Sharma *et al.*
Egyptian Journal of Medical Human Genetics (2024) 25:43
https://doi.org/10.1186/s43042-024-00515-4

Egyptian Journal of Medical Human Genetics

RESEARCH

Open Access

ACE I/D polymorphism in cognitive impairment and depression among North Indian adults: a pilot study

Apoorva Sharma[1], Vineet Chaudhary[1], Mamta Kumari Thakur[2], Naorem Kiranmala Devi[1] and Kallur Nava Saraswathy[1*]

Abstract

Background Cognitive impairment and depression are two common mental health conditions affecting millions worldwide. CI and depression both have complex etiology and multiple genetic and environmental factors are thought to play a role in their onset and progression. Further, CI and depression often occur as comorbidities, indicating an overlap in their etiologies. The likelihood of developing major depressive illness and CI, the prognosis in response to treatments, and the possibility of adverse reactions to antidepressant medicines are all significantly influenced by genetics. Looking at the limited literature on the role of ACE I/D polymorphism in CI and depression among Indian populations, the present population-based pilot study was conducted with the aim to understand the association of ACE I/D polymorphism with CI and depression among North Indian adults.

Results The present study was conducted among 195 individuals aged 30 years and above. The results of the present study show that the distributions of some of the studied sociodemographic variables, viz., gender, educational status, and employment status, were significantly different between those with and without CI, where a higher percentage of females, nonliterate and unemployed participants were in CI group than in the without CI group (p value < 0.05). For cognitive impairment, none of the models showed a statistically significant association with ACE I/D genotypes or alleles. For depression, two of the models showed a statistically significant association with ACE I/D genotypes or alleles. The ID + DD (D allele) and DD genotypes of ACE I/D polymorphism, with II as a reference, were found to pose a significantly reduced risk for depression (p value < 0.05).

Conclusion In conclusion, the findings of this study suggest that the D allele of ACE I/D gene polymorphism poses a potentially reduced risk of depression among North Indian adults. In the case of cognitive impairment, the findings suggest that gender, educational status, and employment status may be important factors to consider when assessing the risk of cognitive impairment. However, more research is needed to better understand the complex interplay between sociodemographic and genetic factors and cognitive impairment and depression.

Keywords Cognitive impairment, Depression, Genes, ACE I/D gene polymorphism, Population genetics

Introduction

Cognitive impairment and depression are two common mental health conditions affecting millions worldwide [1]. Cognitive impairment (CI) is a transitional stage between normal aging and dementia, and it reflects the clinical situation where a person has objective evidence of CI but no evidence of dementia [2]. A large proportion

*Correspondence:
Kallur Nava Saraswathy
knsaraswathy@yahoo.com
[1] Laboratory of Molecular and Biochemical Anthropology, Department of Anthropology, University of Delhi, New Delhi, Delhi 110007, India
[2] Department of Biotechnology, Ministry of Science and Technology, New Delhi, Delhi 110003, India

of people with cognitive disability live in low- or middle-income countries (60% in 2001, estimated to rise to 71% by 2040); it is estimated that the rate of increase over the decades is only 100% for high-income countries, whereas it is around 300% for India [1]. In the case of depression, 4.3% of the world's population was found to have depression which was estimated to exceed 300 million in 2015. The National Mental Health Survey 2015–2016 revealed that nearly 1 in 5% of Indian adults need active intervention for one or more mental health issues and one in 20 Indians suffers from depression [3].

