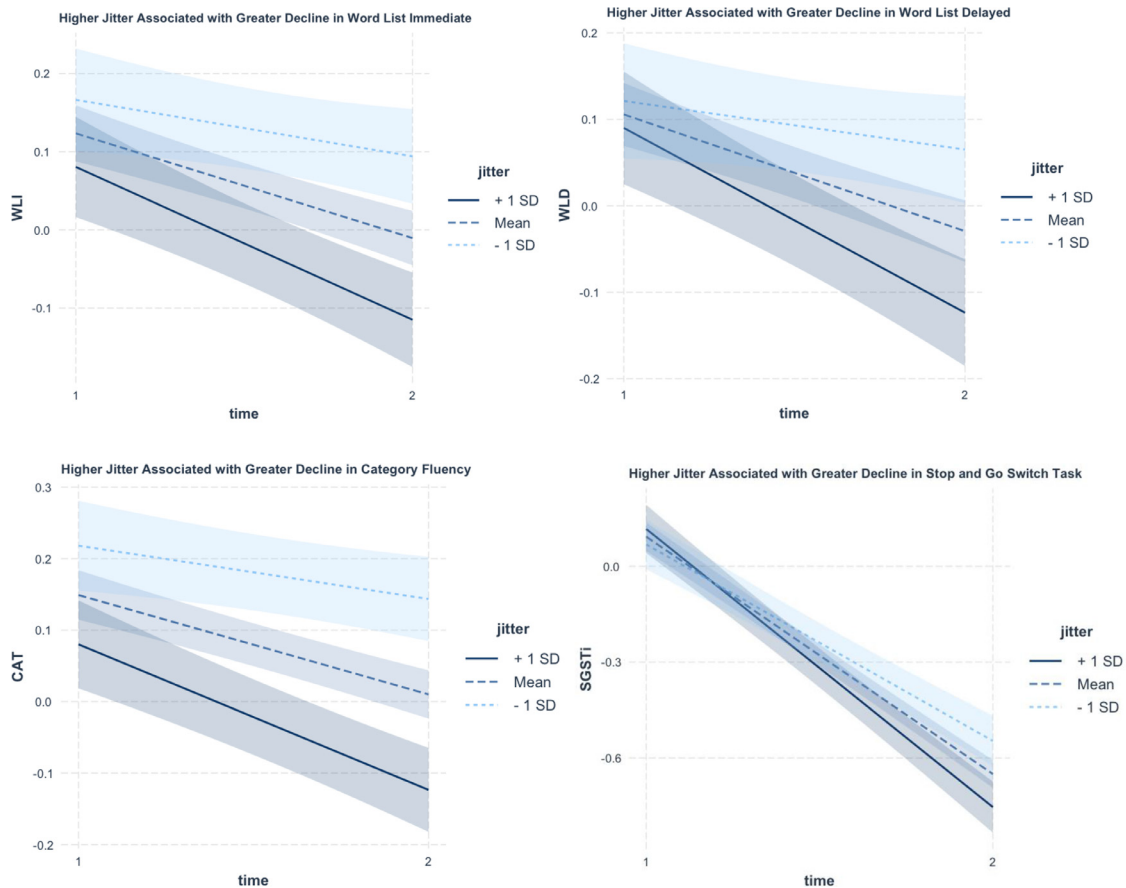


Fig. 1. Relationship of jitter to cognitive change.

Table 4
Multilevel model results for Word List Immediate.

