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RESEARCH ARTICLE

Underlying brain and genetic mechanisms linking historic phone use patterns, visual decline, and dementia risk in middle-aged and older adults

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Abstract

BACKGROUND: This study aimed to investigate associations between historic phone use, visual decline, and risk of dementia, as well as underlying biological mechanisms.

METHODS: A total of 494,359 participants from UK Biobank were included in the prospective study. Historic phone use, visual acuity, brain imaging, and leukocyte telomere lengths (LTLs) were assessed. Incident dementia was tracked via hospital episode records and mortality data.

RESULTS: Over a median follow-up of 12.2 years, participants with better visual acuity were associated with longer use of mobile phone. Longer historic phone use was associated with a 31% lower risk of dementia. Both hippocampal gray matter volumes and LTLs were associated with historic phone use length and significantly mediated the relationship between historic phone use and dementia. Mediation still exists in participants with visual decline.

CONCLUSION: Our findings suggest mobile phone use may serve as a modifiable factor to prevent dementia, even in older adults with visual decline.

KEYWORDS
dementia, hippocampus, mobile phone use, telomere length, vision

Highlights

- A strong inverse association was observed between longer mobile phone use and lower dementia incidence, potentially mediated by changes in hippocampal gray matter volume and LTL.

Xiayin Zhang, Yuling Xu, and Shan Wang contributed equally to this study.Xianwen Shang, Mingguang He, and Zhuoting Zhu are co-senior authors

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- Mobile phone use may benefit individuals with age-related visual decline by reducing dementia risk, given the well-established link between vision impairment and increased dementia risk.
- Middle-aged and older adults should be encouraged to use mobile phones as a means to enhance social connectivity.

1 | INTRODUCTION

With an aging population, dementia has become an emerging concern worldwide and has severely detrimental social and economic impacts.[1] Currently, there are 50 million people with dementia worldwide, with 9.9 million new cases rising annually.[2] Therefore, it is critical to improve our understanding of modifiable factors that could protect against dementia. Although various lifestyle factors have been shown to contribute to dementia,[3–4] evidence regarding the use of digital devices, such as mobile phones, during midlife and later life remains limited.

The advent of digital technology has revolutionized the engagement of mobile phones in the elderly population.[5,6] Notably, the mobile device can be regarded as a double-edged sword in public health. There are concerns that radiofrequency exposure and excessive phone abuse cause psychological issues,[7,8] but these claims are mainly unsupported. Instead, studies have reported the benefits of mobile devices for health coaching, shared decision-making, and reduced feelings of stress in the elderly.[9,10] Recent studies have emphasized the significance of mobile devices for cognitive exercises and daily activities that are designed to support cognitively impaired or demented patients.[11–14] Nevertheless, research evaluating the correlation between mobile phone use, particularly focusing on social connections through making and receiving calls, and dementia in the general healthy population remains scarce. Existing studies are often limited by small sample sizes, the relatively young age of participants, and reliance on cross-sectional designs.[15,16]

Possible mechanisms underlying dementia development have been pointed out, with possible biomarkers including neuropathological damage in the hippocampus[17] and reduced leukocyte telomere length (LTL).[18] Progressive hippocampal atrophy is a notable biomarker of dementia representing neuronal loss,[19,20] whereas significantly enhanced hippocampal long-term potentiation has been observed under the modulation of physical exercise and environmental factors.[21,22] Similarly, LTL shortening is another important biomarker of dementia[18,23–25] and linked to age, sex, ethnicity, and environmental and lifestyle factors such as exercise, smoking, and alcohol consumption.[26,27] With the paucity of evidence that mobile phone use may change neuroplasticity and telomere length in older adults, we aimed to investigate whether the hippocampal gray matter volume and LTL could mediate the interaction between mobile phone use and dementia. In addition, given that age-related visual decline has been associated with an elevated risk of dementia,[28] we propose that voice-based phone interactions, as a low-cost and universally accessible intervention, may serve as a potential modifiable factor in the relationship between visual decline and dementia among older adults.

The current study leveraged the large prospective cohort of the UK Biobank, containing pre-smartphone era digital device use patterns, longitudinal dementia surveillance with extended follow-up, detailed imaging assessments of the eye and brain, as well as in-depth genetic data.[29] Considering the current literature gap, our objectives were fourfold. First, we aim to explore the associations between historic phone use and the risk of dementia; second, to examine whether the above associations could be modified by age or sex; third, to explore the underlying mediating effect for hippocampal gray matter volume and LTL between historic phone use and dementia; and finally, to identify whether mobile phone use is a modifiable factor for the association between visual acuity and dementia, and explore relationships between visual acuity, historic phone use, dementia, hippocampal gray matter volume, and LTL using structural equation modeling. We hypothesized that mobile phone use is associated with lower risks of dementia that might be supported by brain structure and genetic mechanisms, and could be used as a modifiable factor for mid-to-late life participants.

2 | METHODS

2.1 | Participants

The data were obtained from the UK Biobank (application ID 86091). The UK Biobank cohort study enrolled over 500,000 volunteers between 38 and 73 years of age across 22 research centers in England, Scotland, and Wales.[30,31] All participants completed detailed demographic and health assessments and had physical measurements taken. UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). All participants provided informed consent. Figure S1 illustrates the inclusion of participants.

2.2 | Measurements of electronic device use

Historic phone use was recorded through touchscreen questionnaires, including the question for mobile phone use length "For approximately how many years have you been using a mobile phone at least once per week to make or receive calls?" with responses of (I) Never used mobile phone at least once per week, (II) 1 year or less, (III) 2–4 years, (IV) 5–8 years, or (V) More than 8 years. If the participant selected the Help button they were shown the message: "Do not include time spent text

messaging. If you are unsure, please provide an estimate or select Do not know." Histograms of historic phone use length are shown in Figure S1a,b. According to the median of historic phone use length, the historic phone use length was categorized into shorter use (<5 years) and longer use (≥5 years).