CI and depression both have complex etiology and multiple genetic and environmental factors are thought to play a role in their onset and progression. Further, CI and depression often occur as comorbidities, indicating an overlap in their etiologies. The likelihood of developing major depressive illness and CI, the prognosis in response to particular treatments, and the possibility of adverse reactions to antidepressant medicines are all significantly influenced by genetics [4]. The renin-angiotensin system (RAS), in addition to monoamine neurotransmitters, also plays a significant role in the pathophysiology of depression and CI. The most important enzyme in this system is angiotensin-converting enzyme (ACE). ACE is thought to be responsible for the degeneration of neurokinins, a family of neurotransmitters in the central nervous system (CNS) that are crucial for the regulation of emotions in addition to playing a significant role in the RAS by catalyzing the conversion of angiotensin I to angiotensin II [5, 6]. ACE gene is involved in the regulation of blood pressure, electrolyte balance, and fluid homeostasis [7]. The ACE I/D polymorphism is characterized by the insertion (I) or deletion (D) of a 287-base pair Alu repeat sequence in intron 16 of the ACE gene [8]. The ACE I/D polymorphism has been extensively studied in relation to various health conditions, including hypertension, cardiovascular disease, kidney diseases, and diabetes [8, 9]. Though the presence of the D allele of ACE I/D polymorphism has been associated with an increased risk of certain conditions, the associations can vary depending on the population studied and other environmental factors. Looking at the limited literature on the role of ACE I/D polymorphism in CI and depression among Indian populations, the present population-based pilot study was conducted with the aim to understand the association of ACE I/D polymorphism with CI and depression among North Indian adults.

Methods

Area and participants

The present study is a cross-sectional study which draws its participants from a larger cohort of 808 apparently healthy individuals of both sexes aged 30–75 years (median age of 52 years) from Palwal, Haryana, North India, recruited for another related study. Of these 808 individuals, 195 (62.6% females) were randomly selected for the present study. Those individuals suffering from major chronic diseases (cancers and cardiovascular diseases) or on long-term medication were excluded from the study. Pregnant and lactating mothers were also excluded. Informed written consent, typed in Hindi, was obtained from each participant before recruitment.

Data collection

Data collection was done by visiting the participants at their residences. Sociodemographic data (age, sex, literacy, employment, family type, marital status, and smoking status) were collected using a pretested and modified interview schedule.

Sample size calculation

To calculate the sample size, the following sample size formula was used: $n = z^2 * p * (1 - p)/e^2$ [37]; where n is the required sample size, $z = 1.30$ (for a 95% level of confidence) [20], p is the expected prevalence of CI which was taken as 60% [1], which is expressed as a decimal, e is the margin of error, expressed as a decimal, which was taken 0.05. The calculated sample size was 162 with a 20% margin, a total of 195 individuals were recruited.

Blood sample collection

A sample of 5 ml intravenous blood was collected from each participant by a trained technician. DNA extraction was done using the salting-out protocol [10]. DNA samples were stored at − 80 °C until further analysis.

Assessment for cognitive impairment

Mini-Mental State Examination (MMSE), a 30-point scale, was used to assess the cognition status of the participants [11]. Participants scoring 24 or above were considered to have normal cognition, and those scoring below 24 were considered to have cognitive impairment.

Assessment for depression

Beck Depression Inventory-II (BDI-II) at cutoff 14 was used to ascertain depression status [12]. For the present study, participants who scored 13 or below were considered non-depressed, and those who scored 14 or above were considered depressed.

Genetic analysis and genotyping

Allele-specific PCR of the ACE I/D gene polymorphism was used for genotyping, with the following primer sequences used: 5′ CTG GAG ACC ACT CCC ATC CTT TCT 3′; and 5′ GAT GTG GCC ATC ACA TCC GTC AGAT 3′ for the reverse primer [13]. Using a

Fig. 1 Electrophoresis on 2% agarose gel displaying PCR products of the ACE I/D gene polymorphism alongside a 100 bp DNA ladder

thermocycler, the DNA was amplified for 30 cycles of the Polymerase Chain Reaction: denaturation for 1 min at 94 °C, annealing for 1 min at 58 °C, and extension for 2 min at 72 °C (C-1000 Touch TM, Bio-Rad, USA). Using 20.0 µl reaction volumes, the PCR amplification mixture included 1U of Taq, 10 mM Tris–HCL pH 9.0 (Bangalore Genei), 0.2 mM dNTPs, and 0.5 mM of each primer (Sigma), a polymerase (Bangalore Genei), and 50–100 ng of genomic DNA. Based on the number of base pairs (bp), the PCR products were genotyped using ethidium bromide-containing two percent agarose gel electrophoresis: DD (190 bp), ID (490 bp, 190 bp), and II (490 bp). The PCR results showed that an insertion was present in a 490 bp segment and a deletion in a 190 bp fragment (Fig. 1). To prevent Del/Del mistyping, a second round of PCR amplification was performed on each sample with a DD genotype using insertion-specific primers (5′TGG GAC CAC AGC GCC CGC CAC TAC 3′ and 5′ TCG CCA GCC CTC CCA TGC CCA TAA 3′) (13).