Model	B	SE	p	CI ₉₅
1 (Intercept)	-0.217	0.331	0.513	-0.866; 0.433
Time	-0.036	0.179	0.840	-0.388; 0.315
Pitch	0.001	0.001	0.306	-0.001; 0.003
Pulse	0.000	0.000	0.897	0.000; 0.000
Voice breaks	-0.001	0.003	0.605	-0.007; 0.004
Jitter	0.022	0.062	0.718	-0.099; 0.143
Shimmer	0.001	0.020	0.956	-0.039; 0.041
Amplitude	0.384	0.409	0.347	-0.417; 1.185
Age	-0.021 ^a	0.001	<0.001	-0.024; -0.018
Sex	0.398 ^a	0.042	<0.001	0.316; 0.5481
Education	0.067 ^a	0.006	<0.001	0.055; 0.078
Neurological conditions	-0.157 ^a	0.042	<0.001	-0.240; -0.075
Depressive symptoms	-0.018	0.052	0.730	-0.119; 0.084
Chronic conditions	-0.017 ^c	0.008	0.033	-0.032; -0.001
Time x pitch	-0.001	0.001	0.288	-0.002; 0.001
Time x pulse	0.000 ^c	0.000	0.045	0.000; 0.000
Time x voice breaks	0.005 ^b	0.002	0.006	0.001; 0.008
Time x jitter	-0.073 ^c	0.036	0.040	-0.143; -0.003
Time x shimmer	0.000	0.012	0.989	-0.024; 0.023
Time x amplitude	-0.205	0.205	0.317	-0.607; 0.197

^a Significant at the 0.001 level (2-tailed).
^b Significant at the 0.01 level (2-tailed).
^c Significant at the 0.05 level (2-tailed).

Table 5
Multilevel model results for Word List Delayed.

Model	B	SE	p	CI ₉₅
1 (Intercept)	0.509	0.338	0.133	-0.155; 1.172
Time	-0.267	0.180	0.139	-0.620; 0.086
Pitch	-0.001	0.001	0.626	-0.003; 0.002
Pulse	0.000	0.000	0.462	0.000; 0.000
Voice breaks	-0.005	0.003	0.056	-0.011; 0.000
Jitter	0.075 ^c	0.061	0.223	-0.045; 0.195
Shimmer	-0.023	0.021	0.253	-0.064; 0.017
Amplitude	0.352	0.405	0.384	-0.441; 1.145
Age	-0.021 ^a	0.001	<0.001	-0.024; -0.018
Sex	0.391 ^a	0.043	<0.001	0.307; 0.476
Education	0.056 ^a	0.006	<0.001	0.044; 0.067
Neurological conditions	-0.107 ^c	0.043	0.013	-0.192; -0.022
Depressive symptoms	-0.035	0.053	0.518	-0.139; 0.070
Chronic conditions	-0.028 ^a	0.008	0.001	-0.044; -0.012
Time x pitch	0.000	0.001	0.586	-0.001; 0.002
Time x pulse	0.000	0.000	0.188	0.000; 0.000
Time x voice breaks	0.006 ^a	0.002	0.000	0.003; 0.009
Time x jitter	-0.093 ^b	0.035	0.008	-0.162; -0.024
Time x shimmer	0.006	0.012	0.603	-0.017; 0.030
Time x amplitude	-0.169	0.203	0.404	-0.567; 0.228

^a Significant at the 0.001 level (2-tailed).
^b Significant at the 0.01 level (2-tailed).
^c Significant at the 0.05 level (2-tailed).

Speed of Processing (Backward Counting) shows significant declines that begin in midlife. Although not definitive, these longitudinal results provide some evidence for the validity of the changes found. The consistency of results with past work supports the assumption that the changes reflect meaningful differences in cogni-

tive performance over 10 years. In future work, it will be essential to include additional time points for both cognition and voice measures to better understand the trajectory of cognitive changes related to voice changes and to link cognitive and voice changes directly with risk of impairment.

Table 6
Multilevel model results for Category Fluency.