The UK Biobank questionnaire item on historic phone use specifically captured the time spent making or receiving calls on a mobile phone during the pre-smartphone era, and excluded text messaging. For participants who indicated they had used a mobile phone at least once per week, they completed questionnaires including "Over the last 3 months, on average how much time per week did you spend making or receiving calls on a mobile phone? (Weekly usage of mobile phone)"; "Over the last 3 months, how often have you used a hands-free device/speakerphone when making or receiving calls on your mobile? (Hands-free device/speakerphone use)"; and "Is there any difference between your mobile phone use now compared to two years ago? (Difference in mobile phone use)." Finally, computer game playing was collected through the question, "Do you play computer games?" (Table S1).

2.3 | Ascertainment of incidence of dementia

The primary outcomes of this study were incidence of all-cause dementia and its common subtypes, Alzheimer's disease (AD) and vascular dementia (VD), during the follow-up until the end of April 2021. We defined incidence dementia (both non-fatal and fatal) from hospital admission and death register records using the International Classification of Diseases, 9th Revision (ICD-9) and 10th Revision (ICD-10) diagnostic codes. ICD-9 and ICD-10 diagnostic codes for ascertaining all-cause dementia, AD, and VD are summarized in Table S2. All outcomes were followed up to December 31, 2021.

Follow-up years were calculated from the date of baseline assessment to either the date of dementia onset, the date of death, or the end of follow-up, whichever came first. This study included 492,878 participants with available dementia outcomes (Figure S2).

2.4 | Structural brain imaging

The hippocampal gray matter volumes were acquired from T1 structural brain magnetic resonance imaging (MRI) assessed during the neuroimaging visit (2014+, $n = 34,867$). Structural MRI data were collected with a standard Siemens Skyra 3T scanner with a 32-channel RF-receive head coil. After the acquisition, images underwent an automated image processing pipeline developed by the UK Biobank (Supplementary Methods).[32] The histogram of hippocampal gray matter volumes used in this study is shown in Figure S1c.

2.5 | Telomere length measurements

LTL measurements were ascertained on DNA extracted from blood samples collected at the baseline assessment (2006–2010, $n = 465,330$) using a well-validated quantitative polymerase chain reaction (qPCR) assay.[33] Samples with no genetic data or failed quality control were excluded. Measurements were reported as a ratio of the telomere repeat number to single-copy gene (T/S ratio), which were then log-transformed to approximate the normal distribution and *Z*-standardized to facilitate comparison with other datasets. The histogram of the adjusted LTL is shown in Figure S1d. Multiple quality checks to control and adjust for technical factors were undertaken as described elsewhere.[34]

RESEARCH IN CONTEXT

1. **Systematic review**: Previous studies have emphasized the significance of mobile devices for cognitive exercises and daily activities that are designed to support cognitively impaired or demented patients. We searched PubMed and medRxiv for articles published before October 30, 2022, without language restrictions, using the terms "phone/mobile phone/mobile devices/digital devices"and "dementia/Alzheimer." In addition, we searched the reference lists of the retrieved articles. The literature search identified 29 studies in total, and 6 were further reviewed through title screening. Research evaluating the correlation between mobile phone use and dementia among the general healthy population is rare and limited by small sample sizes, young ages of participants, and cross-sectional design.
2. **Interpretation**: As technologies continue to have a greater impact on human life, the interventions such as learning programs or classes that assist elderly people to connect with technology should be prioritized to ensure their independence in this world. Our study suggests that mobile phone use may assist in the prevention or delayed onset of dementia through the mediation of leukocyte telomere length and hippocampal structural changes and should be encouraged in middle-aged to older adults, even in those with visual decline.
3. **Future directions**: Future investigations should prospectively collect data from smartphones to provide information about the protective effect of multimedia and the internet on dementia.

2.6 | Visual acuity measurements

The ocular examinations at baseline assessment (2006–2010, $n = 115,306$) included distance visual acuity measured in the logarithm of the minimum angle of resolution (logMAR; Precision Vision, LaSalle, IL). LogMAR visual acuity charts use the design principles suggested by Bailey and Lovie, and a higher value of logMAR means

worse visual acuity.[35] A value of 0 logMAR is considered normal visual acuity(Supplementary Methods).[36]

2.7 | Demographic data

Demographic information included age, sex, and the Townsend deprivation index (an area-based proxy measure for socioeconomic status). The ethnicity was self-reported and recorded as White and non-White (Asian, Black, Chinese, mixed, or other ethnic groups), and White genetic ancestry was confirmed by genotypes. Other covariates are shown in the Supplementary Methods.

2.8 | Statistical analyses

Normally distributed continuous variables were reported using mean (SD), whereas categorical variables were summarized as count (percentage). We used Cox proportional hazard regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of outcomes associated with dementia (including AD and VD). Linear regression models were applied to evaluate the association between electronic device use, hippocampal gray matter volume, and LTL. Logistic regression models were applied to assess the association between better visual acuity and measurements of electronic device use. The false discovery rate approach is used for multiple comparisons.

Restricted cubic splines (package rms 6.2-0 in R) with five knots were used to model the non-linear associations between the historic phone use length logarithmically transformed as a continuous variable and the key measures. A non-linear quadratic regression model ($y = bx^2+ax+c$) was further used to confirm the association between historic phone use length (x) with the measure of interest such as LTL (y). Sensitivity analyses, additionally excluding people diagnosed with dementia in the first 2 years during the follow-up, were conducted to reduce reverse causality. We further explored whether electronic device use was associated with dementia, hippocampal gray matter volume, LTL measurements, and visual acuity across different ages and sexes. Multivariable-adjusted regression analysis was conducted to observe the interaction between age and mobile use length. *T*-tests were conducted to identify the significance of the coefficient of each interaction term. In addition, a similar method was used to explore the interaction between electronic device use and sex, with "electronic device use×sex" added to the original model.

Three mediation models were used in the current study (Supplementary Methods). Total, direct, and indirect associations were estimated by the 1000-iteration nonparametric bootstrap approach. A structural equation model was investigated to determine the directional dependencies with visual acuity, historic phone use, hippocampal gray matter volume, LTL, and dementia via path modeling. For mediation analysis and structural equation models, age, sex, Townsend index, educational qualifications, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, and family history of dementia were used as covariates.