Statistical analysis

Statistical analysis was done using SPSS version 22 (IBM -SPSS Inc. Chicago, IL). Chi-square tests were used to check the difference in the frequency distribution of categorical variables. Logistic regression analyses, after adjusting for sociodemographic and lifestyle confounders, were performed to determine the odds ratios. The Hardy–Weinberg equilibrium (HWE) was used to evaluate genotype and allele distribution variance within the population. All the statistical tests computed in the present study were considered significant at a two-tailed p value < 0.05.

Results

The present study was conducted among 195 individuals aged 30 years and above. 195 people aged 30 and older participated in the current investigation. According to their level of cognitive impairment (CI) and depression, study participants' sociodemographic characteristics are distributed as shown in Table 1. The findings of the current study demonstrate that there were significant differences in the distributions of some of the studied sociodemographic variables, such as gender, educational, and employment status, between groups with and without CI, with a higher proportion of females, illiterate participants, and unemployed participants in the CI group than in the non-CI group. Between individuals with and without depression, there was not a significant difference in the distribution of the sociodemographic factors under consideration.

The data reveals that out of 195 individuals analyzed, 38 (19.5%) were found to have the II genotype, 63 (32.3%) had the ID genotype, and 94 (48.2%) had the DD genotype. The allele frequency of the I allele was found to be 0.36, and the frequency of the D allele was 0.64. The observed genotype frequencies were significantly different from the expected frequencies p value < 0.00003, indicating a deviation from the Hardy–Weinberg equilibrium. This suggests the presence of selective pressures or other evolutionary factors that have affected the ACE I/D gene polymorphism in the studied population. The distribution of ACE I/D genotypes and alleles in participants with and without CI and with and without depression is shown in Table 2. There was not a significant distribution between the groups with and without CI and depression in the distribution of ACE I/D genotypes and alleles. However, it was discovered that the frequency of the ACE I/D polymorphism's II genotype was considerably higher in the depressed group.

Table 1 General characteristics of study participants

Variables	Status	Without CI (67)		With CI (128)		*p* value	Without depression (120)		With depression (75)		*p* value
		n	%	*n*	%		*n*	%	*n*	%	
Age Cohort (years)	30–40	14	20.9	11	8.6	0.07	16	13.3	9	12.0	0.68
	40–50	20	29.9	37	28.9		34	28.3	23	30.7	
	50–60	13	19.4	37	28.9		28	23.3	22	29.3	
	≥60	20	29.9	43	33.6		42	35.0	21	28.0	
Sex	Male	44	65.7	29	22.7	< 0.01*	47	39.2	26	34.7	0.80
	Female	23	34.3	99	77.3		73	60.8	49	65.3	
Education status	Literate	59	88.1	29	22.7	< 0.01*	55	45.8	33	44.0	0.40
	Nonliterate	8	11.9	99	77.3		65	54.2	42	56.0	
Employment status	Employed	11	16.4	1	0.8	< 0.01*	6	5.0	6	8.0	0.39
	Unemployed	56	83.6	127	99.2		114	95.0	69	92.0	
Family structure	Joint	44	65.7	96	75.0	0.17	84	70.0	56	74.7	0.48
	Nuclear	23	34.3	32	25.0		36	30.0	19	25.3	
Marital status	Married	64	95.5	116	90.6	0.22	111	92.5	69	92.0	0.90
	Unmarried	0	0	0	0		0	0	0	0	
	Widowed	3	4.5	12	9.4		9	7.5	6	8.0	
Smoking	No	24	38.7	64	52.0	0.09	55	48.7	33	45.8	0.71
	Yes	38	61.3	59	48.0		58	51.3	39	54.2	

*Significant at *p* value < 0.05

Table 2 Distribution of ACE I/D genotypes and alleles among the total population and participants with and without CI as well as with and without depression