Model	B	SE	p	CI ₉₅
1 (Intercept)	0.263	0.295	0.373	-0.315; 0.840
Time	-0.401 ^b	0.146	0.005	-0.692; -0.121
Pitch	-0.001	0.001	0.420	-0.003; 0.001
Pulse	0.000	0.000	0.987	0.000; 0.000
Voice breaks	0.004	0.002	0.102	-0.001; 0.009
Jitter	-0.005	0.053	0.920	-0.109; 0.099
Shimmer	0.010	0.018	0.556	-0.024; 0.045
Amplitude	0.108	0.355	0.761	-0.587; 0.803
Age	-0.021 ^a	0.001	<0.001	-0.023; -0.018
Sex	-0.054	0.043	0.222	-0.139; 0.031
Education	0.095 ^a	0.006	<0.001	0.083; 0.107
Neurological conditions	-0.104 ^c	0.043	0.017	-0.189; -0.019
Depressive symptoms	0.036	0.053	0.504	-0.069; 0.140
Chronic conditions	-0.024 ^b	0.008	0.003	-0.040; -0.008
Time x pitch	0.001	0.001	0.283	0.000; 0.002
Time x pulse	0.000	0.000	0.131	0.000; 0.000
Time x voice breaks	0.005 ^a	0.001	0.001	0.002; 0.007
Time x jitter	-0.077 ^b	0.029	0.009	-0.134; -0.019
Time x shimmer	0.014	0.010	0.156	-0.005; 0.033
Time x amplitude	-0.068	0.178	0.703	-0.416; 0.281

^a Significant at the 0.001 level (2-tailed).
^b Significant at the 0.01 level (2-tailed).
^c Significant at the 0.05 level (2-tailed).

Some results were consistent with predictions based on past work on voice and dementia. The results for jitter supported past AD work in that higher jitter was associated with greater decline in WLI, WLD, CAT, and SGST reaction time. These cognitive changes are consistent with other studies of cognitive aging. Jitter is generally explained as tiny tremors in the voice, inaudible to the human

ear, due to the unstable change of pitch frequency affected by executive function decline over time. Jitter has been significantly associated with AD in past work. The present findings extend this to a link with cognitive changes in midlife and later life adults who have not been diagnosed with MCI or AD.

Some results were inconsistent with past research on voice and AD. First, lower pulse was associated greater decline in WLI in contrast to past work in which higher pulse has been associated with AD. However, pulse is less commonly researched as a voice biomarker of AD than other voice prosody measures. Past work

Lower Pulse Associated with Greater Decline in Word List Immediate

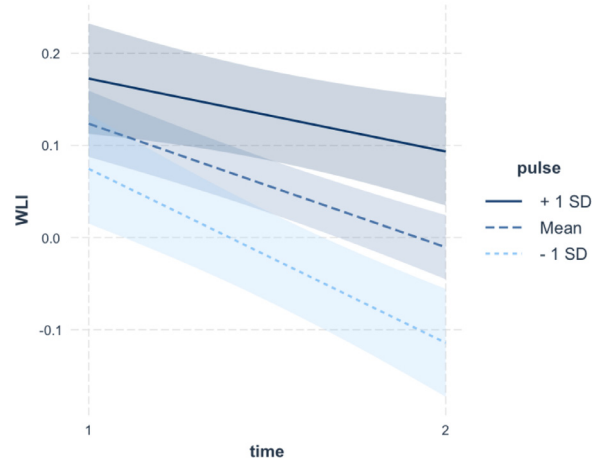
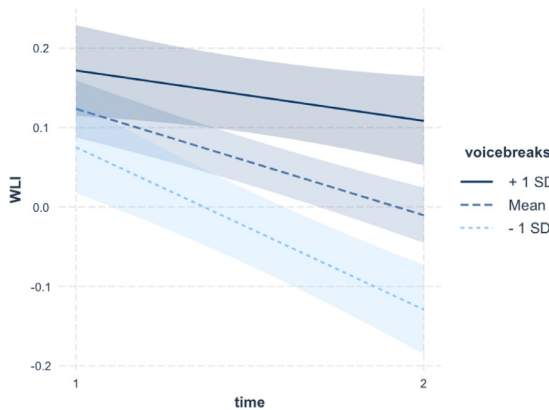
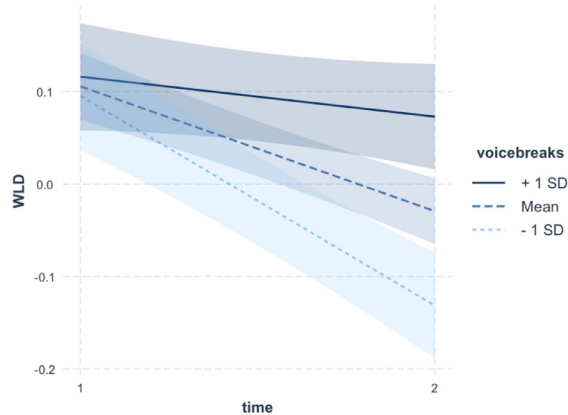