R 3.6.1 (using the packages "survival," "rms 6.2-0",: and "lavaan 0.8") and Stata 17 statistical software (StataCorp LP) were used to perform the analyses. A *p*-value below .05 was considered statistically significant.

3 | RESULTS

3.1 | Population characteristics

Figure 1 provides a general schema of the current study. Of the 502,405 participants in the UK Biobank cohort, 494,359 participants 38–73 years of age (54.3% female) completed touchscreen questions about electronic device use at baseline between 2006 and 2010. The median historic phone use length was 5∼8 years. Participants were separated into two groups: shorter phone use (<5 years, $n = 174,637$) and longer phone use (≥5 years, $n = 319,722$) at baseline. The cohort characteristics stratified by historic phone use length are presented in Table S3.

A total of 53,101 participants 44–82 years of age also completed questionnaire for electronic device use at the follow-up neuroimaging visit collected from 2014. Brain imaging of 34,867 participants was used in the current study. In addition, genetic data for the LTL of 465,330 participants at baseline were also included. Table 1 shows the demographic information of the participants used in the study.

3.2 | Associations between electronic device use and key measures

During a median follow-up of 12.2 years (interquartile range [IQR] 11.5–12.9 years), 2465 individuals (0.5%) were diagnosed with dementia (including 875 AD and 499 VD) after excluding 215 with pre-baseline dementia. Compared to those with shorter mobile phone use, those using phones for >5 years had a 31% lower risk of dementia (HR = 0.69, 95% CI = 0.63–0.76, $p = 5.28e{-}14$). Similar results were found for AD (HR = 0.69, 95% CI = 0.58–0.80, $p = 3.53e{-}06$) and VD (HR = 0.75, 95% CI = 0.60–0.92, $p = 5.77e{-}03$) (Table 2). To further assess dose-dependent associations between historic phone use length and risks of dementia incidences, the historic phone use length was divided into three groups. Table S4 shows strong dose-related relationships between historic phone use length, all-cause dementia, and AD. The risk of all-cause dementia was 34% lower (HR = 0.66, 95% CI = 0.58–0.74, $p < .001$) among those with longest mobile phone use (≥8 y) compared with those with shortest phone use length (≤4 y). Restricted cubic splines were further used to test the non-linear effects of historic phone use length (transformed as a continuous variable) on the incidence of dementia, with no significant non-linearity discovered (Figure 2A–C).

In addition, we explored the associations between visual acuity and electronic device use. Participants with better visual acuity (≤0

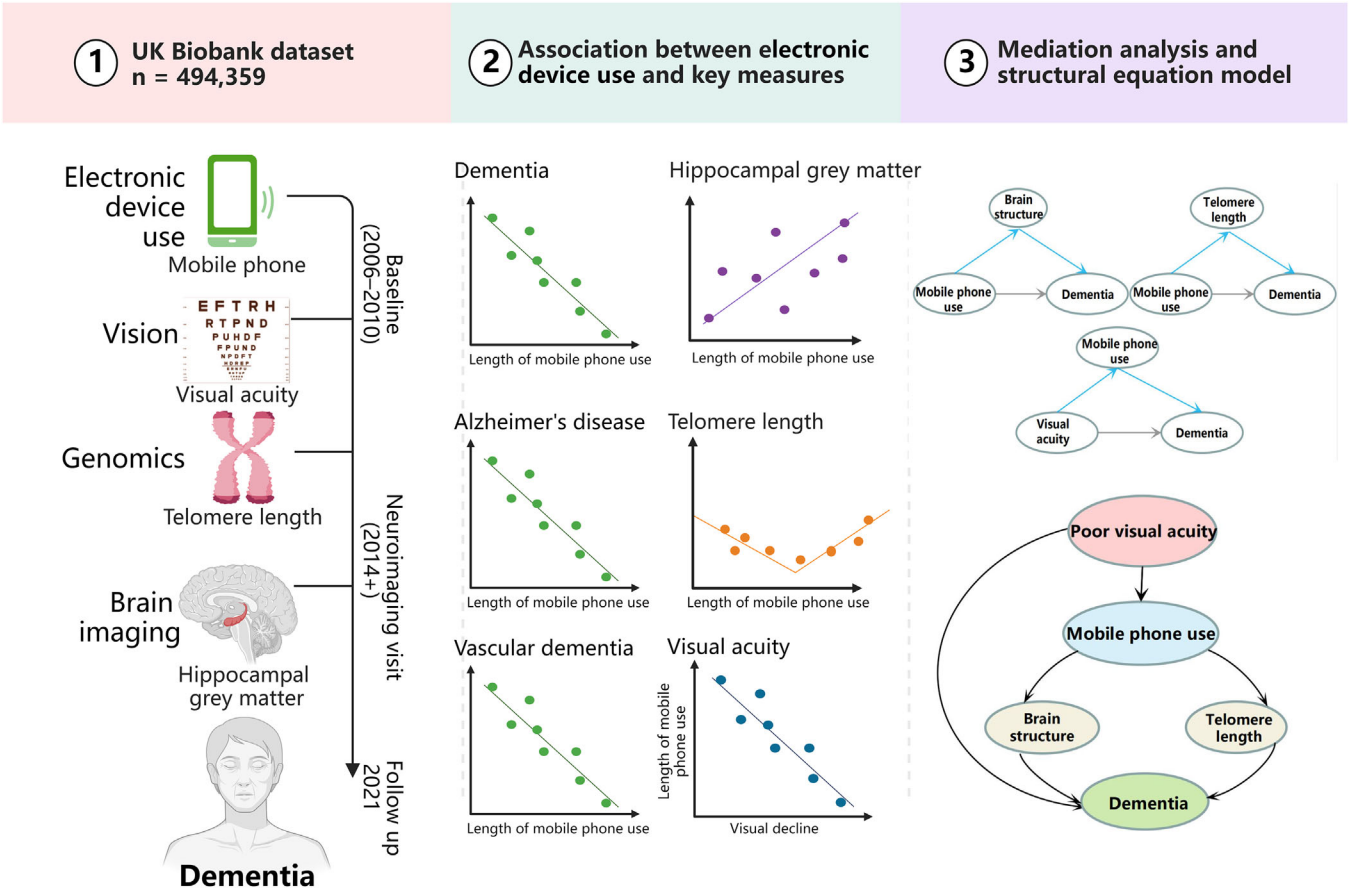

FIGURE 1 Guideline of this study. Left, UK Biobank data used in the study, including electronic device use, visual acuity, telomere length, brain imaging, and longitudinal follow-up of dementia incidences. Middle, associations between electronic device use and key measures. Right, mediation analysis and structural equation model specifying the directional association between mobile phone use, visual acuity, volumes of hippocampal gray matter, telomere length, and dementia.