Genetic marker	Genotype/allele	Without CI		With CI		*p* value	Without depression		With depression		*p* value	Observed Frequency *N* = 195	*p* value
		n = 67	%	*n* = 128	%		*n* = 120	%	*n* = 75	%			
ACE	II	11	16.4	27	21.1	0.73	18	15.0	20	26.7	0.08	38 (19.5)	< 0.00*
	ID	22	32.8	41	32.0		38	31.7	25	33.3		63 (32.3)	
	DD	34	50.7	60	46.9		64	53.3	30	40.0		94 (48.2)	
	I											0.36	
	D											0.64	

*Significant at *p* value < 0.05; CI cognitive impairment

Table 3 Odds ratio analysis

Genetic marker	Model	Cognitive impairment OR[a] (95% CI)	*p* value	Depression OR (95% CI)	*p* value
ACE	II + ID vs DD (Recessive)	0.79 (0.36–1.74)	0.56	0.58 (0.33–1.05)	0.07
	II v/s ID + DD (Dominant)	0.53 (0.18–1.55)	0.24	0.49 (0.24–0.99)	0.04*
	II vs DD (Codominant)	0.55 (0.17–1.76)	0.32	0.42 (0.2–0.91)	0.03*
	II vs ID (Codominant)	0.46 (0.13–1.6)	0.22	0.59 (0.26–1.33)	0.21
	II + DD vs ID (Over dominant)	0.88 (0.38–2.01)	0.76	1.08 (0.58–2)	0.81

*Significant at *p* value < 0.05; 95% CI 95% confidence interval; [a]OR adjusted for sex, education, and occupation

The odds ratio (OR) analysis for the ACE I/D genotypes and alleles with respect to depression and cognitive impairment is shown in Table 3. None of the models demonstrated a statistically significant association between ACE I/D genotypes or alleles and cognitive impairment. Two of the models for depression demonstrated a statistically significant relationship between ACE I/D genotypes or alleles. With II as a reference, it was found that the ID + DD (D allele) and DD genotypes of the ACE I/D polymorphism pose significantly reduced risks for depression.

Discussion

The present study offers significant insights about the associations between depression and cognitive impairment caused by the ACE gene polymorphism and sociodemographic variables. The results of this study indicate the potential that depression in North Indian adults may be associated with the D allele of the ACE I/D gene polymorphism. CI was found to be associated with a number of sociodemographic characteristics, including gender, education, and employment. According to the present study's findings, the ACE gene's D allele is protective against depression. Numerous other studies with similar findings [5, 14, 15] have found that the D allele does not increase the risk of depression. According to one study, having the ACE heterozygous genotype (ID) carries a greater risk [16]. According to earlier research, homozygosity for the D allele is related to an earlier onset of treatment efficacy, whereas the I allele is associated with a later onset of response in major depression [17–19]. In contrast to the current study, Wu et al.'s meta-analysis from 2012 demonstrated that compared to the I/I and I/D polymorphisms, the D/D homozygote increased the incidence of major depressive disorders by 18% [20]. The D allele may be associated to increased levels of ACE activity, which could then result in higher synthesis of angiotensin II, a vasoconstrictor that has been linked to the pathophysiology of depression, as one explanation for this association. By increasing oxidative stress and inflammation, two factors known to be important in the pathophysiology of depression, the ACE D allele has been hypothesized to contribute to the emergence of depression. Contrarily, it is somewhat puzzling that there was not a significant difference in the distribution of ACE I/D genotypes and alleles between people with and without CI. Previous research on the association between ACE I/D polymorphism and cognitive function has produced mixed findings. The D allele has been linked to considerable cognitive impairment in some studies, but not in others [21, 22].