Fig. 2. Relationship of pulse to cognitive change.

Lower Voice Breaks Associated with Greater Decline in Word List Immediate



Lower Voice Breaks Associated with Greater Decline in Word List Delayed



Lower Voice Breaks Associated with Greater Decline in Category Fluency

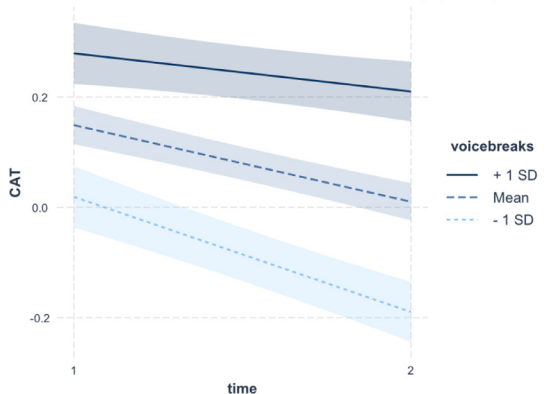


Fig. 3. Relationship of voice breaks to cognitive change.

Table 7
Multilevel model results for Stop and Go Switch Task.

Model	B	SE	p	CI ₉₅
1 (Intercept)	1.830 ^a	0.447	<0.001	0.954; 2.705
Time	-0.585 ^c	0.260	0.024	-1.094; -0.076
Pitch	0.001	0.002	0.524	-0.002; 0.004
Pulse	0.000	0.000	0.220	0.000; 0.000
Voice breaks	-0.001	0.004	0.890	-0.008; 0.007
Jitter	0.197 ^c	0.085	0.020	0.031; 0.362
Shimmer	-0.017	0.027	0.542	-0.069; 0.036
Amplitude	-0.366	0.527	0.487	-1.400; 0.668
Age	-0.021 ^a	0.002	<0.001	-0.024; -0.017
Sex	-0.194 ^a	0.051	<0.001	-0.294; -0.094
Education	0.040 ^a	0.007	<0.001	-0.026; 0.053
Neurological conditions	-0.262 ^a	0.051	<0.001	-0.362; -0.161
Depressive symptoms	-0.002	0.063	0.972	-0.125; 0.121
Chronic conditions	-0.022 ^c	0.010	0.020	-0.041; -0.004
Time x pitch	-0.001	0.001	0.213	-0.003; 0.001
Time x pulse	0.000	0.000	0.129	0.000; 0.000
Time x voice breaks	0.002	0.003	0.558	-0.004; 0.007
Time x jitter	-0.166 ^b	0.053	0.002	-0.270; -0.061
Time x shimmer	0.013	0.016	0.444	-0.020; 0.045
Time x amplitude	0.163	0.264	0.538	-0.356; 0.682

^a Significant at the 0.001 level (2-tailed).^b Significant at the 0.01 level (2-tailed).^c Significant at the 0.05 level (2-tailed).**Table 8**
Multilevel model results for Digits Backward.