logMAR) used mobile phones longer (odds ratio [OR] = 1.13, 95% CI = 1.09–1.17, $p < .001$, Table 2). This was also true for hands-free devices (OR = 1.09, 95% CI = 1.04–1.14, $p < .001$, Table S5), with no significant non-linearity detected (Figure 2F).

Next, we assessed whether historic phone use affected hippocampal gray matter volume. The mean volume of gray matter in the hippocampus was used after normalization to determine whether electronic device use and brain hippocampal gray matter volume was associated. Longer use was associated with larger hippocampal volume (Coefficient = 29.08, 95% CI = 13.39–44.78, p = 6.43e−05, Table 2). No non-linear relationship was found (p overall = .005, p non-linear > .05, Figure 2D). No significant associations were found with other electronic devices (p adjusted > .05, Table S5).

Historic phone use duration (≥5 years) was not associated with LTL (Table 2). However, a *U*-shaped relationship between mobile phone use and LTL was observed (p non-linear = .013, Figure 2E). Quadratic regression confirmed this association, with 5 years as the breakpoint. In addition, LTL was longer for those using hands-free devices (Coefficient = 0.0131, 95% CI = 0.0041–0.0222, p adjusted = .013, Table S5).

3.3 | The effects of age, sex, and ethnicity on the associations between electronic device use and key measures

Considering that age significantly differed by mobile phone use (Table S3), we further divided the participants into two age groups. Among 261,589 participants aged ≤58 years at baseline, 311 (0.12%) developed all-cause dementia during long-term follow-up, including 87 (0.03%) with AD and 47 (0.02%) with VD. In contrast, among the 232,555 participants >58 years of age, the incidence was substantially higher: 2057 (0.88%) developed dementia, including 740 (0.32%) AD and 418 (0.18%) VD cases. The relationship between the longer use of mobile phones and a decreased risk of all-cause dementia was significant in the older group aged 58–73 years (p interaction = .005, Figure 3A and Table S6). Similar trends were observed in AD and VD, with no significant interaction observed (both p interaction > .05, Table S6). For hippocampal gray matter volumes, the significant positive relationship between longer use of mobile phones and larger gray matter volumes of hippocampus was significant in the younger group, and the association curve flattened with increasing age (p interaction < 0.001, Figure 3B). In addition, the non-linear association between length of

TABLE 1 Demographic characteristics of study participants.

Variables	Baseline (2006–2010) *N* = 494,359	Genetic data (2006–2010) *N* = 465,330	Imaging visit (2014+) *N* = 53,101
Age (years), mean ± SD	56.5 (8.1)	56.5 (8.1)	64.1 (7.7)
Sex (female), no. (%)	268,621 (54.3)	251,883 (54.1)	27,347 (51.5)
Townsend index, mean ± SD	−1.3 (3.1)	−1.3 (3.1)	−1.9 (2.7)
Educational qualification, no. (%)			
College or university degree	160,062 (32.4)	151,792 (32.6)	24,071 (45.3)
Others	334,297 (67.6)	313,538 (67.4)	29,030 (54.7)
Smoking status, no. (%)			
Never	269,399 (54.7)	253,398 (54.7)	31,921 (60.2)
Former/current	223,204 (45.3)	210,286 (45.3)	21,076 (39.8)
Drinking status, no. (%)			
Never	21,436 (4.3)	20,009 (4.3)	1327 (2.5)
Former/current	472,395 (95.7)	444,839 (95.7)	51,757 (97.5)
Obesity, no. (%)			
No	371,802 (75.6)	350,723 (75.7)	43,171 (81.4)
Yes	119,971 (24.4)	112,838 (24.3)	9=852 (18.6)
Physical activity, no. (%)			
Not meeting recommendation	73,801 (18.5)	69,889 (18.5)	8405 (18.5)
Meeting recommendation	324,883 (81.5)	308,399 (81.5)	36,897 (81.5)
Family history of dementia, no. (%)			
No	436,678 (88.3)	411,026 (88.3)	46,751 (88.0)
Yes	57,681 (11.7)	54,304 (11.7)	6350 (12.0)
History of diabetes, no. (%)			
No	464,935 (94.0)	437,648 (94.1)	51,398 (96.8)
Yes	29,424 (6.0)	27,682 (5.9)	1703 (3.2)
History of hypertension, no. (%)			
No	137,039 (27.7)	127,893 (27.5)	17,532 (33.0)
Yes	357,320 (72.3)	337,437 (72.5)	35,569 (67.0)
History of hyperlipidemia, no. (%)			
No	268,456 (54.3)	249,957 (53.7)	31,574 (59.5)
Yes	225,903 (45.7)	215,373 (46.3)	21,527 (40.5)
Length of mobile phone use at baseline, no. (%)			
<5 years	174,637 (35.3)	163,770 (35.2)	6792 (12.8)
≥5 years	319,722 (64.7)	301,560 (64.8)	46,309 (87.2)
Visual acuity (logMAR) at baseline, mean ± SD	−0.04 (0.15)	−0.04 (0.15)	−0.07 (0.14)

Abbreviations: LogMAR, logarithm of the minimum angle of resolution; SD, standard deviation.

mobile phone use and LTL was significant in the younger group, compared to the linear relationship observed in the older age groups (*p* interaction > .05, Figure 3C). The association between better visual acuity and longer mobile phone use was also more significant in the younger group (*p* non-linear = .004, Figure 3D).