The CI group had a higher proportion of female, illiterate, and unemployed individuals than the group without CI. The results of this study are in line with earlier studies that have demonstrated a higher prevalence of cognitive impairment among females [23, 24] and people with lower levels of education and employment [25]. Studies have revealed that women are more prone than males to experience cognitive impairment, presumably as a result of variations in a number of characteristics like brain shape and function [26, 27]. Women often live longer than males, and getting older is a major risk factor for cognitive decline. In North India, discrimination against women also restricts access to financial resources and education, which could further contribute to CI [29]. Additionally, menopause-related hormonal alterations may be a factor in certain women's cognitive deterioration [30]. Women should make efforts to preserve their cognitive health by engaging in regular physical activity, eating a nutritious diet, and taking care of any associated medical disorders. The detrimental effects of unemployment on mental health may account for the higher incidence of CI among unemployed people in this study. Cognitive decline may be exacerbated by the stress and social isolation that frequently come with unemployment [31]. Indians' cognitive health outcomes were found to be negatively impacted by their rural location, low socioeconomic status, history of violence, and other sociocultural traits that downplay the value of elderly people in their households [32–35].

In the study, there were not significant sociodemographic differences between people with and without depression. Given that depression is frequently related to sociodemographic characteristics including low income, low education, and unemployment, this conclusion is somewhat unexpected. Additional factors, such as personality traits, life experiences, or biological variables might be more strongly linked to depression than sociodemographic characteristics. The study's population comes primarily from a farming community, which has higher levels of physical activity and may be the cause for the population's lower rates of depression. In addition, the majority of people live in joint families. The availability of a big workforce for professions like agriculture is one of the key benefits of a joint family structure [36]. The cost of housing is also split. Depression is typically decreased by a shared economic production that distributes the burden among family members.

The study has some drawbacks, such as a limited sample size and an absence of data on additional potential confounding factors, like lifestyle factors and comorbidities. Furthermore, the study's cross-sectional design made it difficult to determine causality. To validate these results and understand the underlying mechanisms, more research with bigger sample sizes and longitudinal designs is required.

Conclusion

The results of this study imply that the D allele of the ACE I/D gene polymorphism may be associated with a potential decrease in the incidence of depression in North Indian adults. According to the research, when determining the risk of cognitive impairment, it may be crucial to take into account a person's gender, educational, and employment status. To further comprehend the intricate interactions between sociodemographic, genetic, and depression and cognitive impairment, more research is nonetheless required.

Abbreviations

ACE	Angiotensin-converting enzyme
BDI-II	Beck Depression Inventory-II
CI	Cognitive impairment
CNS	Central nervous system
I/D	Insertion or deletion
MMSE	Mini-Mental State Examination
O.R.	Odds ratio
PCR	Polymerase chain reaction
RAS	Renin-angiotensin system
SPSS	Statistical Package for Social Science

Acknowledgements

We are very grateful to the Department of Biotechnology for the financial assistance. We are very much thankful to all the participants for their kind patience and cooperation and are grateful to the Laboratory of Biochemical and Molecular Anthropology for the resources provided for the accomplishment of the work.

Author contributions

AS, VC, and KNS analyzed the data and drafted the manuscript. DM, KNS, and NK designed the study and directed implementation and data collection. MT collected the data and KNS provided the necessary logistical support. KNS and NK edited the manuscript for intellectual content and provided critical comments on the manuscript.

Funding

The work was supported by the Department of Biotechnology, Government of India (DBT) under grant number BT/PRI14378/MED/30/535/2010.

Availability of data and materials

The data are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Departmental Ethics Committee, Department of Anthropology, University of Delhi, Delhi (Ref No. Anth/2018/2890/1/28-12-2018).

Informed written consent

Typed in local language, was obtained from each participant before recruitment.

Consent for publication

Not applicable.

Competing interests

No potential conflict of interest was reported by the authors.