Model	B	SE	p	CI ₉₅
1 (Intercept)	-0.930 ^b	0.335	0.005	-1.586; -0.274
Time	0.182	0.176	0.302	-0.164; 0.528
Pitch	0.001	0.001	0.346	-0.001; 0.003
Pulse	0.000	0.000	0.170	0.000; 0.000
Voice breaks	0.000	0.003	0.966	-0.005; 0.006
Jitter	-0.031	0.062	0.610	-0.152; 0.090
Shimmer	0.0476 ^c	0.020	0.026	0.006; 0.086
Amplitude	-0.014	0.413	0.973	-0.823; 0.795
Age	-0.012 ^a	0.002	<0.001	-0.001; -0.009
Sex	0.081	0.045	0.069	-0.006; 0.167
Education	0.069 ^a	0.006	<0.001	0.058; 0.081
Neurological conditions	-0.020	0.045	0.648	-0.108; 0.067
Depressive symptoms	-0.001	0.055	0.987	-0.109; 0.107
Chronic conditions	-0.024 ^b	0.008	0.005	-0.040; -0.007
Time x pitch	-0.001	0.001	0.310	-0.002; 0.001
Time x pulse	0.000	0.000	0.444	0.000; 0.000
Time x voice breaks	0.002	0.002	0.143	-0.001; 0.006
Time x jitter	0.003	0.035	0.935	-0.066; 0.072
Time x shimmer	-0.017	0.012	0.140	-0.041; 0.006
Time x amplitude	0.006	0.207	0.977	-0.399; 0.412

^a Significant at the 0.001 level (2-tailed).^b Significant at the 0.01 level (2-tailed).^c Significant at the 0.05 level (2-tailed).

on pulse and AD has mainly used small clinical samples. Our results contribute information on the relationships between voice measures and cognitive change in a broader sample and suggest the need for more research on low pulse as an indicator of cognitive impairment. Additionally, the association between fewer voice breaks and greater decline in WLI, WLD, and CAT is the reverse of what was expected based on prior AD literature. This result could be due to using voice recordings from cognitive assessments rather than conversational speech. Breaks in conversation may indicate cognitive problems, whereas breaks during responses to a cognitive test may reflect something about test performance. In other words, those who remember more words on a memory or category fluency test may have more voice breaks if they pause between words recalled. Future work could compare voice breaks in different protocols to examine whether voice breaks are valuable biomarkers for cognitive changes in midlife and later life.

Table 9
Multilevel model results for Number Series.

Model	B	SE	p	CI ₉₅
1 (Intercept)	-0.066	0.303	0.828	-0.659; 0.527
Time	-0.308 ^c	0.152	0.043	-0.605; -0.010
Pitch	0.000	0.001	0.799	-0.002; 0.002
Pulse	0.000	0.000	0.583	0.000; 0.000
Voice breaks	0.003	0.002	0.243	-0.002; 0.008
Jitter	0.020	0.055	0.721	-0.088; 0.127
Shimmer	-0.016	0.018	0.381	-0.051; 0.020
Amplitude	0.117	0.364	0.749	-0.598; 0.831
Age	-0.019 ^a	0.002	<0.001	-0.022; -0.016
Sex	-0.180 ^a	0.044	<0.001	-0.267; -0.094
Education	0.138 ^a	0.006	<0.001	0.126; 0.150
Neurological conditions	-0.077	0.044	0.082	-0.164; 0.010
Depressive symptoms	-0.062	0.055	0.253	-0.169; 0.045
Chronic conditions	-0.026 ^b	0.008	0.002	-0.042; -0.010
Time x pitch	0.000	0.001	0.595	-0.001; 0.001
Time x pulse	0.000	0.000	0.734	0.000; 0.000
Time x voice breaks	0.001	0.001	0.666	-0.002; 0.003
Time x jitter	-0.046	0.030	0.128	-0.106; 0.013
Time x shimmer	0.018	0.010	0.071	-0.002; 0.038
Time x amplitude	-0.077	0.183	0.674	-0.435; 0.281

^a Significant at the 0.001 level (2-tailed).^b Significant at the 0.01 level (2-tailed).^c Significant at the 0.05 level (2-tailed).**Table 10**
Multilevel model results for Backwards Counting.