We further explored the interaction between electronic device use and sex (Table S7, Figure 3E–H). In addition, based on previously observed ethnicity differences in LTL,[34] the association between length of mobile phone use and LTL stratified by ethnicity was shown in Table S8.

3.4 | The mediating effects of hippocampal gray matter volume and LTL between mobile phone use and dementia

We further examined whether hippocampal gray matter volume and LTL contributed to the longitudinal association between historic phone use with dementia incidences. Therefore, we conducted two mediation pathway analyses, namely (1) historic phone use→hippocampal gray matter volume→dementia, and (2) historic phone use→LTL→dementia. We found that longer historic phone use

TABLE 2 The correlations between length of mobile phone use[a] and key measures.

Dementia	HR (95% CI)	*p*-value
All-cause dementia	0.69 (0.63–0.76)	**5.28e−14**
AD	0.69 (0.58–0.80)	**3.53e−06**
VD	0.75 (0.60–0.92)	**5.77e−03**
Brain structure[b]	**Coefficient (95% CI)**	***p*-value**
The mean volume of gray matter in the Hippocampus (mm^3)	29.08 (13.39–44.78)	**6.43e−05**
The volume of gray matter in the hippocampus (lh, mm^3)	28.96 (13.74–44.19)	**1.97e−04**
The volume of gray matter in the hippocampus (rh, mm^3)	31.58 (15.65–47.51)	**1.02e−04**
Telomere length	**Coefficient (95% CI)**	***p*-value**
Technically adjusted leukocyte telomere length (ratio)[c]	−0.0031 (−0.0036 to 0.0098)	0.37
Visual acuity	**OR (95% CI)**	***p*-value**
Better visual acuity (≤0 logMAR)[d]	1.13 (1.09–1.17)	**< 1e−15**

Note: All models have been adjusted for age, sex, Townsend index, educational qualifications, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, and family history of dementia. Bold values denote statistical significance at $p < .05$ level.
Abbreviations: AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; lh, left hemisphere; logMAR, logarithm of the minimum angle of resolution; OR, odds ratio; rh, right hemisphere; VD, vascular dementia.
[a]The length of mobile phone use was categorized into shorter use (<5 y) and longer use (≥5 y), according to the median of mobile phone use length at baseline.
[b]The length of mobile phone use assessed at the neuroimaging visit (2014+) was used to determine the association with brain structures.
[c]The technically adjusted leukocyte telomere length has been both loge-transformed to obtain a normal distribution and Z-standardized to allow comparison to other studies.
[d]The visual acuity categorized into better visual acuity (≤0 logMAR) and worse visual acuity (≤0 logMAR) was used to determine the association with longer use of mobile phones at baseline.

had a significant negative effect on dementia incidence ($\beta = -9.72e{-}04$, $p < .001$); longer mobile phone use was also associated with larger volumes of gray matter in the hippocampus ($\beta = 15.58$, $p = .005$). Larger volumes of gray matter in the hippocampus were negatively associated with incident dementia ($\beta = -9.14e{-}07$, $p < .001$, Figure 4A). The indirect pathway of the effect of longer phone use on dementia via volumes of gray matter in the hippocampus was significant (path $\beta' = -1.42e{-}05$, $p = .019$). For the mediation of telomere length, we used a latent variable represented by historic phone use length and hands-free device/speakerphone use, both of which are associated with LTL. The results demonstrated that historic phone use was positively associated with longer LTL ($\beta = 3.81e{-}02$, $p = .015$), and longer LTL was significantly associated with decreased risks of dementia ($\beta = -3.55e{-}04$, $p = .001$, Figure 4B). The indirect pathway of the effect of historic phone use on dementia via LTL was also significant (path $\beta' = -1.35e{-}05$, $p = .049$).

3.5 | The associations between visual acuity, mobile phone use, and dementia

Finally, we explored whether mobile phone use is a modifiable factor for the association between visual acuity and dementia. We first confirmed that the risk of dementia was 35% lower (HR = 0.65, 95% CI = 0.51–0.81, $p < .001$) in those individuals with normal visual acuity (≤0 logMAR) compared with those with poorer vision, with no significant non-linearity discovered. We then conducted a third mediation pathway analysis in the general population, namely visual acuity→mobile phone use→dementia. The results revealed that mobile phone use significantly mediated the association between visual acuity and dementia (p indirect $< .05$, Figure 4C). In participants with poorer vision, longer use of mobile phone was still significantly associated with a 37% lower risk of dementia (HR = 0.63, 95% CI = 0.45–0.88, $p = .007$), and the above mediating effect still exists.

Using structural equation modeling, we further specified the directional association between visual acuity, mobile phone use, dementia, hippocampal gray matter volume, and LTL. Confirmatory factor analysis was used to examine the latent variable for historic phone use, represented by historic phone use length and hands-free device/speakerphone use ($\beta = 1.00$ and 1.76, respectively; $p < .001$), both of which are significantly associated with visual acuity and dementia incidences. All associations in the path model (Figure 4D) were in the expected direction. Visual acuity was significantly associated with historic phone use ($\beta = -0.004$, $p < .001$) and was a significant predictor of dementia ($\beta = 3.39e{-}04$, $p = .025$). All paths represent significant associations except for the ones related to hippocampal gray matter volume in the pathway model.

4 | DISCUSSION

In this study, we demonstrated that long-term (>5 year) historic phone use is associated with decreased risk of dementia incidence and its subtypes, and pathways may underlie this relationship. Moreover, our mediation analyses suggest a potential inverse association between mobile phone use and dementia risk, potentially mediated by