Received: 1 July 2023 Accepted: 18 March 2024
Published online: 29 March 2024

References

1. Arevalo-Rodriguez I, Smailagic N, Roqué-Figuls M, Ciapponi A, Sanchez-Perez E, Giannakou A et al (2021) Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 7(7):CD010783. https://doi.org/10.1002/14651858.CD010783.pub3
2. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M et al (2005) Global prevalence of dementia: a Delphi consensus study. Lancet 366(9503):2112–2117. https://doi.org/10.1016/S0140-6736(05)67889-0
3. Depression [Internet]. Who.int. [cited 2023 Jun 27]. Available from: https://www.who.int/india/health-topics/depression
4. Jaspard E, Wei L, Alhenc-Gelas F (1993) Differences in the properties and enzymatic specificities of the two active sites of angiotensin I-converting enzyme (kininase II). Studies with bradykinin and other natural peptides. J Biol Chem 268(13):9496–9503. https://doi.org/10.1016/s0021-9258(18)98378-x
5. Segman RH, Shapira Y, Modai I, Hamdan A, Zislin J, Heresco-Levy U et al (2002) Angiotensin converting enzyme gene insertion/deletion polymorphism: case–control association studies in schizophrenia, major affective disorder, and tardive dyskinesia and a family-based association study in schizophrenia. Am J Med Genet 114:310–314
6. López-León S, Janssens ACJW, Hofman A, Claes S, Breteler MMB, Tiemeier H et al (2006) No association between the angiotensin-converting enzyme gene and major depression: a case-control study and meta-analysis. Psychiatr Genet 16(6):225–226. https://doi.org/10.1097/01.ypg.0000242191.51397.3d
7. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F (1990) An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 86(4):1343–1346. https://doi.org/10.1172/JCI114844
8. Tiret L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F et al (1992) Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. Am J Hum Genet 51(1):197–205
9. Qi G-M, Jia L-X, Li Y-L, Li H-H, Du J (2014) Adiponectin suppresses angiotensin II-induced inflammation and cardiac fibrosis through activation of macrophage autophagy. Endocrinology 155(6):2254–2265. https://doi.org/10.1210/en.2013-2011
10. Miller S, Dykes D, Polesky H (1988) Extraction of high molecular weight DNA from human nucleated cells. Nucleic Acids Res 16
11. Folstein MF, Folstein SE, Mchugh PR (1975) Mini-mental state. J Psychiatr Res 12(3):189–198
12. Beck AT, Steer RA, Brown G (1996) Beck depression inventory-II. PsycTESTS Dataset
13. Rigat B, Hubert C, Corvol P, Soubrier F (1992) PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Res 20(6)
14. Furlong RA, Keramatipour M, Ho LW, Rubinsztein JS, Michael A, Walsh C, et al (2000) No association of an insertion/deletion polymorphism in the angiotensin I converting enzyme gene with bipolar or unipolar affective disorders. Am J Med Genet 96(6):733–5. https://doi.org/10.1002/1096-8628(20001204)96:6<733::aid-ajmg7>3.0.co;2-8
15. Pauls J, Bandelow B, Rüther E, Kornhuber J (2000) Polymorphism of the gene of angiotensin converting enzyme: lack of association with mood disorder. J Neural Transm (Vienna) 107(11):1361–1366. https://doi.org/10.1007/s007020070023
16. Bondy B, Baghai TC, Zill P, Bottlender R, Jaeger M, Minov C et al (2002) Combined action of the ACE D-and the G-protein β3 T-allele in major depression: a possible link to cardiovascular disease? Mol Psychiatry 7:1120–1126
17. Baghai TC, Schüle C, Zwanzger P, Minov C, Schwarz MJ, De Jonge S et al (2001) Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on theraputic outcome in affective disorders. Mol Psychiatry 6:258–259
18. Baghai TC, Schule C, Zill P, Deiml T, Eser D, Zwanzger P et al (2004) The angiotensin I converting enzyme insertion/deletion polymorphism influences therapeutic outcome in major depressed women, but not in men. Neurosci Lett 363(1):38–42. https://doi.org/10.1016/j.neulet.2004.03.052
19. Bondy B, Baghai TC, Zill P, Schule C, Eser D, Deiml T et al (2005) Genetic variants in the angiotensin I-converting-enzyme (ACE) and angiotensin II