Model	B	SE	p	CI ₉₅
1 (Intercept)	1.345 ^a	0.254	<0.001	0.847; 1.843
Time	-0.191	0.010	0.055	-0.386; 0.004
Pitch	0.000	0.001	0.907	-0.002; 0.001
Pulse	0.000	0.000	0.321	0.000; 0.000
Voice breaks	0.001	0.002	0.457	-0.002; 0.005
Jitter	0.049	0.042	0.245	-0.033; 0.131
Shimmer	0.015	0.014	0.275	-0.012; 0.043
Amplitude	-0.176	0.258	0.495	-0.682; 0.330
Age	-0.032 ^a	0.002	<0.001	-0.035; -0.029
Sex	-0.254 ^a	0.046	<0.001	-0.343; -0.164
Education	0.082 ^a	0.006	<0.001	0.070; 0.095
Neurological conditions	-0.149 ^b	0.046	0.001	-0.239; -0.059
Depressive symptoms	0.001	0.056	0.980	-0.109; 0.112
Chronic conditions	-0.029 ^a	0.009	0.001	-0.045; -0.012
Time x pitch	0.000	0.000	0.376	0.000; 0.001
Time x pulse	0.000	0.000	0.422	0.000; 0.000
Time x voice breaks	0.002	0.001	0.077	0.000; 0.003
Time x jitter	-0.027	0.020	0.182	-0.066; 0.013
Time x shimmer	-0.005	0.007	0.424	-0.018; 0.008
Time x amplitude	0.068	0.129	0.600	-0.185; 0.320

^a Significant at the 0.001 level (2-tailed).^b Significant at the 0.01 level (2-tailed).

4.1. Limitations

The study was limited in that the voice measures were obtained from several tests used to examine cognitive change. Significant voice measures associated with cognitive change were found mainly for the 3 tests from which the voice measures were derived. Thus, a dependency between test performance and voice measures should be addressed in future research. Voice prosody may reflect the level of performance on a given test. For example, if someone is doing well on a memory test, they may have less jitter. We attempted to address this limitation with sensitivity analyses that controlled for speech duration (related to how many words were recalled) and intrusion errors. The same results were obtained as the primary analyses. It is also noteworthy that the voice measures were related to change in cognition rather than the level of performance. In future work, voice measures could be obtained from independent speech that is not tied to cognitive test-

ing. Nevertheless, there are also some advantages of using cognitive interviews to obtain voice measures in that it controls the possible range of responses across participants. However, the results may not generalize to free conversational speech.

Another potential limitation was that the audio files were recorded in MP3 format, which is not considered optimal for voice quality. However, although participant voice recordings were not recorded in an ideal format (WAV), the optimization function in Praat enhanced the quality of the voice data. Many past studies have used the Praat optimization method to make their audio analyses of various formats more reliable. Therefore, this is a minor concern that likely did not affect the parameters of our study. Future research should record participant voices in WAV format, an option that can be set as default in most recording devices currently available.

The MIDUS data set we used had some limiting factors. Although ~10% of the original cognitive sample at M2 was nonwhite, there was a larger percentage of participants in the dropout group from M2 to M3 that were nonwhite (12.5%) compared to the longitudinal group (7.5%) (Hughes et al., 2018; Radler and Ryff, 2010). Future research with more diverse samples could provide more generalizable results. Future research should include additional covariates such as medication use, smoking, and anxiety to control for other possible factors that could be related to vocal qualities. Also, the sample did not have assessments of cognitive status or clinical diagnosis. Thus, we do not know if any participants have some form of cognitive impairment. Future studies should consider examining the relationships between voice prosody measures and cognitive change in a sample that has midlife and later life participants assessed as healthy or with mild cognitive impairment or dementia by medical professionals.