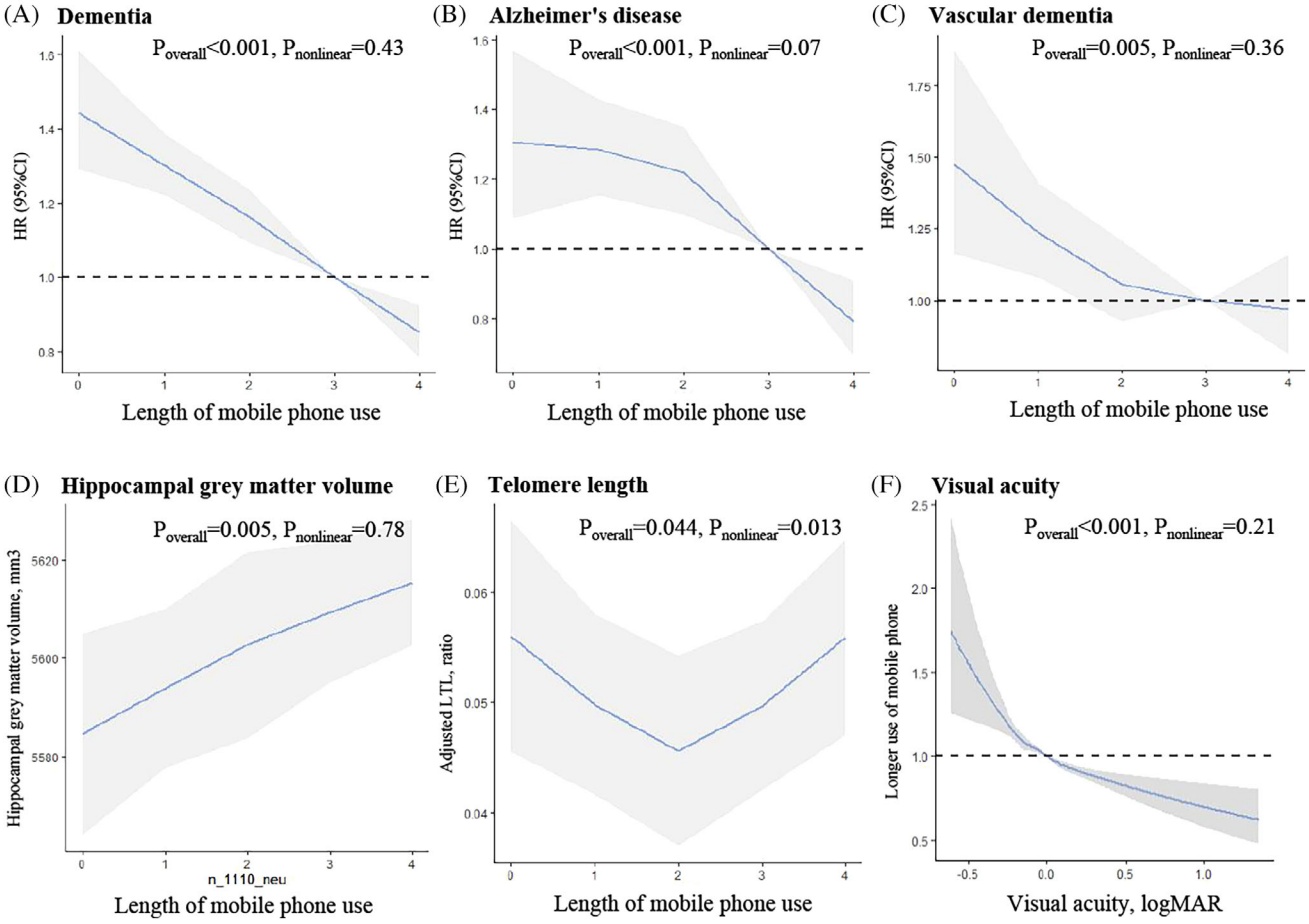

FIGURE 2 Associations between mobile phone use length and key measures. (A–C) Significant overall associations were observed between mobile phone use length, all-cause dementia, and its common subtypes, with no non-linearity discovered (All *p*'s non-linear > .05). (D) Longer use of mobile phone use was linearly associated with larger volumes of gray matter in the hippocampus, with no non-linearity discovered (*p* non-linear > .05). (E) A significant non-linear association between mobile phone use length and telomere length was identified (*p* non-linear = .013). (F) Poorer visual acuity was negatively associated with mobile phone use length, with no non-linearity discovered (*p* non-linear > .05). All models have been adjusted for age, sex, Townsend index, educational qualifications, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, and family history of dementia. Lines show fitted mean values with 95% CIs shaded. **p*'s overall were adjusted for multiple comparisons using the FDR correction method. CI, confidence intervals; FDR, false discovery rate.

hippocampal preservation and LTL maintenance. Thus, mobile phone use may assist in the prevention or delayed onset of dementia through the mediation of LTL and hippocampal structural changes and should be encouraged in middle-aged to older adults, even in those with visual decline.

As dementia could be preceded by a long "silent" clinical period, there is great importance in examining longitudinal associations in mid- and late life. Our study provides robust longitudinal associations of mobile phone use with dementia. The associations between mobile phone use and dementia in middle-aged to older adults in the UK population align with previous studies demonstrating that mobile phone use is associated with lower risks of cognitive decline in older adults and enhanced memory functioning.[15,37,38] Of interest, the age-stratified analysis revealed that the associations between mobile phone use and dementia were significant only among older participants, whereas the associations between mobile phone use and hippocampal gray matter volume were significant exclusively among younger participants. We hypothesize that younger individuals may exhibit greater neuroplasticity, rendering them more susceptible to environmental enrichment, such as mobile phone use, which could influence hippocampal neurogenesis.[39] For older participants, age-related structural and functional brain changes may overshadow these associations.

Notably, we took hippocampal gray matter volume and LTL into consideration in exploring the underlying pathway between historic phone use and dementia and its subtypes. It is estimated that social isolation is one of the modifiable risk factors contributing to ≈35% of dementia cases worldwide.[40] And long-term use of mobile phones could alleviate the social isolation of the elderly. Studies have shown that hippocampal sclerosis and atrophy are important factors contributing to the decline of cognitive ability and dementia in old age, especially in AD, whereas up to 25% of patients with VD have severe hippocampal atrophy.[41–42] Research indicates that telomere shortening may lead to an increased risk of all-cause dementia, particularly in AD and VD.[43] Longitudinal