receptor (AT1) gene and clinical outcome in depression. Prog Neuro-Psychopharmacol Biol Psychiatry. 29(6):1094–1099. https://doi.org/10.1016/j.pnpbp.2005.03.015
20. Wu Y, Wang X, Shen X, Tan Z, Yuan Y (2012) The I/D polymorphism of angiotensin-converting enzyme gene in major depressive disorder and therapeutic outcome: a case–control study and meta-analysis. J Affect Disord 136(3):971–978. https://doi.org/10.1016/j.jad.2011.08.019
21. Li Y, Zhang Z, Deng L, Bai F, Shi Y, Yu H et al (2017) Genetic variation in angiotensin converting-enzyme affects the white matter integrity and cognitive function of amnestic mild cognitive impairment patients. J Neurol Sci 380:177–181. https://doi.org/10.1016/j.jns.2017.06.026
22. Zhang Z, Deng L, Yu H, Shi Y, Bai F, Xie C et al (2012) Association of angiotensin-converting enzyme functional gene I/D polymorphism with amnestic mild cognitive impairment. Neurosci Lett 514(1):131–135. https://doi.org/10.1016/j.neulet.2012.02.074
23. Gao L, Xie Y, Jia C, Wang W (2020) Prevalence of depression among Chinese university students: a systematic review and meta-analysis. Sci Rep 10(1):15897
24. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Norman PE, Flicker L (2015) Depression, frailty, and all-cause mortality: a cohort study of men older than 75 years. J Am Med Dir Assoc 16(4):296–300. https://doi.org/10.1016/j.jamda.2014.10.023
25. Prince M, Acosta D, Ferri CP (2011) The association between common physical impairments and dementia in low and middle income countries, and among people with dementia, their association with cognitive function and disability. A 10/66 Dementia Research Group population-based study. Int J Geriatr Psychiatry 26(5):511–519. https://doi.org/10.1002/gps.2567
26. Ruigrok ANV, Salimi-Khorshidi G, Lai M-C, Baron-Cohen S, Lombardo MV, Tait RJ et al (2014) A meta-analysis of sex differences in human brain structure. Neurosci Biobehav Rev 39:34–50. https://doi.org/10.1016/j.neubiorev.2013.12.004
27. Ingalhalikar M, Smith A, Parker D, Satterthwaite TD, Elliott MA, Ruparel K et al (2014) Sex differences in the structural connectome of the human brain. Proc Natl Acad Sci USA 111(2):823–828. https://doi.org/10.1073/pnas.1316909110
28. Oltra J, Uribe C, Campabadal A, Inguanzo A, Monté-Rubio GC, Martí MJ et al (2021) Sex Differences in Brain and Cognition in de novo Parkinson's Disease. Front Aging Neurosci. 13:791532. https://doi.org/10.3389/fnagi.2021.791532
29. India Discrimination Report (2022) Women in India earn less and get fewer jobs By Abhirr VP
30. Conde DM, Verdade RC, Valadares ALR, Mella LFB, Pedro AO, Costa-Paiva L (2021) Menopause and cognitive impairment: A narrative review of current knowledge. World J Psychiatry. 11(8):412–428. https://doi.org/10.5498/wjp.v11.i8.412
31. Paul KI, Moser K (2009) Unemployment impairs mental health: meta-analyses. J Vocat Behav 74(3):264–282. https://doi.org/10.1016/j.jvb.2009.01.001
32. Fisher GG, Stachowski A, Infurna FJ, Faul JD, Grosch J, Tetrick LE (2014) Mental work demands, retirement, and longitudinal trajectories of cognitive functioning. J Occup Health Psychol 19(2):231–242. https://doi.org/10.1037/a0035724
33. Singh PK, Jasilionis D, Oksuzyan A (2018) Gender difference in cognitive health among older Indian adults: a cross-sectional multilevel analysis. SSM Popul Health. 5:180–187. https://doi.org/10.1016/j.ssmph.2018.06.008
34. Chanda S, Mishra R (2019) Impact of transition in work status and social participation on cognitive performance among elderly in India. BMC Geriatr 19(1):251. https://doi.org/10.1186/s12877-019-1261-5
35. Mani A, Mullainathan S, Shafir E, Zhao J (2013) Poverty impedes cognitive function. Science 341(6149):976–980. https://doi.org/10.1126/science.1238041
36. Taqui AM, Itrat A, Qidwai W, Qadri Z (2007) Depression in the elderly: does family system play a role? A cross-sectional study. BMC Psychiatry 7(1):57. https://doi.org/10.1186/1471-244X-7-57
37. Daniel WW (1999) Biostatistics: a foundation for analysis in the health sciences, 7th edn. Wiley, New York

Publisher's Note