4.2. Future work

When considering the next steps for this area of research, it will be essential to test possible mechanisms linking voice features and cognitive changes. Voice features can potentially be affected over time by peripheral mechanisms in the body. For example, changes in pulmonary function can impact vocal cord vibrations and result in altered jitter and shimmer or can impact subglottal pressure in the vocal tract and increase amplitude (Johns et al., 2011). Further, respiratory illness and smoking can cause excessive larynx constriction, resulting in changed pitch (Garellek, 2014). Though less harmful, smaller mechanisms that are common in respiratory illnesses, such as sustained contractions of the laryngeal muscle and excessive cricothyroid muscle tightening over the vocal fold, can raise pitch and amplitude due to peripheral vocal fatigue (Roubeau et al., 1997; Sieck and Prakash, 1995; Simpson and Rosen, 2008). Even without these dysfunctions, the aging of these muscles over time may lead to dopaminergic deficit, resulting in lower pitch and amplitude (Baker, 1998; Rampello et al., 2016; Zarzur et al., 2007).

The central nervous system can also be explored as a mechanism for understanding the association between voice prosody and cognitive changes. Brain damage due to trauma or disease is associated with changes in voice features. Specifically, lesions to the central nervous systems can result in higher pitch and lower amplitude (Arenaza-Urquijo et al., 2015; Honer et al., 2012; Ljitona et al., 2016; Lesuis et al., 2018; Stacey et al., 2017). However, because the brain plays a central role throughout life in physiological changes, brain aging is the ultimate cause of cognitive decline and degeneration of voice. Age-related changes in cognition and voice are both associated with more structural alterations, more cortical thickness, and reduced gray matter volume in cortical and subcortical regions related to executive function

and speech production (Diaconescu et al., 2013; Funahashi, 2001; Guenther, 2006; Hirano et al., 2004; Lieberman, 2007; Porter et al., 2011; Tremblay and Deschamps, 2016). In these regions, subtle age-related changes in the dopamine binding potential and receptor densities of the neural networks can later result in significant deterioration in more overt voice parameters, such as speech response time and articulation accuracy (Bäckman et al., 2010; Duchin and Mysak, 1987; Erixon-Lindroth et al., 2005; MacDonald et al., 2009; Nyberg et al., 2016; Wang et al., 1998). Peripheral changes due to aging may happen years before cognitive decline is apparent. It is vital to identify the underlying mechanisms that link voice biomarkers with cognitive change so that AD risk can be calculated decades before serious neuropathology appears.

4.3. Conclusion

As the prevalence of AD continues to rise, identifying biomarkers that can distinguish significant patterns of cognitive change from normal cognitive aging as early as possible could be useful for delaying or reducing dementia. Voice, the primary method of human communication, has the potential for long-term self-monitoring and medical monitoring of cognitive status because specific vocal prosody measures are related to changes in cognitive functioning. Voice recordings are a convenient and low-burden way to obtain biomarkers that may be useful for early detection of cognitive changes. Analysis of voice biomarkers has the potential to become a simple and noninvasive procedure for rapid and precise data collection at any timepoint, ultimately enabling the identification of risks for cognitive changes and impairment and early diagnosis of dementia.

Author contributions

Elizabeth Mahon: Conceptualization, Methodology, Software, Data curation, Visualization, Investigation, Writing- Original draft preparation. Margie Lachman: Conceptualization, Funding acquisition, Methodology, Supervision, Writing- Reviewing and Editing.

Disclosure statement

The authors have no potential financial or personal conflicts of interest including relationships with other people or organizations within 3 years of beginning the work submitted that could influence this work.

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We verify that the voice data and the analyses contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

The study was conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, and U.S. 21 CFR Part 50 – Protection of Human Participants, and Part 56 – Institutional Review Boards. Informed consent was obtained from all participants before protocol-specific procedures were performed.

We verify that all authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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