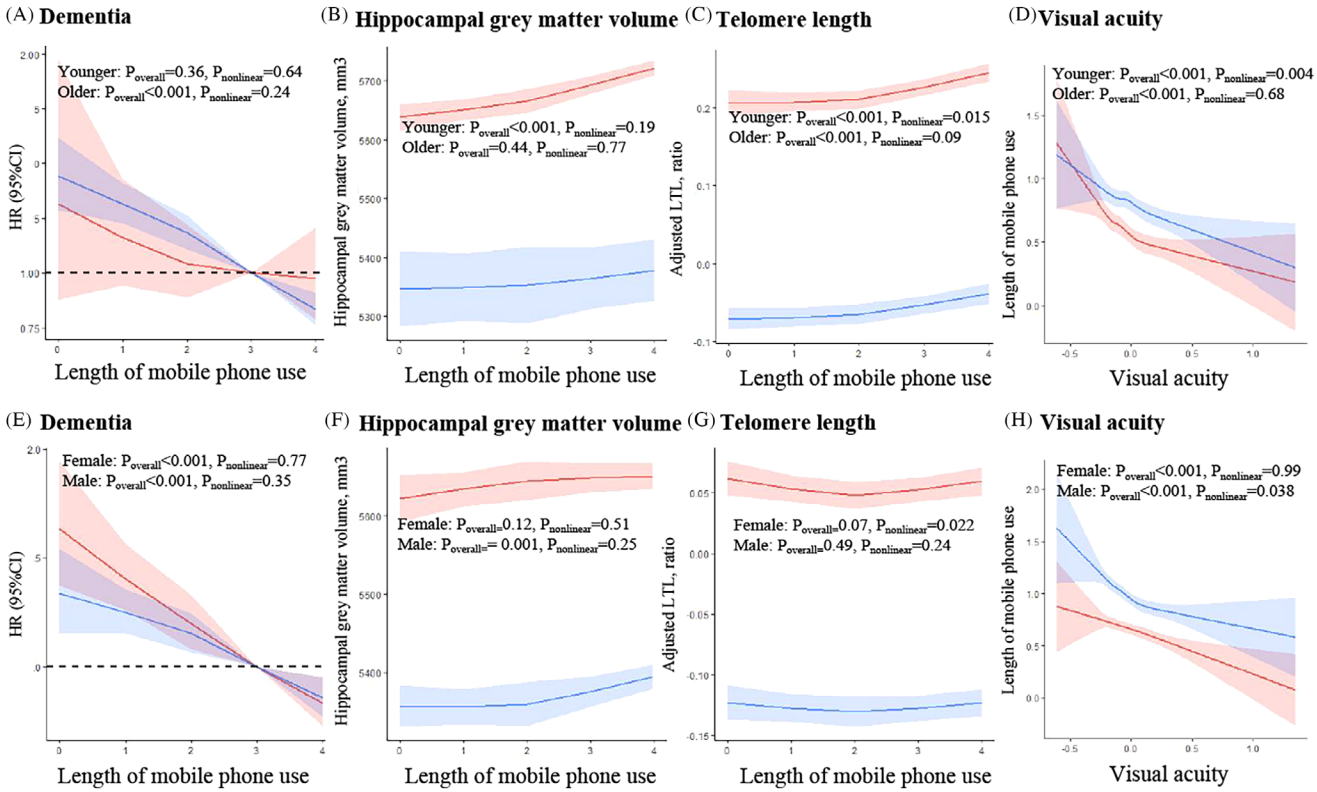

FIGURE 3 Interactions between age, sex, and mobile phone use duration. Top, associations between mobile phone use duration and key measures in each age group. Participants were divided into two age groups: 38–58 and 58–73 years for baseline measures, and 44–65 years and 65–82 years for hippocampal gray matter volumes. Blue and red lines represent younger and older age groups, respectively. Bottom, associations between mobile phone use duration and key measures in each sex group. Blue and red lines represent females and males, respectively. Mobile phone use duration was log-transformed as a continuous variable. All models have been adjusted for age, sex, Townsend index, educational qualifications, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, and family history of dementia. Lines show fitted mean values with 95% CIs shaded. CI, confidence intervals.

data showed that pre-smartphone era mobile phone use was associated significantly with hippocampal volume and LTL in middle-aged and older adults. These findings are congruent with previous structural neuroimaging studies and LTL studies.[44]

Globally, with the rising prevalence of vision impairment, particularly age-related cataracts, there is growing recognition of age-related visual decline as a significant risk factor for subsequent cognitive decline.[28] Although this association is well-documented, modifiable factors that may mitigate dementia risk in mid-to-late life populations remain underexplored. Our study proposes long-term mobile phone use as a potential modifier in the relationship between visual decline and elevated dementia risk. This association may be mediated through complementary neurobiological pathways. Specifically, sustained mobile phone engagement could exert neuroprotective effects via cognitive reserve enhancement (e.g., neurogenesis and increased synaptic density) through sustained neural engagement, stress modulation via cortisol reduction and hippocampal integrity preservation, and promotion of health behaviors linked to social and cognitive stimulation.[45] These mechanisms align with the concept of compensatory neuroplasticity, wherein meaningful digital interaction may optimize brain network efficiency, reduce neurodegeneration, and alleviate loneliness, collectively offering a practical strategy for dementia prevention.[46,47] Our findings demonstrate a correlation between better baseline visual acuity and longer mobile phone use duration, possibly because preserved vision facilitates easier reading of phone displays among older adults. Future randomized controlled trials should evaluate structured phone conversation protocols (e.g., daily 30-min calls) as potential dementia prevention strategies in high-risk groups. Currently, digital technologies perform promising functions in preventing multiple diseases.[48–50] From a translational perspective, voice-based phone interactions represent a low-cost, universally accessible intervention modality that shows promise for mitigating dementia risk in aging populations.

4.1 | Limitations

First, phone use data (2006–2010) predated widespread smartphone adoption, limiting analysis to basic calling functions. Future studies should examine smartphone-specific features. Second, prolonged use (>5–8 years) was uncommon during baseline due to technological constraints (cost, limited penetration). Third, unmeasured confounders (social interactions, socioeconomic factors) may affect results. Fourth, as an observational study, causality cannot be established. In addi-

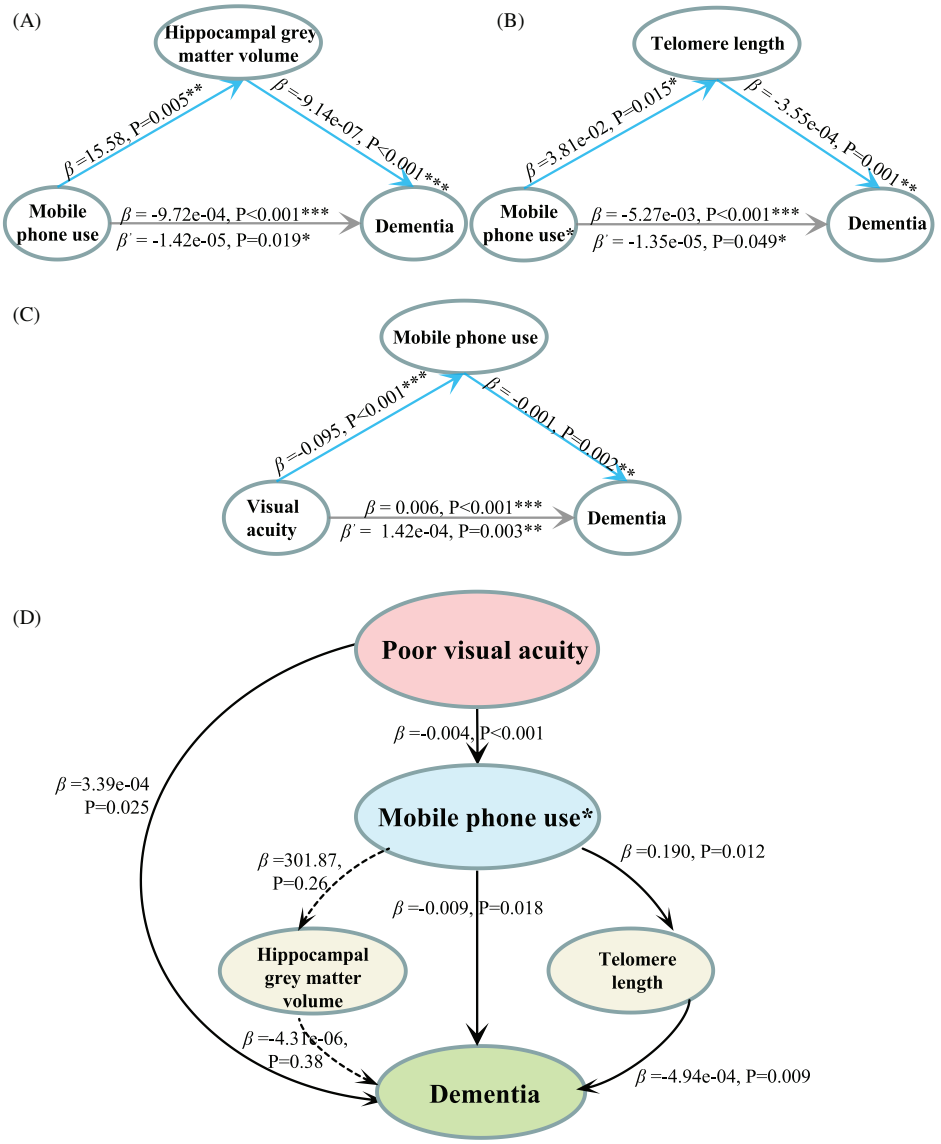

FIGURE 4 Mediation analysis and the structural equation model. (A) The mediation model was conducted to analyze the relationship between mobile phone use length and dementia with hippocampal gray matter volumes as the mediator. (B) The mediation model was conducted to analyze the relationship between mobile phone use and dementia with telomere lengths as the mediator. *The latent variable mobile phone use was represented by mobile phone use length and hands-free device/speakerphone use. (C) The mediation model was conducted to analyze the relationship between visual acuity and dementia with mobile phone use as the mediator. *The latent variable mobile phone use was represented by mobile phone use length and hands-free device/speakerphone use. (D) Visual acuity was significantly associated with mobile phone use and was a significant predictor of dementia. *The latent variable mobile phone use was represented by mobile phone use length and hands-free device/speakerphone use. All models have been adjusted for age, sex, Townsend index, educational qualifications, smoking, alcohol consumption, obesity, physical activity, history of hypertension, diabetes, hyperlipidemia, and family history of dementia.

tion, reverse causality may exist if cognitively healthier individuals used phones more frequently. Last but not least, we didn't exclude familial early-onset AD (potentially differing from sporadic AD), thereby limiting generalizability to genetic cases.

5 | CONCLUSION

Our findings emphasize that longer historic mobile phone use is associated with lower dementia incidence and identifies possible underlying genetic and neural pathways.

AUTHOR CONTRIBUTIONS

Study concept and design: Xiayin Zhang and Honghua Yu. *Acquisition, analysis, or interpretation*: Xiayin Zhang, Yuling Xu, Seth Ishith, Yu Huang, Zijing Du, and Shunming Liu. *Drafting of the manuscript*: Xiayin Zhang and Yuling Xu. *Critical revision of the manuscript for important intellectual content*: Zhuoting Zhu, Seth Ishith, Shan Wang, Xueli Zhang, Dongli Zhuang, Xianwen Shang, Yijun Hu, Mingguang He, and Honghua Yu. *Statistical analysis*: Xiayin Zhang and Yuling Xu. *Obtained funding*: Honghua Yu, Zhuoting Zhu, and Xiayin Zhang. *Administrative, technical, or material support*: Zhuoting Zhu and Honghua Yu. *Study supervision*: Honghua Yu.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Author disclosures are available in the Supporting Information

DATA AVAILABILITY STATEMENT

This project corresponds to UK Biobank application ID 86091. Neuroimaging, genotype, and vision data from the UK Biobank dataset are available at https://biobank.ndph.ox.ac.uk/ by application. The variables used here are detailed in Table S1.

CONSENT STATEMENT

All participants provided written informed consent.

CODE AVAILABILITY

The package rms 6.2-0 in R was used to perform non-linear association analysis, and package lavaan 0.8 in R was used to perform mediation analyses and construct the structural equation model.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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